

Preface

As we complete our work on this sixth edition of *Lehninger Principles of Biochemistry*, we are again struck by the remarkable changes in the field of biochemistry that have occurred between editions. The sheer volume of new information from high-throughput DNA sequencing, x-ray crystallography, and the manipulation of genes and gene expression, to cite only three examples, challenges both the seasoned researcher and the first-time biochemistry student. Our goal here is to strike a balance: to include new and exciting research findings without making the book overwhelming for students. The primary criterion for inclusion is that the new finding helps to illustrate an important *principle of biochemistry*.

The image on our cover, a map of the known metabolic transformations in a mitochondrion, illustrates the richness of factual material now available about biochemical transformations. We can no longer treat metabolic “pathways” as though they occurred in isolation; a single metabolite may be simultaneously part of many pathways in a three-dimensional network of metabolic transformations. Biochemical research focuses more and more upon the interactions among these pathways, the regulation of their interactions at the level of gene and protein, and the effects of regulation upon the activities of a whole cell or organism.

This edition of *LPOB* reflects these realities. Much of the new material that we have added reflects our increasingly sophisticated understanding of regulatory mechanisms, including those involved in altering the synthesis of enzymes and their degradation, those responsible for the control and timing of DNA synthesis and the cell cycle, and those that integrate the metabolism of carbohydrates, fats, and proteins over time in response to changes in the environment and in different cell types.

Even as we strive to incorporate the latest major advances, certain hallmarks of the book remain unchanged. We continue to emphasize the relevance of biochemistry

to the molecular mechanisms of disease, highlighting the special role that biochemistry plays in advancing human health and welfare. A special theme is the metabolic basis of diabetes and the factors that predispose to the disease. This theme is interwoven through many chapters and serves to integrate the discussion of metabolism. We also underscore the importance of evolution to biochemistry. Evolutionary theory is the bedrock upon which all biological sciences rest, and we have not wasted opportunities to highlight its important role in our discipline.

To a significant degree, research progress in biochemistry runs in parallel with the development of better tools and techniques. We have therefore highlighted some of these crucial developments. Chapter 9, DNA-Based Information Technologies, in particular, has been significantly revised to include the latest advances in genomics and next-generation sequencing.

Finally, we have devoted considerable attention to making the text and the art even more useful to students learning biochemistry for the first time. To those familiar with the book, some of these changes will be obvious as soon as you crack the cover.

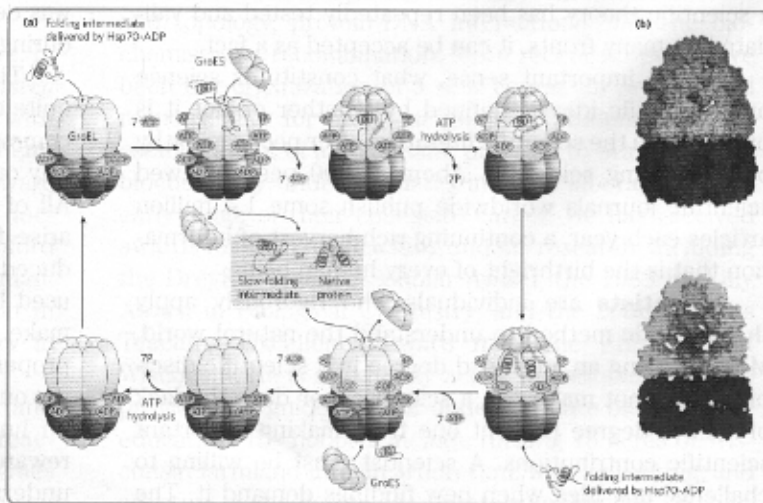
With every revision of this textbook, we have striven to maintain the qualities that made the original Lehninger text a classic—clear writing, careful explanations of difficult concepts, and insightful communication to students of the ways in which biochemistry is understood and practiced today. The authors have written together for almost 25 years and taught introductory biochemistry together for nearly 30. Our thousands of students at the University of Wisconsin–Madison over those years have been an endless source of ideas about how to present biochemistry more clearly; they have enlightened and inspired us. We hope that this sixth edition of *Lehninger* will in turn enlighten and inspire current students of biochemistry everywhere, and perhaps lead some of them to love biochemistry as we do.

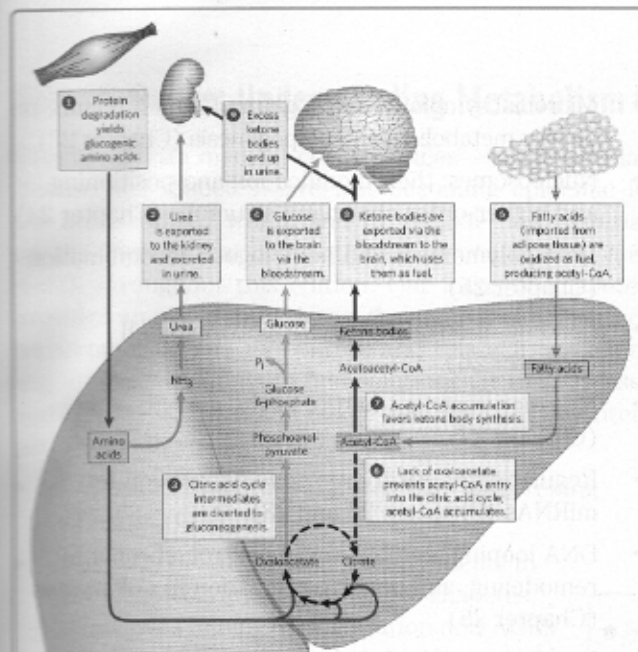
New Art

The most obvious change to the book is the completely revamped art program. Our goal throughout has been to improve pedagogy, drawing on modern graphic resources to make our subject as clear as humanly possible. Many figures illustrate new topics, and much of the art has been reconceived and modernized in style. Defining features of the new art program include:

- ▶ **Smarter renditions of classic figures** are easier to interpret and learn from;

Chaperonins in protein folding





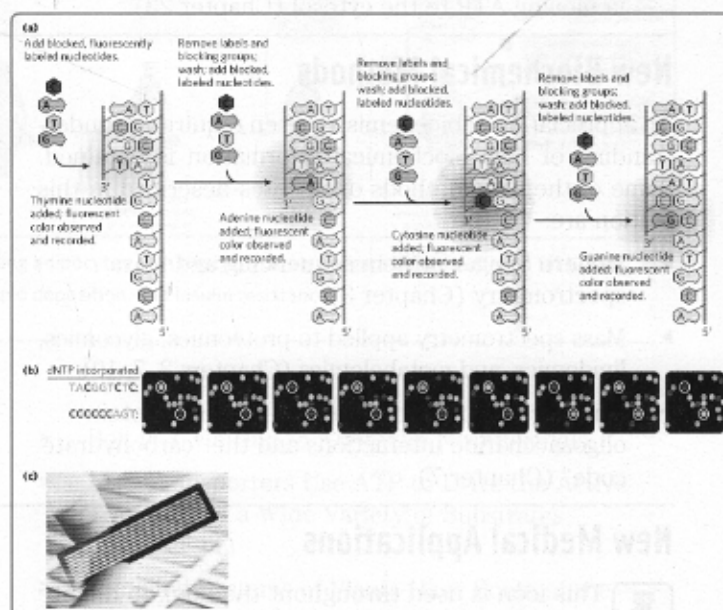
- **Figures that pair molecular models with schematic cartoons**, generated specifically for this book, use shapes and color schemes that are internally consistent;
- Figures with **numbered, annotated steps** help explain complex processes; in many cases, we have moved descriptive text out of the legends and into the figure itself;
- **Summary figures** help the student to keep the big picture in mind while learning the specifics.

Fuel metabolism in the liver during prolonged fasting or in uncontrolled diabetes mellitus

Updated Genomics

Modern genomic techniques have transformed our understanding of biochemistry. In this edition, we have dramatically updated our coverage of genomic methods and their applications. Chapter 9, DNA-Based Information Technologies, has been completely revised to incorporate the latest genomic methods. Many other chapters have been updated to reflect advances gained from these methods. Among the new genomic methods discussed in this edition are:

- Next-generation DNA sequencing, including the Illumina and 454 sequencing methods and platforms (Chapter 9)
- Applications of genomics, including the use of haplotypes to trace human migrations and phylogenetics to locate human genes associated with inherited diseases (Chapter 9)
- Forensic genotyping and the use of personalized genomics in medicine (Chapter 9)

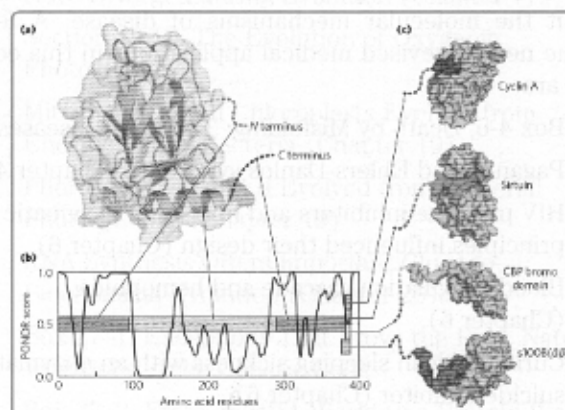


Next-generation reversible terminator sequencing

New Science

Every chapter has been thoroughly revised and updated to include both the most important advances in biochemistry and information needed in a modern biochemistry text. Among the new and updated topics in this edition are:

- Prebiotic evolution, black smokers, and the RNA world (Chapter 1)
- Intrinsically disordered proteins (Chapter 4)
- Transition-state analogs and irreversible inhibition (Chapter 6)
- Blood coagulation pathways in the context of enzymatic regulation (Chapter 6)



Binding of the intrinsically disordered carboxyl terminus of p53 to its binding partners

- ▶ Asymmetric lipid distribution in bilayers (Chapter 11)
- ▶ Role of BAR superfamily proteins in membrane curvature (Chapter 11)
- ▶ Scaffold proteins (AKAPS and others) and their regulatory roles (Chapter 12)
- ▶ Reactive oxygen species as byproducts and as signals (Chapter 19)
- ▶ Structure and function of the oxygen-evolving metal cluster in PSII (Chapter 19)
- ▶ Formation and transport of lipoproteins in mammals, including the roles of SREBP SCAP, and Insig in cholesterol regulation (Chapter 21)
- ▶ Integration of carbohydrate and lipid metabolism by PPARs, SREBPs, mTORC1, and LXR (Chapters 21, 23)
- ▶ Creatine phosphate and the role of creatine kinase in moving ATP to the cytosol (Chapter 23)
- ▶ Microbial symbionts in the gut and their influence on energy metabolism and adipogenesis (Chapter 23)
- ▶ Nucleosomes: their modification and positioning and higher-order chromatin structure (Chapter 24)
- ▶ DNA polymerases and homologous recombination (Chapter 25)
- ▶ Loading of eukaryotic RNA polymerase II (Chapter 26)
- ▶ Mutation-resistant nature of the genetic code (Chapter 27)
- ▶ Regulation of eukaryotic gene expression by miRNAs (Chapters 26 and 28).
- ▶ DNA looping, combinatorial control, chromatin remodeling, and positive regulation in eukaryotes (Chapter 28)
- ▶ Regulation of the initiation of transcription in eukaryotes (Chapter 28)
- ▶ Steroid-binding nuclear receptors (Chapter 28)

New Biochemical Methods

An appreciation of biochemistry often requires an understanding of how biochemical information is obtained. Some of the new methods or updates described in this edition are:

- ▶ Modern Sanger protein sequencing and mass spectrometry (Chapter 3)
- ▶ Mass spectrometry applied to proteomics, glycomics, lipidomics, and metabolomics (Chapters 3, 7, 10)
- ▶ Oligosaccharide microarrays to explore protein-oligosaccharide interactions and the "carbohydrate code" (Chapter 7)
- ▶ Modern genomic methods (Chapter 9)
- ▶ Genetic engineering of photosynthetic organisms (Chapter 20)
- ▶ Use of positron emission tomography (PET) to visualize tumors and brown adipose tissue (Chapter 23)
- ▶ Development of bacterial strains with altered genetic codes for site-specific insertion of novel amino acids into proteins (Chapter 27)

New Medical Applications

 This icon is used throughout the book to denote material of special medical interest. As teachers, our goal is for students to learn biochemistry and to understand its relevance to a healthier life and a healthier planet. Many sections explore what we know about the molecular mechanisms of disease. A few of the new or revised medical applications in this edition are:

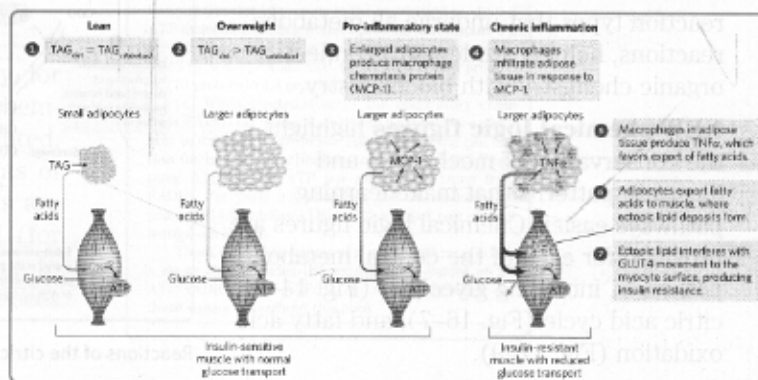
- ▶ Box 4-6, Death by Misfolding: The Prion Diseases
- ▶ Paganini and Ehlers-Danlos syndrome (Chapter 4)
- ▶ HIV protease inhibitors and how basic enzymatic principles influenced their design (Chapter 6)
- ▶ Blood coagulation cascade and hemophilia (Chapter 6)
- ▶ Curing African sleeping sickness with an enzymatic suicide inhibitor (Chapter 6)
- ▶ How researchers locate human genes involved in inherited diseases (Chapter 9)
- ▶ Multidrug resistance transporters and their importance in clinical medicine (Chapter 11)
- ▶ Multistep progression to colorectal cancer (Chapter 12)
- ▶ Cholesterol metabolism, cardiovascular disease, and mechanism of plaque formation in atherosclerosis (Chapter 21)
- ▶ P-450 and drug interactions (Chapter 21)
- ▶ HMG-CoA reductase (Chapter 21) and Box 21-3, The Lipid Hypothesis and the Development of Statins
- ▶ Box 24-1, Curing Disease by Inhibiting Topoisomerases, describing the use of topoisomerase inhibitors in the treatment of bacterial infections and cancer, including material on ciprofloxacin (the antibiotic effective for anthrax)
- ▶ Stem cells (Chapter 28)

Special Theme: Understanding Metabolism through Obesity and Diabetes

Obesity and its medical consequences—cardiovascular disease and diabetes—are fast becoming epidemic in the industrialized world, and we include new material on the biochemical connections between obesity and health throughout this edition. Our focus on diabetes provides an integrating theme throughout the chapters on metabolism and its control, and this will, we hope, inspire some students to find solutions for this disease. Some of the sections and boxes that highlight the interplay of metabolism, obesity, and diabetes are:

- ▶ Untreated Diabetes Produces Life-Threatening Acidosis (Chapter 2)
- ▶ Box 7-1, Blood Glucose Measurements in the Diagnosis and Treatment of Diabetes, introduces hemoglobin glycation and AGEs and their role in the pathology of advanced diabetes
- ▶ Glucose Uptake Is Deficient in Type 1 Diabetes Mellitus (Chapter 14)
- ▶ Ketone Bodies Are Overproduced in Diabetes and during Starvation (Chapter 17)
- ▶ Some Mutations in Mitochondrial Genomes Cause Disease (Chapter 19)
- ▶ Diabetes Can Result from Defects in the Mitochondria of Pancreatic β Cells (Chapter 19)

- ▶ Adipose Tissue Generates Glycerol 3-phosphate by Glyceroneogenesis (Chapter 21)
- ▶ Diabetes Mellitus Arises from Defects in Insulin Production or Action (Chapter 23)
- ▶ Section 23.4, Obesity and the Regulation of Body Mass, includes a new discussion of the roles of TORC1 in regulating cell growth
- ▶ Section 23.5, Obesity, the Metabolic Syndrome, and Type 2 Diabetes, discusses the role of ectopic lipids and inflammation in the development of insulin resistance and the management of type 2 diabetes with exercise, diet, and medication



Overloading adipocytes with triacylglycerols triggers inflammation in fat tissue, ectopic lipid deposition, and insulin resistance.

Special Theme: Evolution

Every time a biochemist studies a developmental pathway in nematodes, identifies key parts of an enzyme active site by determining what parts are conserved between species, or searches for the gene underlying a human genetic disease, he or she is relying on evolutionary theory. Funding agencies support the work in nematodes knowing that the insights will be relevant to humans. The conservation of functional residues in an enzyme active site telegraphs the shared history of every organism on the planet. More often than not, the search for a disease gene is a sophisticated exercise in phylogenetics. Evolution is thus a foundational concept to our discipline. Some of the many sections and boxes that deal with evolution include:

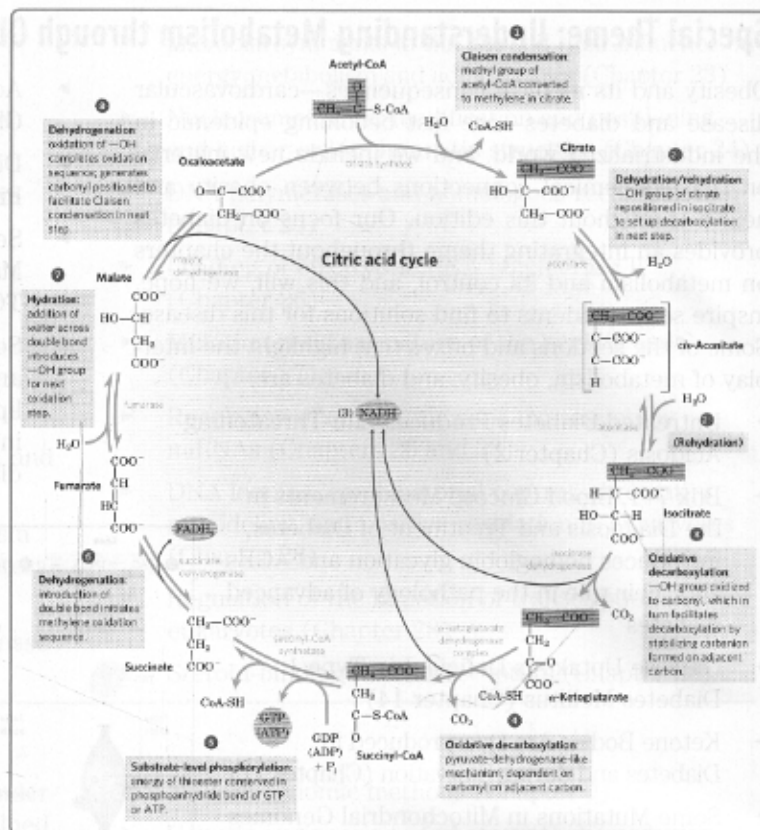
- ▶ Section 1.5, Evolutionary Foundations, discusses how life may have evolved and recounts some of the early milestones in the evolution of eukaryotic cells
- ▶ Genome Sequencing Informs Us about Our Humanity (Chapter 9)
- ▶ Genome Comparisons Help Locate Genes Involved in Disease (Chapter 9)
- ▶ Genome Sequences Inform Us about Our Past and Provide Opportunities for the Future (Chapter 9)
- ▶ Box 9-3, Getting to Know the Neanderthals
- ▶ ABC Transporters Use ATP to Drive the Active Transport of a Wide Variety of Substrates (Chapter 11)
- ▶ Signaling Systems of Plants Have Some of the Same Components Used by Microbes and Mammals (Chapter 12)
- ▶ The β -Oxidation Enzymes of Different Organelles Have Diverged during Evolution (Chapter 17)
- ▶ Section 19.10, The Evolution of Oxygenic Photosynthesis
- ▶ Mitochondria and Chloroplasts Evolved from Endosymbiotic Bacteria (Chapter 19)
- ▶ Photosystems I and II Evolved from Bacterial Photosystems (Chapter 19)
- ▶ RNA Synthesis Offers Important Clues to Biochemical Evolution (Chapter 26)
- ▶ Box 27-1, Exceptions That Prove the Rule: Natural Variations in the Genetic Code
- ▶ Box 27-2, From an RNA World to a Protein World
- ▶ Box 28-1, Of Fins, Wings, Beaks, and Things

Lehninger Teaching Hallmarks

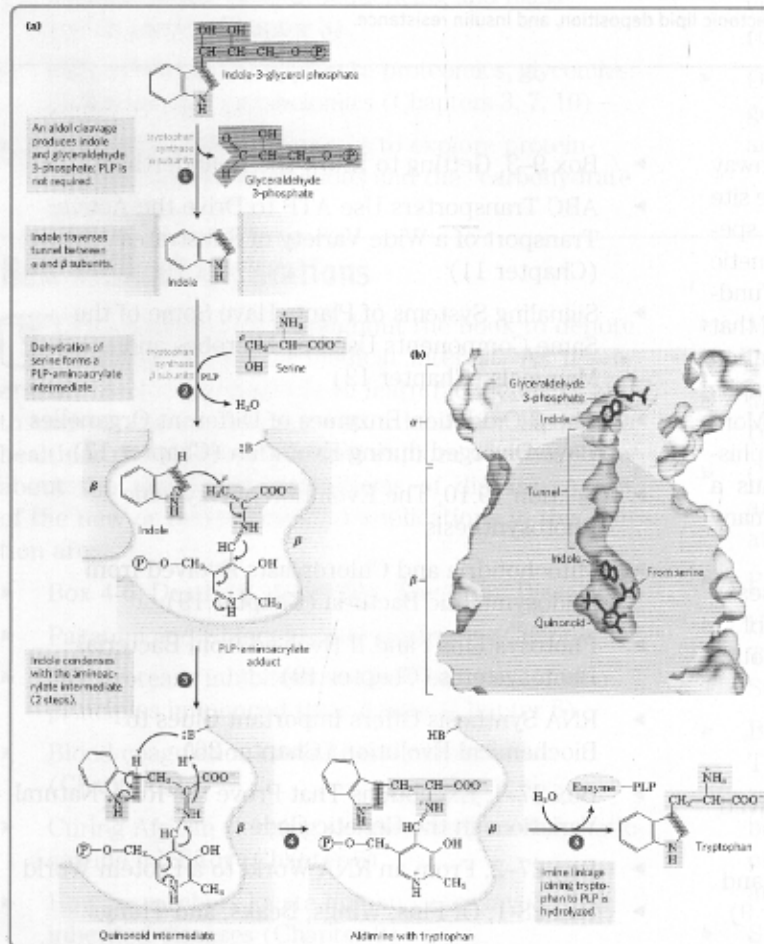
Students encountering biochemistry for the first time often have difficulty with two key aspects of the course: approaching quantitative problems and drawing on what they learned in organic chemistry to help them understand biochemistry. Those same students must also learn a complex language, with conventions that are often unstated. To help students cope with these challenges, we provide the following study aids:

Focus on Chemical Logic

- ▶ Section 13.2, **Chemical Logic and Common Biochemical Reactions**, discusses the common biochemical reaction types that underlie all metabolic reactions, helping students to connect organic chemistry with biochemistry.
- ▶ **NEW chemical logic figures** highlight the conservation of mechanism and illustrate patterns that make learning pathways easier. Chemical logic figures are provided for each of the central metabolic pathways, including glycolysis (Fig. 14-3), citric acid cycle (Fig. 16-7), and fatty acid oxidation (Fig. 17-9).



Reactions of the citric acid cycle



- ▶ **Mechanism figures** feature step-by-step descriptions to help students understand the reaction process. These figures use a consistent set of conventions introduced and explained in detail with the first enzyme mechanism encountered (chymotrypsin, pp. 216-217).

Tryptophan synthase reaction

Problem-Solving Tools

- **In-text Worked Examples** help students improve their quantitative problem-solving skills, taking them through some of the most difficult equations. New worked examples appear in Chapters 1, 2, and 19.
- **More than 600 end-of-chapter problems (about 25 of them new)** give students further opportunity to practice what they have learned.
- **Data Analysis Problems** (one at the end of each chapter), contributed by Brian White of the University of Massachusetts–Boston, encourage students to synthesize what they have learned and apply their knowledge to the interpretation of data from the literature.

Key Conventions

Many of the conventions that are so necessary for understanding each biochemical topic and the biochemical literature are broken out of the text and highlighted. These **Key Conventions** include clear statements of many assumptions and conventions that students are often expected to assimilate without being told (for example, peptide sequences are written from amino- to carboxyl-terminal end, left to right; nucleotide sequences are written from 5' to 3' end, left to right).

Media and Supplements

A full package of media resources and supplements provides instructors and students with innovative tools to support a variety of teaching and learning approaches. All these resources are fully integrated with the style and goals of the sixth-edition textbook.

NEW BiochemPortal

(courses.bfwpub.com/lehninger6e)

This comprehensive and robust online teaching and learning tool incorporates the e-Book, all instructor and student resources, instructor assignment and gradebook functionality, and a new LearningCurve quizzing tool.

- BiochemPortal includes the **e-Book**, with the full contents of the text, highlighting and note-taking tools, and links to important media assets (listed below).
- In addition to all **instructor resources** (listed below), BiochemPortal provides instructors with the **ability to assign** any resource, as well as e-Book readings, discussion board posts, and their own materials. A gradebook tracks all student scores and can be easily exported to Excel or a campus Course Management System.
- **New BiochemPortal** also includes **LearningCurve**, a self-paced adaptive quizzing tool. With questions tailored to students' target difficulty level and an engaging scoring system, LearningCurve encourages students to incorporate content from

WORKED EXAMPLE 19-2 Stoichiometry of ATP Production: Effect of c Ring Size

(a) If bovine mitochondria have 8 c subunits per c ring, what is the predicted ratio of ATP formed per NADH oxidized? (b) What is the predicted value for yeast mitochondria, with 10 c subunits? (c) What are the comparable values for electrons entering the respiratory chain from FADH₂?

Solution: (a) The question asks us to determine how many ATP are produced per NADH. This is another way of asking us to calculate the P/O ratio, or x in Equation 19-11. If the c ring has 8 c subunits, then one full rotation will transfer 8 protons to the matrix and produce 3 ATP molecules. But this synthesis also requires the transport of 3 P_i into the matrix, at a cost of 1 proton each, adding 3 more protons to the total number required. This brings the total cost to (11 protons)/(3 ATP) = 3.7 protons/ATP. The consensus value for the number of protons pumped out per pair of electrons transferred from NADH is 10 (see Fig. 19-19). So, oxidizing 1 NADH produces (10 protons)/(3.7 protons/ATP) = 2.7 ATP.

(b) If the c ring has 10 c subunits, then one full rotation will transfer 10 protons to the matrix and produce 3 ATP molecules. Adding in the 3 protons to transport the 3 P_i into the matrix brings the total cost to (13 protons)/(3 ATP) = 4.3 protons/ATP. Oxidizing 1 NADH produces (10 protons)/(4.3 protons/ATP) = 2.3 ATP.

(c) When electrons enter the respiratory chain from FADH₂ (at ubiquinone), only 6 protons are available to drive ATP synthesis. This changes the calculation for bovine mitochondria to (6 protons)/(3.7 protons/ATP) = 1.6 ATP per pair of electrons from FADH₂. For yeast mitochondria, the calculation is (6 protons)/(4.3 protons/ATP) = 1.4 ATP per pair of electrons from FADH₂.

These calculated values of x or the P/O ratio define a range that includes the experimental values of 2.5 ATP/NADH and 1.5 ATP/FADH₂, and we therefore use these values throughout this book.

the text into their study routine and provides them with a study plan on completion.

- Students can access any of the **student resources** provided with the text (see below) through links in the e-Book or the handy Resources tab.

e-Book (ebooks.bfwpub.com/lehninger6e)

This online version of the textbook combines the contents of the printed book with electronic study tools and a full complement of student media specifically created to support the text. The e-Book also provides useful material for instructors.

- **e-Book study tools** include instant navigation to any section or page of the book, bookmarks, highlighting, note-taking, instant search for any term, pop-up key-term definitions, and a spoken glossary.
- The text-specific **student media**, fully integrated throughout the e-Book, include animated enzyme mechanisms, animated biochemical techniques, problem-solving videos, molecular structure tutorials in Jmol, Protein Data Bank IDs in Jmol, and Living Graphs (each described under "Student Resources" below).
- **Instructor features** include the ability to add notes or files to any page and to share these notes with students. Notes may include text, Web links, animations, or photos. Instructors can also assign the entire text or a custom version of the e-Book.

Instructor Resources

Instructors are provided with a comprehensive set of teaching tools, each developed to support the text, lecture presentations, and individual teaching styles. All instructor media are available for download on the **book website** (www.whfreeman.com/lehninger6e) and on the **Instructor Resource DVD** (ISBN 1-4641-0969-9).

- ▶ **New clicker questions** provide instructors with dynamic multiple-choice questions to be used with iClicker or other classroom response systems. The clicker questions have been written specifically to foster active learning in the classroom and better inform instructors on student misunderstandings.
- ▶ **Fully optimized JPEG files** of every figure, photo, and table in the text feature enhanced color, higher resolution, and enlarged fonts. The files have been reviewed by course instructors and tested in a large lecture hall to ensure maximum clarity and visibility. The JPEGs are also offered in separate files and in **PowerPoint** format for each chapter.
- ▶ **Animated Enzyme Mechanisms** and **Animated Biochemical Techniques** are available in Flash files and preloaded into PowerPoint, in both PC and Macintosh formats, for lecture presentation.
- ▶ A list of **Protein Data Bank IDs** for the structures in the text are arranged by figure number. A new feature in this edition is an index to all structures in the Jmol interactive Web browser applet.
- ▶ **Living Graphs**, illustrating key equations from the textbook, show the graphic results of changing parameters.
- ▶ A comprehensive **Test Bank** in PDF and editable Word formats includes 150 multiple-choice and short-answer problems per chapter, rated by level of difficulty.

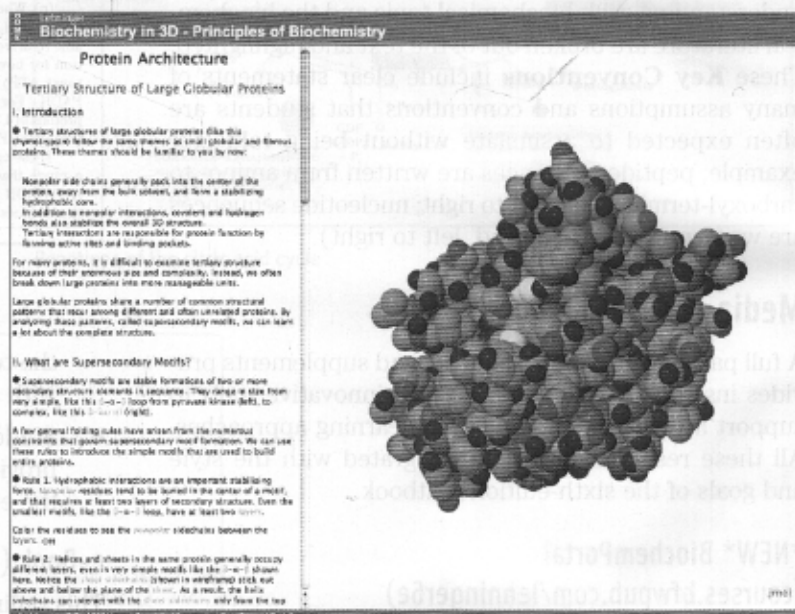
Student Resources

Students are provided with media designed to enhance their understanding of biochemical principles and improve their problem-solving ability. All student media, along with the **PDB Structures** and **Living Graphs**, are also in the e-Book, and many are available on the book website (www.whfreeman.com/lehninger6e). Icons in the text indicate the availability of relevant animation, Living Graph, or Molecular Structure Tutorial.

- ▶ **Problem-Solving Videos**, created by Scott Ensign of Utah State University, provide 24/7 online

problem-solving help to students. Through a two-part approach, each 10-minute video covers a key textbook problem representing a topic that students traditionally struggle to master. Dr. Ensign first describes a proven problem-solving strategy and then applies the strategy to the problem at hand in clear, concise steps. Students can easily pause, rewind, and review any steps as they wish until they firmly grasp not just the solution but also the reasoning behind it. Working through the problems in this way is designed to make students better and more confident at applying key strategies as they solve other textbook and exam problems.

- ▶ Student versions of the **Animated Enzyme Mechanisms** and **Animated Biochemical Techniques** help students understand key mechanisms and techniques at their own pace.



Protein Architecture Molecular Structure Tutorial

- ▶ **Molecular Structure Tutorials**, using the Jmol-Web browser applet, allow students to explore in more depth the molecular structures included in the textbook, including:
 - Protein Architecture
 - Bacteriorhodopsin
 - Lac Repressor
 - Nucleotides
 - MHC Molecules
 - Trimeric G Proteins
 - Oxygen-Binding Proteins
 - Restriction Endonucleases
 - Hammerhead Ribozyme

The Absolute, Ultimate Guide to Lehninger Principles of Biochemistry, Sixth Edition, Study Guide and Solutions Manual, by Marcy Osgood (University of New Mexico School of Medicine) and Karen Ocorr (Sanford-Burnham Medical Research Institute); ISBN 1429294760

The Absolute, Ultimate Guide combines an innovative study guide with a reliable solutions manual (providing extended solutions to end-of-chapter problems) in one convenient volume. Thoroughly class-tested, the study guide includes for each chapter:

- ▶ **Major Concepts:** a road map 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 discussion
- ▶ **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!

Acknowledgments

This book is a team effort, and producing it would be impossible without the outstanding people at W. H. Freeman and Company who supported us at every step along the way. Susan Moran (Senior Developmental Editor), Susan Winslow (Publisher), and Lauren Schultz (Senior Acquisitions Editor) helped develop the revision plan for this edition, made many helpful suggestions, encouraged us, and tried valiantly (if not always successfully) to keep us on schedule. Matthew Tontono (Developmental Editor) provided extremely helpful feedback on many chapters. Our outstanding Project Editor, Jane O'Neill, somehow kept the book moving through production in spite of our missed deadlines and last-minute changes, and did so with her usual grace and skill. We thank Art Director Diana Blume for her artistry in designing both the text and cover for the book. We appreciate the work of present and past copyeditors, including Karen Taschek, Liz Geller, and Linda Strange. Although Linda did not copyedit this edition, her lasting contributions from the first through the fifth editions are still clearly evident in the text. We thank Photo Research Manager Ted Szczepanski and Photo Researcher Elyse Rieder for their help in locating images and Courtney Lyons for help in orchestrating reviews and providing administrative assistance at many turns. We also thank Allison Michael, Media Editor, for assembling the ever more important media components to accompany the text. Our gratitude also goes to Debbie Clare, Associate Director of Marketing, for her creativity and good humor in coordinating the sales and marketing effort. A very special thanks goes to Kate Parker, who oversaw this project for the past three editions, and contributed much to its success, before moving on to other things; we will miss her insight, humor, and excellent taste in restaurants.

In Madison, Brook Soltvedt is (and has been for all the editions we have worked on) our first-line editor and critic. She is the first to see manuscript chapters, aids in manuscript and art development, ensures internal consistency in content and nomenclature, and keeps us on task with more-or-less gentle prodding. As she did

for the fourth and fifth editions, Shelley Lusetti of New Mexico State University read every word of the text in proofs, caught numerous mistakes, and made many suggestions that improved the book.

The new art in this edition, including the new molecular graphics, was done by Adam Steinberg, here in Madison, who often made valuable suggestions that led to better and clearer illustrations. We feel very fortunate to have such gifted partners as Brook, Shelley, and Adam on our team.

We are also deeply indebted to Brian White of the University of Massachusetts–Boston, who wrote the data analysis problems at the end of each chapter.

Many colleagues played a special role through their interest in the project and their timely input. Prominent among these are Jeffrey D. Esko of the University of California, San Diego; and Jack Kirsch and his students at the University of California, Berkeley. Charles G. Hoogstraten of Michigan State University made many incisive and helpful comments on the manuscript and figures. We also thank Jeffrey A. Cohlberg of California State University at Long Beach for his critical comments. Many others helped us shape this sixth edition with their comments, suggestions, and criticisms. To all of them, we are deeply grateful:

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We want especially to thank our students at the University of Wisconsin-Madison for their numerous comments and suggestions. If something in the book does not work, they are never shy about letting us know it. We are grateful to the students and staff of our research groups, who helped us balance the competing demands on our time; to our colleagues in the Department of Biochemistry at the University of Wisconsin-Madison, who helped us with advice and criticism; and to the many students and teachers who have written to suggest ways of improving the book. We hope our readers will continue to provide input for future editions.

Finally, we express our deepest appreciation to our wives, Brook and Beth, and our families, who showed extraordinary patience with, and support for, our book writing.

David L. Nelson
 Michael M. Cox
 Madison, Wisconsin
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