Lehninger

Principles of Biochemistry

Sixth Edition

David L. Nelson

Michael M. Cox

macmillan

HIGHER EDUCATION

International Edition

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Professor of Biochemistry
University of Wisconsin–Madison

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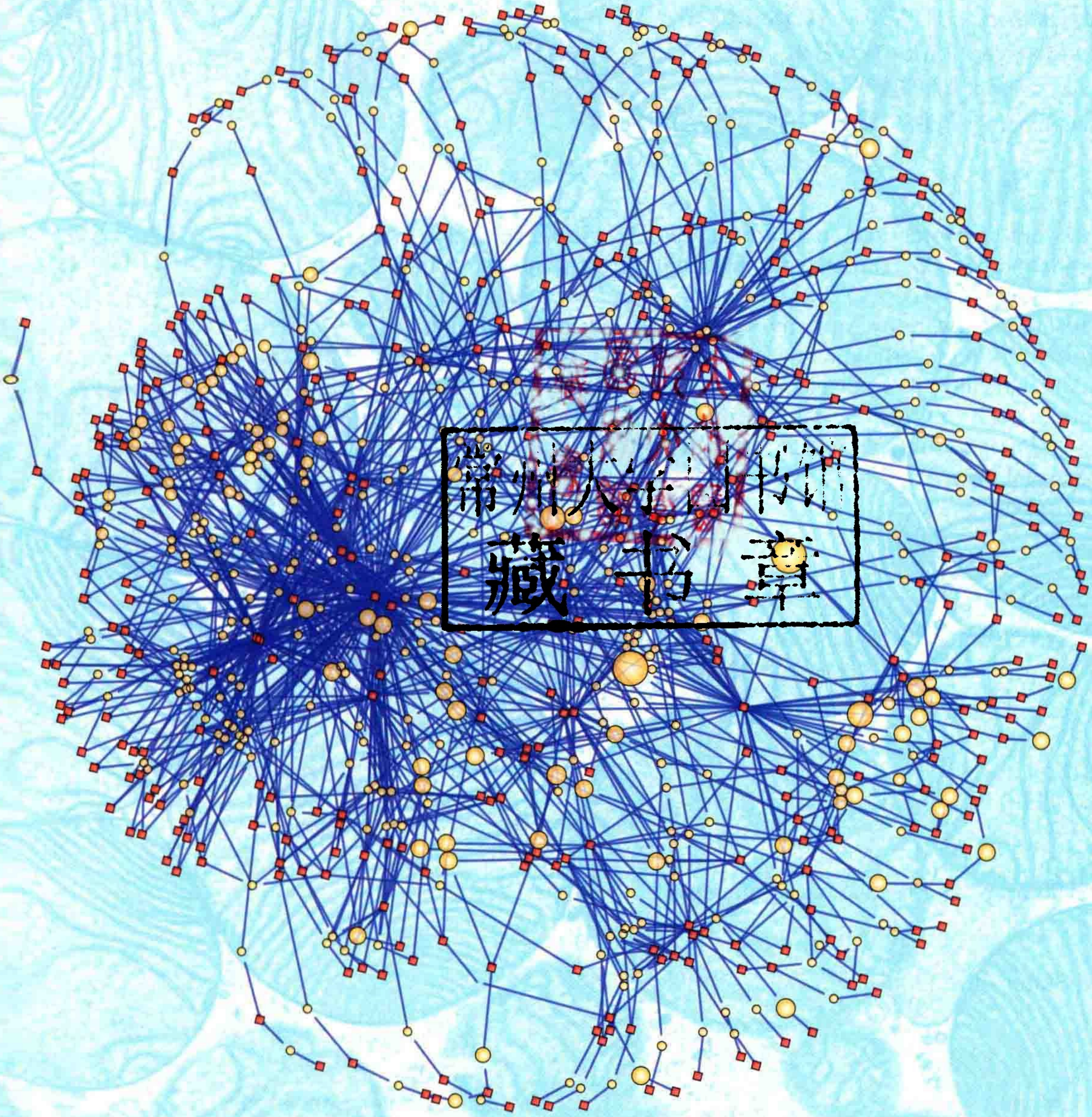

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Cover image: The network of interactions in an animal mitochondrion. Each dot represents a compound, and each line, an enzyme that interconverts the two compounds. The major nodes include ADP, ATP, NAD^+, and NADH. The image was constructed with Cytoscape software by Anthony Smith in the laboratory of Alan Robinson, Medical Research Council Mitochondrial Biology Unit, Cambridge, UK, using data from MitoMiner (Smith, A.C., Blackshaw, J.A., & Robinson, A.J. (2012) MitoMiner: a data warehouse for mitochondrial proteomics data. *Nucleic Acids Res.* 40, D1160–D1167). *Background*: Transmission electron micrograph of interscapular brown adipose cell from a bat. (Don W. Fawcett/Science Source/Photo Researchers)

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About the Authors

David L. Nelson 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 joined the faculty of the University of Wisconsin–Madison in 1971 and became a full professor of biochemistry in 1982. He was for eight years the Director of the Center for Biology Education at the University of Wisconsin–Madison.

Nelson's 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 has used 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 40 years he has taught an intensive survey of biochemistry for advanced biochemistry undergraduates in the life sciences. He has also taught a survey of biochemistry for nursing students, and graduate courses on membrane structure and function and on molecular neurobiology. He has sponsored numerous PhD, MS, and undergraduate honors theses and has received awards for his outstanding teaching, including the Dreyfus Teacher–Scholar Award, the Atwood Distinguished Professorship, and the Unterkofler Excellence in Teaching Award from the University of Wisconsin System. In 1991–1992 he was a visiting professor of chemistry and biology at Spelman College. His second love is history, and in his dotage he has begun to teach the history of biochemistry to undergraduates and to collect antique scientific instruments for use in a laboratory course he teaches.

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 P. 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.

Cox's doctoral research was on general acid and base catalysis as a model for enzyme-catalyzed reactions. At Stanford, he 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, the role of ATP in the RecA system, and the regulation of recombinational DNA repair. Part of the research program now focuses on organisms that exhibit an especially robust capacity for DNA repair, such as *Deinococcus radiodurans*, and the applications of those repair systems to biotechnology.

For almost 30 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. More recent projects have been the organization of a new course on professional responsibility for first-year graduate students and the establishment of a systematic program to draw talented biochemistry undergraduates into the laboratory at an early stage of their collegiate career. He has received awards for both his teaching and his research, including the Dreyfus Teacher–Scholar Award, the 1989 Eli Lilly Award in Biological Chemistry, and the 2009 Regents Teaching Excellence Award from the University of Wisconsin. He is also highly active in national efforts to provide new guidelines for undergraduate biochemistry education. His hobbies include turning 18 acres of Wisconsin farmland into an arboretum, wine collecting, and assisting in the design of laboratory buildings.

A Note on the Nature of Science

In this twenty-first century, a typical science education often leaves the philosophical underpinnings of science unstated, or relies on oversimplified definitions. As you contemplate a career in science, it may be useful to consider once again the terms **science**, **scientist**, and **scientific method**.

Science is both a way of thinking about the natural world and the sum of the information and theory that result from such thinking. The power and success of science flow directly from its reliance on ideas that can be tested: information on natural phenomena that can be observed, measured, and reproduced and theories that have predictive value. The progress of science rests on a foundational assumption that is often unstated but crucial to the enterprise: that the laws governing forces and phenomena existing in the universe are not subject to change. The Nobel laureate Jacques Monod referred to this underlying assumption as the "postulate of objectivity." The natural world can therefore be understood by applying a process of inquiry—the scientific method. Science could not succeed in a universe that played tricks on us. Other than the postulate of objectivity, science makes no inviolate assumptions about the natural world. A useful scientific idea is one that (1) has been or can be reproducibly substantiated and (2) can be used to accurately predict new phenomena.

Scientific ideas take many forms. The terms that scientists use to describe these forms have meanings quite different from those applied by nonscientists. A *hypothesis* is an idea or assumption that provides a reasonable and testable explanation for one or more observations, but it may lack extensive experimental substantiation. A *scientific theory* is much more than a hunch. It is an idea that has been substantiated to some extent and provides an explanation for a body of experimental observations. A theory can be tested and built upon and is thus a basis for further advance and innovation. When a scientific theory has been repeatedly tested and validated on many fronts, it can be accepted as a fact.

In one important sense, what constitutes science or a scientific idea is defined by whether or not it is published in the scientific literature after peer review by other working scientists. About 16,000 peer-reviewed scientific journals worldwide publish some 1.4 million articles each year, a continuing rich harvest of information that is the birthright of every human being.

Scientists are individuals who rigorously apply the scientific method to understand the natural world. Merely having an advanced degree in a scientific discipline does not make one a scientist, nor does the lack of such a degree prevent one from making important scientific contributions. A scientist must be willing to challenge any idea when new findings demand it. The ideas that a scientist accepts must be based on measurable, reproducible observations, and the scientist must report these observations with complete honesty.

The **scientific method** is actually a collection of paths, all of which may lead to scientific discovery. In the *hypothesis and experiment* path, a scientist poses a hypothesis, then subjects it to experimental test. Many of the processes that biochemists work with every day were discovered in this manner. The DNA structure elucidated by James Watson and Francis Crick led to the hypothesis that base pairing is the basis for information transfer in polynucleotide synthesis. This hypothesis helped inspire the discovery of DNA and RNA polymerases.

Watson and Crick produced their DNA structure through a process of *model building and calculation*. No actual experiments were involved, although the model building and calculations used data collected by other scientists. Many adventurous scientists have applied the process of *exploration and observation* as a path to discovery. Historical voyages of discovery (Charles Darwin's 1831 voyage on H.M.S. *Beagle* among them) helped to map the planet, catalog its living occupants, and change the way we view the world. Modern scientists follow a similar path when they explore the ocean depths or launch probes to other planets. An analog of hypothesis and experiment is *hypothesis and deduction*. Crick reasoned that there must be an adaptor molecule that facilitated translation of the information in messenger RNA into protein. This adaptor hypothesis led to the discovery of transfer RNA by Mahlon Hoagland and Paul Zamecnik.

Not all paths to discovery involve planning. *Serendipity* often plays a role. The discovery of penicillin by Alexander Fleming in 1928 and of RNA catalysts by Thomas Cech in the early 1980s were both chance discoveries, albeit by scientists well prepared to exploit them. *Inspiration* can also lead to important advances. The polymerase chain reaction (PCR), now a central part of biotechnology, was developed by Kary Mullis after a flash of inspiration during a road trip in northern California in 1983.

These many paths to scientific discovery can seem quite different, but they have some important things in common. They are focused on the natural world. They rely on *reproducible observation* and/or *experiment*. All of the ideas, insights, and experimental facts that arise from these endeavors can be tested and reproduced by scientists anywhere in the world. All can be used by other scientists to build new hypotheses and make new discoveries. All lead to information that is properly included in the realm of science. Understanding our universe requires hard work. At the same time, no human endeavor is more exciting and potentially rewarding than trying, and occasionally succeeding, to understand some part of the natural world.

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.

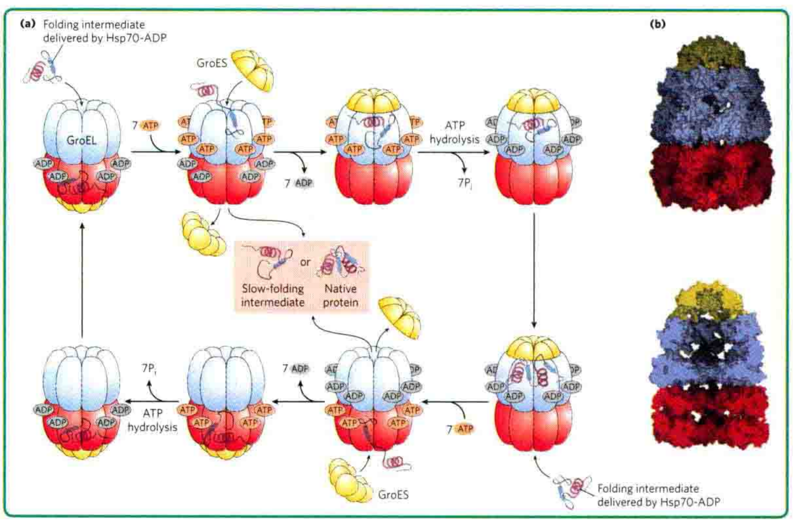
Finally, we have devoted considerable attention to making the text and the art even more useful to students learning biochemistry for the first time. To those familiar with the book, some of these changes will be obvious as soon as you crack the cover.

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.

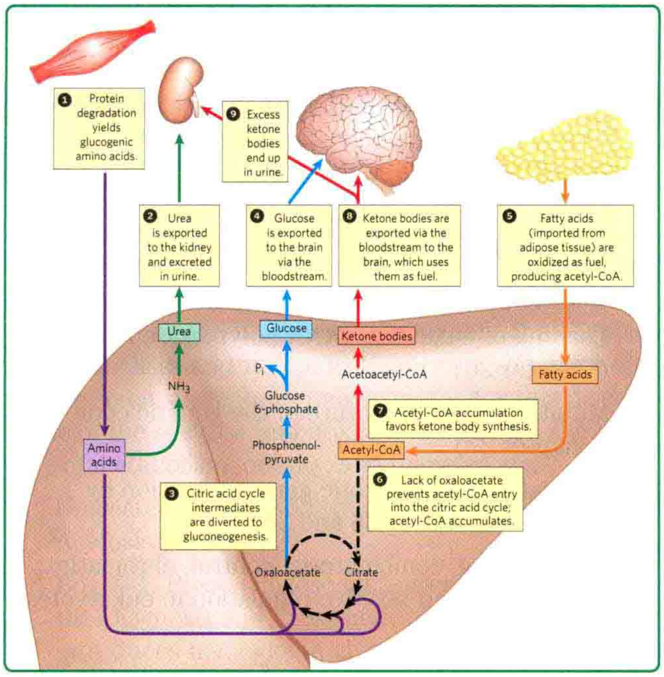
New Art

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



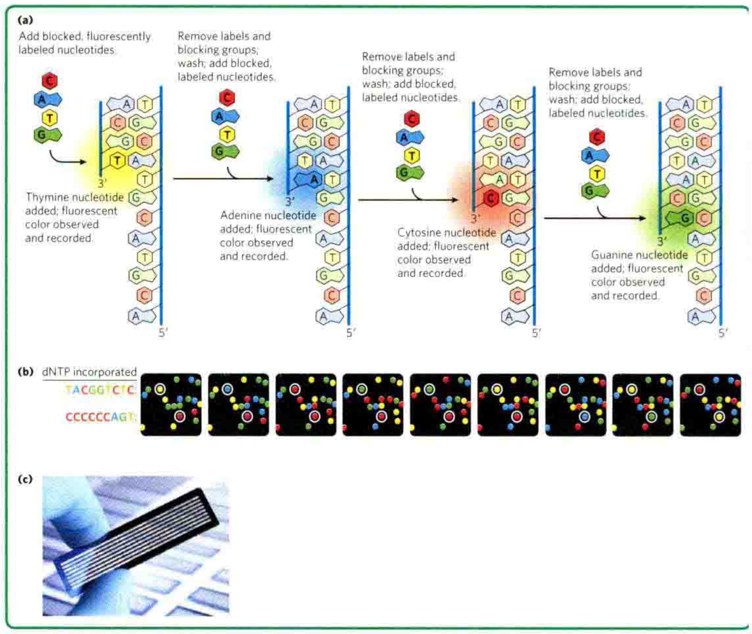
- **Figures that pair molecular models with schematic cartoons**, generated specifically for this book, use shapes and color schemes that are internally consistent;
- Figures with **numbered, annotated steps** help explain complex processes; in many cases, we have moved descriptive text out of the legends 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)

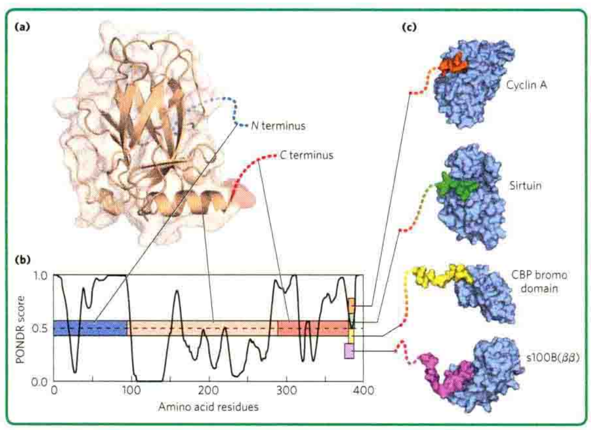


Next-generation reversible terminator sequencing

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

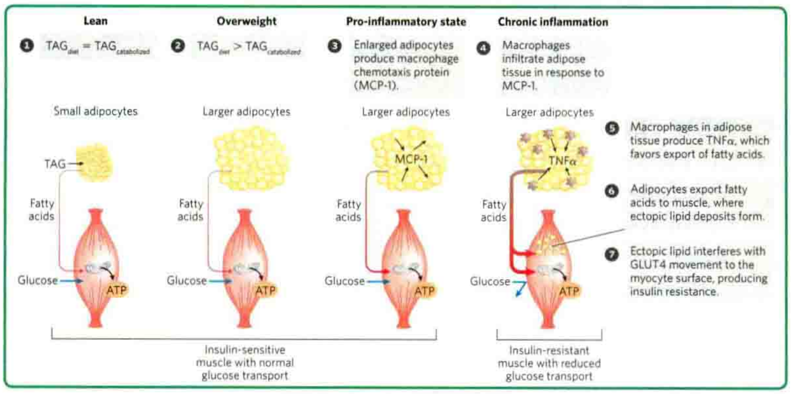
This icon is used throughout the book to denote material of special medical interest. As teachers, our goal is for students to learn biochemistry and to understand its relevance to a healthier life and a healthier planet. Many sections explore what we know about the molecular mechanisms of disease. A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

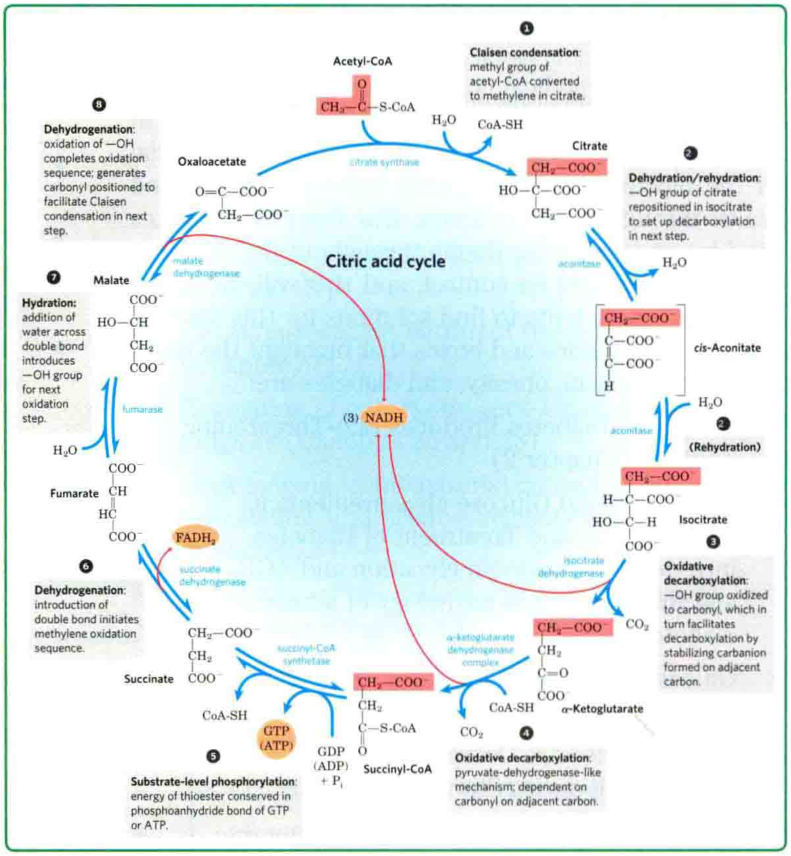
- Section 1.5, Evolutionary Foundations, discusses how life may have evolved and recounts some of the early milestones in the evolution of eukaryotic cells
- Genome Sequencing Informs Us about Our Humanity (Chapter 9)
- Genome Comparisons Help Locate Genes Involved in Disease (Chapter 9)
- Genome Sequences 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

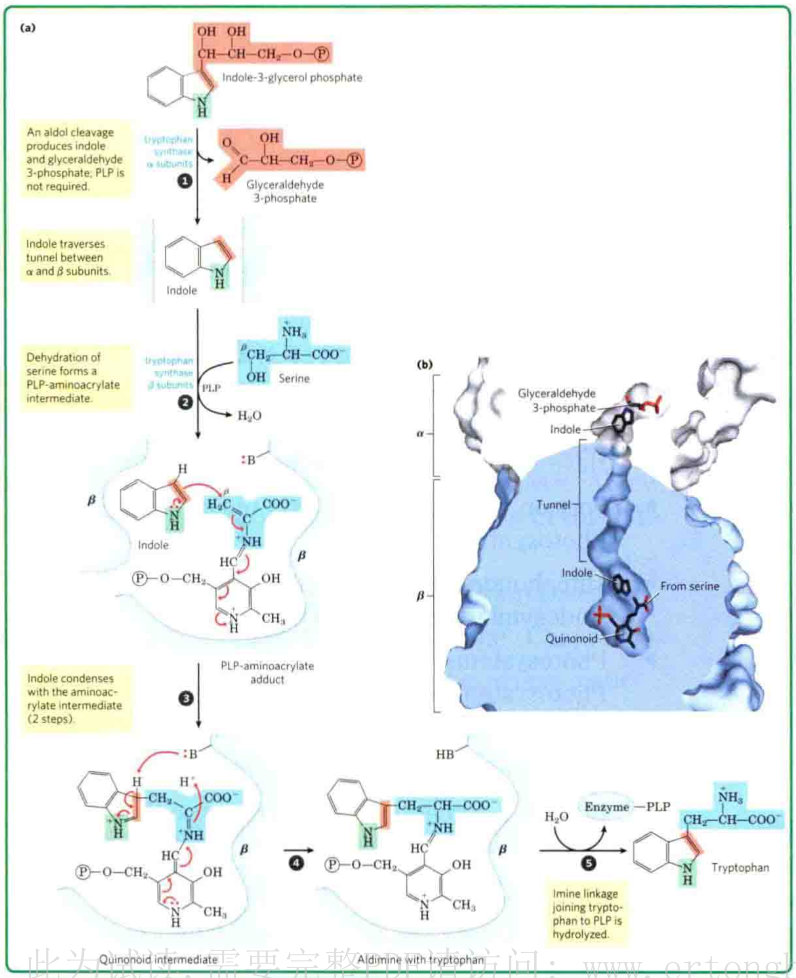
Students encountering biochemistry for the first time often have difficulty with two key aspects of the course: approaching quantitative problems and drawing on what they learned in organic chemistry to help them understand biochemistry. Those same students must also learn a complex language, with conventions 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



Tryptophan synthase reaction

- **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).

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).

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 $FADH_2$?

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 $FADH_2$ (at ubiquinone), only 6 protons are available to drive ATP synthesis. This changes the calculation for bovine mitochondria to (6 protons)/(3.7protons/ ATP) = 1.6 ATP per pair of electrons from $FADH_2$. For yeast mitochondria, the calculation is (6 protons)/(4.3 protons/ATP) = 1.4 ATP per pair of electrons from $FADH_2$.

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/$FADH_2$, and we therefore use these values throughout this book.

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).
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- **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 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

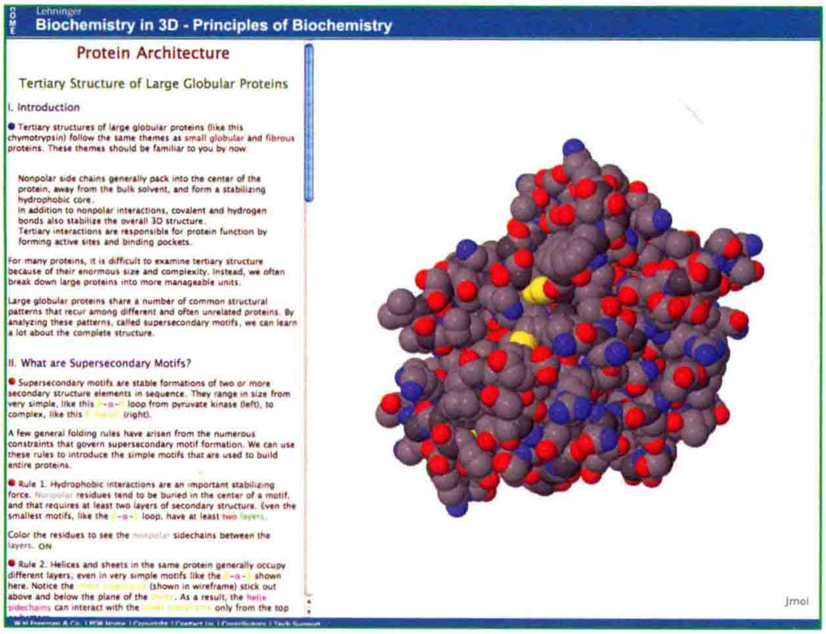
Instructors are provided with a comprehensive set of teaching tools, each developed to support the text, lecture presentations, and individual teaching styles. All instructor media are available for download on the **book website** (www.whfreeman.com/lehninger6e) and on the **Instructor Resource DVD**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

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Contents in Brief

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