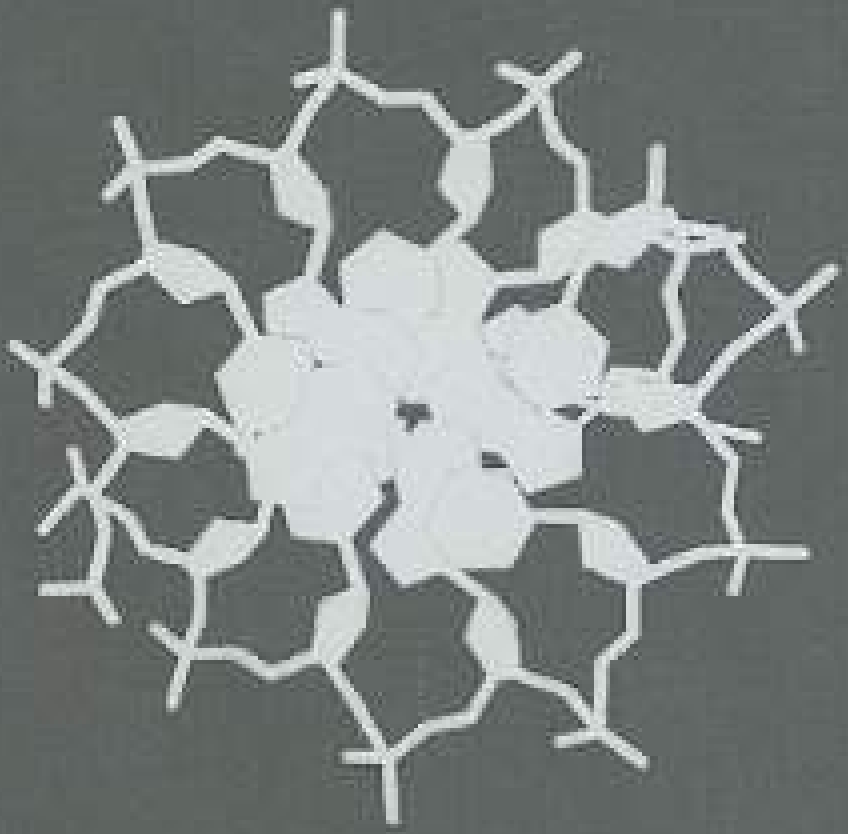
SEVENTH EDITION

Biochemistry



Jeremy M. Berg
John L. Tymoczko
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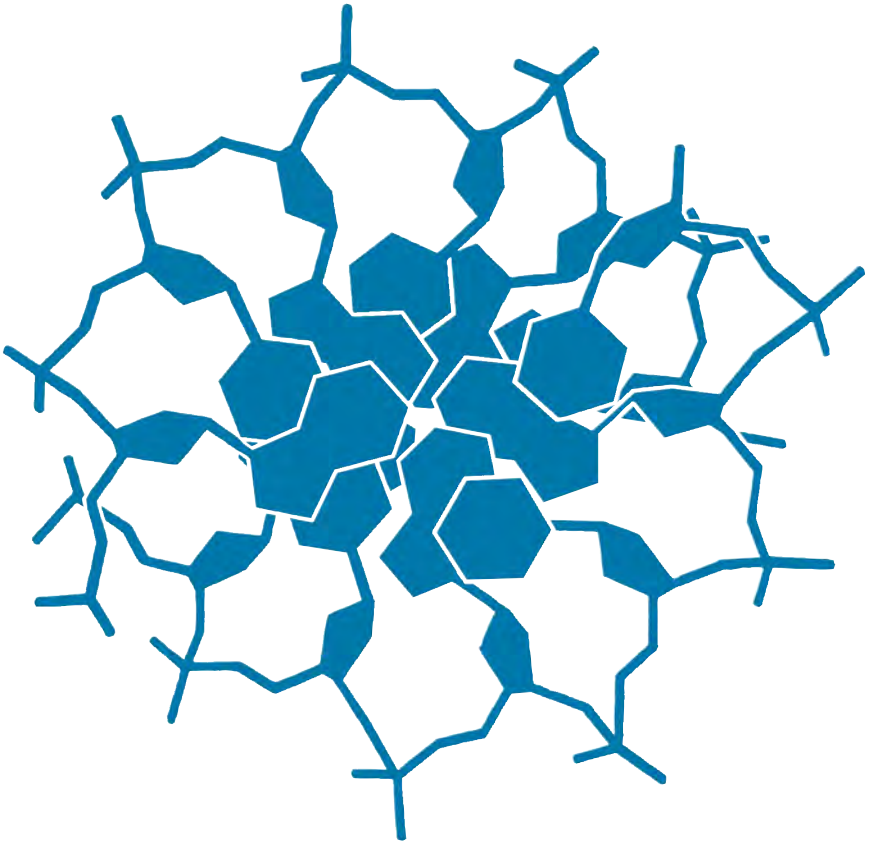

Jeremy M. Berg

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with

Gregory J. Gatto, Jr.

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To our teachers and our students

ABOUT THE AUTHORS

JEREMY M. BERG received his B.S. and M.S. degrees in Chemistry from Stanford (where he did research with Keith Hodgson and Lubert Stryer) and his Ph.D. in Chemistry from Harvard with Richard Holm. He then completed a postdoctoral fellowship with Carl Pabo in Biophysics at Johns Hopkins University School of Medicine. He was an Assistant Professor in the Department of Chemistry at Johns Hopkins from 1986 to 1990. He then moved to Johns Hopkins University School of Medicine as Professor and Director of the Department of Biophysics and Biophysical Chemistry, where he remained until 2003. He then became Director of the National Institute of General Medical Sciences at the National Institutes of Health. He is an elected Fellow of the American Association for the Advancement of Science and an elected member of the Institute of Medicine of the National Academy of Sciences. He received the American Chemical Society Award in Pure Chemistry (1994) and the Eli Lilly Award for Fundamental Research in Biological Chemistry (1995), was named Maryland Outstanding Young Scientist of the Year (1995), received the Harrison Howe Award (1997), the Distinguished Service Award from the Biophysical Society (2009), and the Howard K. Schachman Public Service Award from the American Society for Biochemistry and Molecular Biology (2011). He also received numerous teaching awards, including the W. Barry Wood Teaching Award (selected by medical students), the Graduate Student Teaching Award, and the Professor's Teaching Award for the Preclinical Sciences. He is coauthor, with Stephen J. Lippard, of the textbook *Principles of Bioinorganic Chemistry*.

JOHN L. TYMOCZKO is Towsley Professor of Biology at Carleton College, where he has taught since 1976. He currently teaches Biochemistry, Biochemistry Laboratory, Oncogenes and the Molecular Biology of Cancer, and Exercise Biochemistry and coteaches an introductory course, Energy Flow in Biological Systems. Professor Tymoczko received his B.A. from the University of Chicago in 1970 and his Ph.D. in Biochemistry from the University of Chicago with Shutsung Liao at the Ben May Institute for Cancer Research. He then had a postdoctoral position with Hewson Swift of the Department of Biology at the University of Chicago. The focus of his research has been on steroid receptors, ribonucleoprotein particles, and proteolytic processing enzymes.

LUBERT STRYER is Winzer Professor of Cell Biology, Emeritus, in the School of Medicine and Professor of Neurobiology, Emeritus, at Stanford University, where he has been on the faculty since 1976. He received his M.D. from Harvard Medical School. Professor Stryer has received many awards for his research on the interplay of light and life, including the Eli Lilly Award for Fundamental Research in Biological Chemistry, the Distinguished Inventors Award of the Intellectual Property Owners' Association, and election to the National Academy of Sciences and the American Philosophical Society. He was awarded the National Medal of Science in 2006. The publication of his first edition of *Biochemistry* in 1975 transformed the teaching of biochemistry.

GREGORY J. GATTO, JR., received his A.B. degree in Chemistry from Princeton University, where he worked with Martin F. Semmelhack and was awarded the Everett S. Wallis Prize in Organic Chemistry. In 2003, he received his M.D. and Ph.D. degrees from the Johns Hopkins University School of Medicine, where he studied the structural biology of peroxisomal targeting signal recognition with Jeremy M. Berg and received the Michael A. Shanoff Young Investigator Research Award. He then completed a postdoctoral fellowship in 2006 with Christopher T. Walsh at Harvard Medical School, where he studied the biosynthesis of the macrolide immunosuppressants. He is currently an Investigator in the Heart Failure Discovery Performance Unit at GlaxoSmithKline Pharmaceuticals.

PREFACE

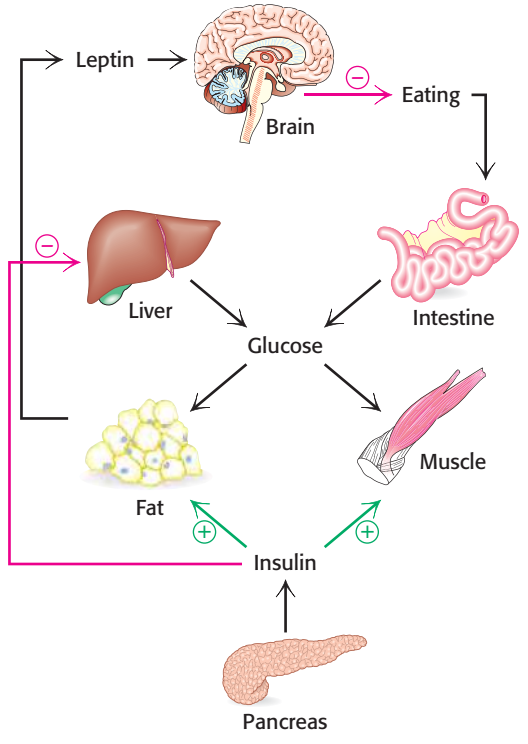
In writing this seventh edition of *Biochemistry,* we have balanced the desire to present up-to-the minute advances with the need to make biochemistry as clear and engaging as possible for the student approaching the subject for the first time. Instructors and students have long relied on *Biochemistry* for:

- **Clear writing** The language of biochemistry is made as accessible as possible. A straightforward and logical organization leads the reader through processes and helps navigate complex pathways and mechanisms.
- **Single-concept illustrations** Illustrations in this book address one point at a time so that each illustration clearly tells the story of a mechanism, pathway, or process without the distraction of excess detail.
- **Physiological relevance** Biochemistry is the study of life on the smallest scale, and it has always been our goal to help students connect biochemistry to their own lives. Pathways and processes are presented in a physiological context so that the reader can see how biochemistry works in different parts of the body and under different environmental and hormonal conditions.
- **Clinical insights** Wherever appropriate, pathways and mechanisms are applied to health and disease. These applications show students how biochemistry is relevant to them while reinforcing the concepts that they have just learned. (For a full list, see p. xi.)
- **Evolutionary perspective** Evolution is evident in the structures and pathways of biochemistry and is woven into the narrative of the textbook. (For a full list, see p. x.)

New to This Edition

Researchers are making new discoveries in biochemistry every day. The seventh edition takes into account the discoveries that have changed how we think about the fundamental concepts in biochemistry and human health. New aspects of the book include:

- **Metabolism integrated in a new context** New information about the role of leptins in hunger and satiety has greatly influenced how we think about obesity and the growing epidemic of diabetes. In this edition, we cover the integration of metabolism in the context of diet and obesity.
- **New chapters on gene regulation** To relate to the rapidly growing understanding of the biochemical aspect of eukaryotic gene regulation, we have greatly expanded our discussion of regulation and have split the chapter in the preceding editions into two: Chapter 31, "The Control of Gene Expression in Prokaryotes," and Chapter 32, "The Control of Gene Expression in Eukaryotes." These chapters address recent discoveries such as quorum sensing in prokaryotes, induced pluripotent stem cells, and the role of microRNAs in regulating gene expression.
- **Experimental techniques updated and clarified** We have revised Chapters 3 ("Exploring Proteins and Proteomes"), 5 ("Exploring Genes and Genomes"), and 6 ("Exploring Evolution and Bioinformatics") to give students a practical understanding of the benefits and limitations of the techniques that they will be using in the laboratory. We have expanded explanations of mass spectrometry and x-ray crystallography, for instance, and made them even clearer for the first-time student. We explain new techniques such as next-generation sequencing and real-time PCR in the context of their importance to modern research in biochemistry. (For a full list, see p. xii.)



Chapter 27 A schematic representation illustrates a few of the many metabolic pathways that must be coordinated to meet the demands of living.

Recent Advances

Some of the exciting advances and new topics that we present in the seventh edition include:

- Osteogenesis imperfecta, or brittle bone disease (Chapter 2)
- Intrinsically unstructured proteins and metamorphic proteins (Chapter 2)
- Recent updates in protein-misfolding diseases (Chapter 2)
- The use of recombinant DNA technology in protein purification (Chapter 3)
- Expanded discussion of mass spectrometry and x-ray crystallography (Chapter 3)
- Next-generation sequencing methods (Chapter 5)
- Real-time PCR (Chapter 5)
- DNA microarrays (Chapter 5)
- Carbon monoxide poisoning (Chapter 7)
- Single-molecule studies of enzyme kinetics (Chapter 8)
- Myosins as a model of a catalytic strategy for ATP hydrolysis (Chapter 9)
- Glycobiology and glycomics (Chapter 11)
- Hurler disease (Chapter 11)
- Avian influenza H5N1 (Chapter 11)
- Lipid rafts (Chapter 12)
- Transferrin as an example of receptor-mediated endocytosis (Chapter 12)
- Long QT syndrome and arrhythmia caused by the inhibition of potassium channels (Chapter 13)
- Defects in the citric acid cycle and the development of cancer (Chapter 17)
- Synthesizing a more efficient rubisco (Chapter 20)
- The structure of mammalian fatty acid synthetase (Chapter 22)
- Pyrimidine salvage pathways (Chapter 25)
- Physical association of enzymes in metabolic pathways (Chapter 25)
- Phosphatidic acid phosphatase in the regulation of lipid metabolism (Chapter 26)
- The regulation of SCAP-SREBP movement in cholesterol metabolism (Chapter 26)
- Mutations in the LDL receptor (Chapter 26)
- The role of HDL in protecting against arteriosclerosis (Chapter 26)

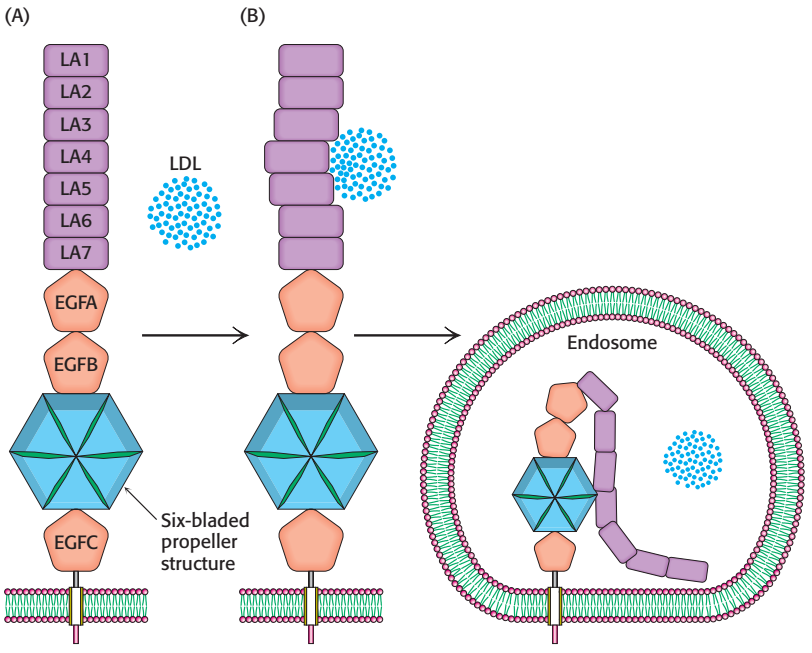


Figure 26.24 LDL receptor releases LDL in the endosomes. [After I. D. Campbell, *Biochem. Soc. Trans.* 31:1107–1114, 2003, Fig 1A.]

- Aromatase inhibitors in the treatment of breast and ovarian cancer (Chapter 26)
- The role of leptin in long-term caloric homeostasis (Chapter 27)
- Obesity and diabetes (Chapter 27)
- Exercise and its effects on cellular biochemistry (Chapter 27)
- Updated detailed mechanism of helicase's action (Chapter 28)
- Updated detailed mechanism of topoisomerase's action (Chapter 28)
- Riboswitches (Chapter 29)
- The production of small regulatory RNAs (Chapter 29)
- Vanishing white matter disease (Chapter 30)
- Quorum sensing (Chapter 31)
- Biofilms (Chapter 31)
- Induced pluripotent stem cells (Chapter 32)
- The role of microRNAs in gene regulation (Chapter 32)
- How vaccines work (Chapter 34)
- The structure of myosin head domains (Chapter 35)

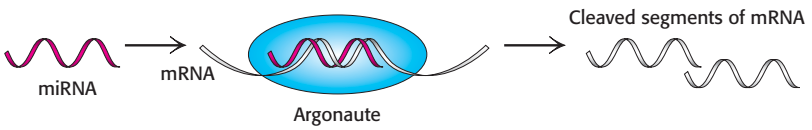


Figure 32.27 MicroRNA action.

New End-of-Chapter Problems

Biochemistry is best learned by practicing it and, to help students practice biochemistry, we have increased the number of end-of-chapter problems by 50%. In addition to many traditional problems that test biochemical knowledge and the ability to use this knowledge, we have three categories of problems to address specific problem-solving skills.

- **Mechanism problems** ask students to suggest or elaborate a chemical mechanism.
- **Data interpretation problems** ask questions about a set of data provided in tabulated or graphic form. These problems give students a sense of how scientific conclusions are reached.
- **Chapter integration problems** require students to use information from several chapters to reach a solution. These problems reinforce a student's awareness of the interconnectedness of the different aspects of biochemistry.

Brief solutions to these problems are presented at the end of the book; expanded solutions are available in the accompanying *Student Companion*.

Visualizing Molecular Structure

All molecular structures have been selected and rendered by Jeremy Berg and Gregory Gatto. To help students read and understand these structures, we include the following tools:

- A **molecular-model "primer"** explains the different types of protein models and examines their strengths and weaknesses (see appendices to Chapters 1 and 2).
- **Figure legends** direct students explicitly to the key features of a model.
- A **great variety of types of molecular structures** are represented, including clearer renderings of membrane proteins.
- For most molecular models, the **PDB number** at the end of the figure legend gives the reader easy access to the file used in generating the structure from the Protein Data Bank Web site (www.pdb.org). At this site, a variety of tools for visualizing and analyzing the structure are available.
- **Living figures** for most molecular structures now appear on the Web site in Jmol to allow students to **rotate three-dimensional molecules** and view alternative renderings online.

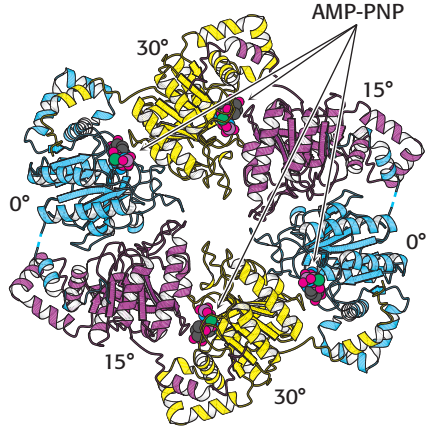


Figure 28.12 Helicase asymmetry. *Notice* that only four of the subunits, those shown in blue and yellow, bind AMP-PNP. [Drawn from 1E0K.pdb.]

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.

eBook
http://ebooks.bfwpub.com/berg7e

This online version of the textbook combines the contents of the printed book, electronic study tools, and a full complement of student media specifically created to support the text. Problems and resources from the printed textbook are incorporated throughout the eBook, to ensure that students can easily review specific concepts. The eBook enables students to:

- Access the complete book and its electronic study tools from any internet-connected computer by using a standard Web browser;
- Navigate quickly to any section or subsection of the book or any page number of the printed book;
- Add their own bookmarks, notes, and highlighting;
- Access all the fully integrated media resources associated with the book;
- Review quizzes and personal notes to help prepare for exams; and
- Search the entire eBook instantly, including the index and spoken glossary.

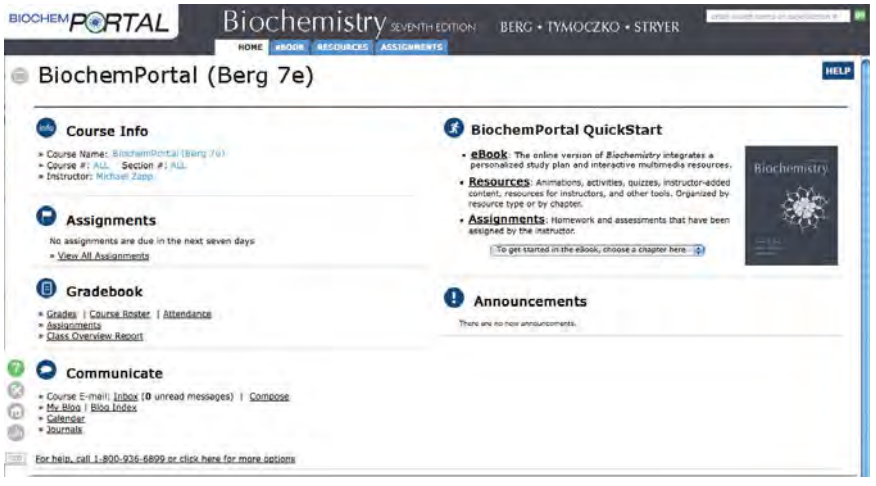
Instructors teaching from the eBook can assign either the entire textbook or a **custom version** that includes only the chapters that correspond to their syllabi. They can choose to add notes to any page of the eBook and share these notes with their students. These notes may include text, Web links, animations, or photographs.

BIOCHEMPORTAL
http://courses.bfwpub.com/berg7e

BiochemPortal is a dynamic, fully integrated learning environment that brings together all of our teaching and learning resources in one place. It features easy-to-use assessment tracking and grading tools that enable instructors to assign problems for practice, as homework, quizzes, or tests. A personalized calendar, an announcement center, and communication tools help instructors manage the course. In addition to all the resources found on the Companion Web site, BiochemPortal includes several other features:

- The **interactive eBook** integrates the complete text with all relevant media resources.
- Hundreds of **self-graded practice problems** allow students to test their understanding of concepts explained in the text, with immediate feedback.
- The **metabolic map** helps students understand the principles and applications of the core metabolic pathways. Students can work through guided tutorials with embedded assessment questions, or explore the Metabolic Map on their own using the dragging and zooming functionality of the map.
- **Jmol tutorials** by Jeffrey Cohlberg, California State University at Long Beach, teach students how to create models of proteins in Jmol based on data from the Protein Database. By working through the tutorial and answering assessment questions at the end of each exercise, students learn to use this important database and fully realize the relationship between structure and function of enzymes.
- **Animated techniques** illustrate laboratory techniques described in the text.
- **Concept tutorials** walk students through complex ideas in enzyme kinetics and metabolism.

BiochemPortal.



Companion Web Site
www.whfreeman.com/berg7e

For students

- **Living figures** allow students to explore protein structure in 3-D. Students can zoom and rotate the "live" structures to get a better understanding of their three-dimensional nature and can experiment with different display styles (space-filling, ball-and-stick, ribbon, backbone) by means of a user-friendly interface.
- **Concept-based tutorials** by Neil D. Clarke help students build an intuitive understanding of some of the more difficult concepts covered in the textbook.
- **Animated techniques** help students grasp experimental techniques used for exploring genes and proteins.
- The **self-assessment tool** helps students evaluate their progress. Students can test their understanding by taking an online multiple-choice quiz provided for each chapter, as well as a general chemistry review.
- The **glossary** of key terms.
- **Web links** connect students with the world of biochemistry beyond the classroom.

For Instructors

All of the student resources plus:

- All **illustrations and tables** from the textbook, in jpeg and PowerPoint formats optimized for classroom projection.
- The **Assessment Bank** offers more than 1500 questions in editable Microsoft Word format.

Instructor's Resource DVD

[1-4292-8411-0]

The CD includes all the instructor's resources from the Web site.

Overhead Transparencies

[1-4292-8412-9]

200 full-color illustrations from the textbook, optimized for classroom projection

Student Companion

[1-4292-3115-7]

For each chapter of the textbook, the *Student Companion* includes:

- Chapter Learning Objectives and Summary
- Self-Assessment Problems, including multiple-choice, short-answer, matching questions, and challenge problems, and their answers
- Expanded Solutions to end-of-chapter problems in the textbook

Molecular Evolution

This icon signals the start of the many discussions that highlight protein commonalities or other molecular evolutionary insights.

Clinical Applications

This icon signals the start of a clinical application in the text. Additional, briefer clinical correlations appear in the text as appropriate.

Tools and Techniques

The seventh edition of *Biochemistry* offers three chapters that present the tools and techniques of biochemistry: "Exploring Proteins and Proteomes" (Chapter 3), "Exploring Genes and Genomes" (Chapter 5), and "Exploring Evolution and Bioinformatics" (Chapter 6). Additional experimental techniques are presented throughout the book, as appropriate.

Exploring Proteins and Proteomes (Chapter 3)

Exploring Proteins (other chapters)

Exploring Genes and Genomes (Chapter 5)

Exploring Genes (other chapters)

Exploring Evolution and Bioinformatics (Chapter 6)

Other Techniques

Animated Techniques

Animated explanations of experimental techniques used for exploring genes and proteins are available at www.whfreeman.com/berg7e.

Acknowledgments

Thanks go first and foremost to our students. Not a word was written or an illustration constructed without the knowledge that bright, engaged students would immediately detect vagueness and ambiguity. We also thank our colleagues who supported, advised, instructed, and simply bore with us during this arduous task. We are also grateful to our colleagues throughout the world who patiently answered our questions and shared their insights into recent developments.

We thank Susan J. Baserga and Erica A. Champion of the Yale University School of Medicine for their outstanding contributions in the sixth edition's revision of Chapter 29. We also especially thank those who served as reviewers for this new edition. Their thoughtful comments, suggestions, and encouragement have been of immense help to us in maintaining the excellence of the preceding editions. These reviewers are:

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University of Pittsburgh

Three of us have had the pleasure of working with the folks at W. H. Freeman and Company on a number of projects, whereas one of us is new to the Freeman family. Our experiences have always been delightful and rewarding. Writing and producing the seventh edition of *Biochemistry* was no exception. The Freeman team has a knack for undertaking stressful, but exhilarating, projects and reducing the stress without reducing the exhilaration and a remarkable ability to coax without ever nagging. We have many people to thank for this experience. First, we would like to acknowledge the encouragement, patience, excellent advice, and good humor of Kate Ahr Parker, Publisher. Her enthusiasm is source of energy for all of us. Lisa Samols is our wonderful developmental editor. Her insight, patience, and understanding contributed immensely to the success of this project. Beth Howe and Erica Champion assisted Lisa by developing several chapters, and we are grateful to them for their help. Georgia Lee Hadler, Senior Project Editor, managed the flow of the entire project, from copyediting through bound book, with her usual admirable efficiency. Patricia Zimmerman and Nancy Brooks, our manuscript editors, enhanced the literary consistency and clarity of the text. Vicki Tomaselli, Design Manager, produced a design and layout that makes the book exciting and eye-catching while maintaining the link to past editions. Photo Editor Christine Beuse and Photo Researcher Jacalyn Wong found the photographs that we hope make the text more inviting. Janice Donnola, Illustration Coordinator, deftly directed the rendering of new illustrations. Paul Rohloff, Production Coordinator, made sure that the significant difficulties of scheduling, composition, and manufacturing were smoothly overcome. Andrea Gawrylewski, Patrick Shriner, Marni Rolfes, and Rohit Phillip did a wonderful job in their management of the media program. Amanda Dunning ably coordinated the print supplemants plan. Special thanks also to editorial assistant Anna Bristow. Debbie Clare, Associate Director of Marketing, enthusiastically introduced this newest edition of *Biochemistry* to the academic world. We are deeply appreciative of the sales staff for their enthusiastic support. Without them, all of our excitement and enthusiasm would ultimately come to naught. Finally, we owe a deep debt of gratitude to Elizabeth Widdicombe, President of W. H. Freeman and Company. Her vision for science textbooks and her skill at gathering exceptional personnel make working with W. H. Freeman and Company a true pleasure.

Thanks also to our many colleagues at our own institutions as well as throughout the country who patiently answered our questions and encouraged us on our quest. Finally, we owe a debt of gratitude to our families—our wives, Wendie Berg, Alison Unger, and Megan Williams, and our children, Alex, Corey, and Monica Berg, Janina and Nicholas Tymoczko, and Timothy and Mark Gatto. Without their support, comfort, and understanding, this endeavor could never have been undertaken, let alone successfully completed.

BRIEF CONTENTS

CONTENTS

Part IV RESPONDING TO ENVIRONMENTAL CHANGES