The Fourth Edition

Scientific understanding of the molecular nature of life is growing at an astounding rate. Significantly, society is the prime beneficiary of this increased understanding. Cures for diseases, better public health, remedies for environmental pollution, and the development of cheaper and safer natural products are just a few practical benefits of this knowledge.

In addition, this expansion of information fuels, in the words of Thomas Jefferson, *"the illimitable freedom of the human mind."* Scientists can use the tools of biochemistry and molecular biology to explore all aspects of an organism—from basic questions about its chemical composition, through inquiries into the complexities of its metabolism, its differentiation and development, to analysis of its evolution and even its behavior. *New procedures based on the results of these explorations lie at the heart of the many modern medical miracles.* Biochemistry is a science whose boundaries now encompass all aspects of biology, from molecules to cells, to organisms, to ecology, and *to all aspects of health care.* This fourth edition of *Biochemistry* embodies and reflects the expanse of this knowledge. We hope that this new edition will encourage students to ask questions of their own and to push the boundaries of their curiosity about science.

Making Connections

As the explication of natural phenomena rests more and more on biochemistry, its inclusion in undergraduate and graduate curricula in biology, chemistry, and the health sciences becomes imperative. The challenge to authors and instructors is a formidable one: how to familiarize students with the essential features of modern biochemistry in an introductory course or textbook. Fortunately, the increased scope of knowledge allows scientists to make generalizations connecting the biochemical properties of living systems with the character of their constituent molecules. As a consequence, these generalizations, validated by repetitive examples, emerge in time as principles of biochemistry, principles that are useful in discerning and describing new relationships between diverse biomolecular functions and in predicting the mechanisms underlying newly discovered biomolecular processes. Nevertheless, it is increasingly apparent that students must develop skills in inquiry-based learning, so that, beyond this first encounter with biochemical principles and concepts, students are equipped to explore science on their own. Much of the design of this new edition is meant to foster the development of such skills.

We are both biochemists, but one of us is in a biology department, and the other is in a chemistry department. Undoubtedly, we each view biochemistry through the lens of our respective disciplines. We believe, however, that our collaboration on this textbook represents a melding of our perspectives that will provide new dimensions of appreciation and understanding for all students.

Our Audience

This biochemistry textbook is designed to communicate the fundamental principles governing the structure, function, and interactions of biological molecules to students encountering biochemistry for the first time. We aim to bring an appreciation of biochemistry to a broad audience that includes undergraduates majoring in the life sciences, physical sciences, or premedical programs, as well as medical students and graduate students in the various health sciences for whom biochemistry is an important route to understanding human physiology. To make this subject matter more relevant and interesting to all readers, we emphasize, where appropriate, the biochemistry of humans.

Objectives and Building on Previous Editions

We carry forward the clarity of purpose found in previous editions; namely, to illuminate for students the principles governing the structure, function, and interactions of biological molecules. At the same time, this new edition has been revised to reflect tremendous developments in biochemistry. Significantly, emphasis is placed on the interrelationships of ideas so that students can begin to appreciate the overarching questions of biochemistry.

Features

- **Clarity of Instruction** This edition was streamlined for increased clarity and readability. Many of the lengthier figure legends were shortened and more information was included directly within illustrations. These changes will help the more visual reader.
- **Visual Instruction** The richness of the Protein Data Bank (www.pdb.org) and availability of molecular graphics software has been exploited to enliven this text. Over 330 images of prominent proteins and nucleic acids involved with essential biological functions illustrate and inform the subject matter and were prepared especially for this book.
- **New End-of-Chapter Problems** More than 600 end-of-chapter problems are provided, about 15 percent of which are new. They serve as meaningful exercises that help students develop problem-solving skills useful in achieving their learning goals. Some problems require students to employ calculations to find mathematical answers to relevant structural or functional questions. Other questions address conceptual problems whose answers require application and integration of ideas and concepts introduced in the chapter. Each set of problems concludes with MCAT practice questions to aid students in their preparation for standardized examinations such as the MCAT or GRE.
- **Human Biochemistry** essays emphasize the central role of basic biochemistry in medicine and the health sciences. These essays often present clinically important issues such as diet, diabetes, and cardiovascular health.
- **A Deeper Look** essays expand on the text, highlighting selected topics or experimental observations.
- **Critical Developments in Biochemistry** essays emphasize recent and historical advances in the field.
- **Up-to-Date References** at the end of each chapter make it easy for students to find additional information about each topic.
- **Laboratory Techniques** The experimental nature of biochemistry is highlighted, and a list of laboratory techniques found in this book can be seen on page xxvi.
- **Essential Questions** Each chapter in this book is framed around an *Essential Question* that invites students to become actively engaged in their learning, and encourages curiosity and imagination about the subject matter. For example, the Essential Question of Chapter 3 asks, "What are the laws and principles of thermodynamics that allow us to describe the flows and interchange of heat, energy,

and matter in systems of interest?" The section heads then pose key questions such as, "What Is the Daily Human Requirement for ATP?" The end-of-chapter summary then brings the question and a synopsis of the answer together for the student. In addition, the CengageNOW site at www.cengage.com/login expands on this Essential Question theme by asking students to explore their knowledge of key concepts. CENGAGENOW™

- **Key Questions** The section headings within chapters are phrased as important questions that serve as organizing principles for a lecture. The subheadings are designed to be concept statements that respond to the section headings.
- **Text-to-Web Instruction** Through icons in the margins, in figure legends, and within boxes, students are encouraged to further test their mastery of the Essential and Key Questions and to explore interactive tutorials and animations at CengageNOW at www.cengage.com/login. CENGAGENOW™
- **Linking Key Questions to Chapter Summaries** The end-of-chapter summaries recite the key questions posed as section heads and then briefly summarize the important concepts and facts to aid students in organizing and understanding the material.
- **Active and Animated Figures at CengageNOW** Many text figures, labeled Active (Figure 3.1) or Animated (Figure 3.5), can be found at www.cengage.com/login. Active Figures have corresponding test questions where students can quiz themselves on the concepts of the figures. Animated Figures give life to the art by allowing students to watch the progress of an animation. This site also includes "Essential Questions" for Biochemistry. These questions are open-ended and can be assigned as student projects by instructors. This website also includes instructor PowerPoint slides with embedded animations/simulations as well as molecular movies for the classroom. CENGAGENOW™

New to This Edition

Biochemistry is an ever-expanding discipline and new research leads to expanding our knowledge. This edition highlights the newest developments in the field.

Chapter 5 Analysis of amino acid sequence information from genomic databases reveals functional relationships between proteins, as well as their evolutionary history.

Chapter 6 The discussion of protein structure now includes protein structure classification databases (SCOP and CATH); the flexible, marginally stable nature of proteins; expanded coverage of intrinsically unstructured proteins; and special features, such as the molecular mousetrap (α_1-antitrypsin).

Chapter 7 Glycomics and the structural code of carbohydrates; galectins as mediators of inflammation, immunity, and cancer; and C-reactive protein, a lectin that limits inflammation damage, highlight this chapter.

Chapter 8 Discussions of healthy dietary oils and fats, including canola oil and Benecol, the novel lipids in archaea, lipids as signals, and lipidomics as a framework for understanding the many roles of lipids are now included.

Chapter 9 New concepts of membrane structure, function, and dynamics, and the recently solved structures of membrane channel proteins, active transport proteins, and ABC transporters are featured.

Chapter 10 The exciting prospects for DNA nanodevices and the applied science of nanotechnology are reviewed, and the evolution of contemporary life from an RNA-based world is presented.

Chapter 11 Nucleic acid sequencing by automated, fluorescence-based or light-emitting techniques has made possible sequencing the DNA of individuals. The structure of DNA multiplexes composed of 3 or 4 polynucleotide strands and the higher orders of structure in RNA molecules are new topics in this chapter.

Chapter 12 The use of RNA interference (RNAi) as a tool to discover gene function and various analytical methods for probing protein-protein interaction are two new methodologies pertinent to this chapter.

Chapter 13 The possibility of creating enzymes designed to catalyze any desired reaction is introduced.

Chapter 14 Enzyme mechanisms (Chapter 14 *Mechanisms of Enzyme Action*) are presented before enzyme regulation (Chapter 15 *Enzyme Regulation*), allowing students to appreciate the catalytic power of enzymes immediately after learning about their kinetic properties (Chapter 13 *Enzymes—Kinetics and Specificity*). The coverage of enzyme mechanisms has been reorganized, shortened, and simplified in this chapter. New topics added in this chapter include medical and commercial applications of enzyme transition state analogs, a primer on how to read and write enzyme mechanisms, the roles of near-attack complexes and protein motion in enzyme catalysis, and a new feature on chorismate mutase.

Chapter 15 The regulation of enzyme activity through allosteric mechanisms is presented in a simplified and integrated form, and the different covalent modifications that alter protein function are characterized.

Chapter 16 The chapter provides substantially revised discussions of myosin, kinesin, and dynein motors; an updated discussion of helicases, including the papilloma virus E1 helicase spiral staircase; and new information on the flagellar rotor structure and mechanism.

Chapter 17 The emerging science of metabolomics and systems biology highlight this chapter.

Chapter 18 The significance of glycolysis to overall metabolism is illustrated through a discussion of hypoxia inducible factor (HIF), a protein that acts in the absence of oxygen to activate transcription of genes for glycolytic enzymes.

Chapter 19 Discussion of the TCA cycle has been updated and a new "A Deeper Look" box on the coenzymes of the TCA cycle has been added.

Chapter 20 The chapter now includes discussions of the structures of the electron transport complexes, the ATP synthase as a rotational molecular motor that uses the energy of a proton gradient to drive synthesis of ATP, and the role of mitochondria in cell signaling and apoptosis.

Chapter 21 The structural details of the photosystems that transduce light energy into chemical energy have given new insights into photosynthesis.

Chapter 22 The identity of xylulose-5-phosphate as a metabolic regulator is a new feature in this chapter.

Chapter 23 This chapter is enhanced by new information on the structure and function of the enzymes of β-oxidation, therapeutic effects of exercise in reversing the consequences of metabolic syndrome, and natural antioxidants in foods that can improve fat metabolism.

Chapter 24 The recent revelation that megasynthases catalyze fatty acid synthesis in eukaryotes is presented in this chapter, along with new information on the structure and function of the LDL receptor.

Chapter 25 Relationships between amino acid metabolism and human disease, such as the significance of aspargine to leukemia, are underscored.

Chapter 26 The phenomenon of metabolic channeling as a principle in metabolic organization and integration is emphasized.

Chapter 27 The role of AMP-activated protein kinase as the sensor of cellular energy levels and regulator of whole-body energy homeostasis is introduced, and the biochemical connections between caloric restriction or red wine consumption to prolonged lifespan are explored.

Chapter 29 The structural studies of RNA polymerase that brought Roger Kornberg the Nobel Prize form the basis for a deeper understanding of transcription. Also presented are chromatin remodeling and histone modifications as processes determining the accessibility of chromatin to the transcriptional apparatus.

Chapter 30 Recent discoveries regarding the molecular structure of ribosomes have provided new insights about the mechanisms by which they synthesize proteins.

Chapter 31 The descriptions of protein folding include new information on how ATP drives and regulates protein folding by chaperonins. It is now clear that AAA+ ATPase modules mediate the unfolding of proteins in the proteasome. Small, ubiquitin-like protein modules (SUMOs) are presented as key modifiers in the post-translational regulation of protein function.

Chapter 32 The chapter has been substantially revised and reorganized to consolidate information on membrane receptor structure and function. Included here is new material about the epidermal growth factor receptor, the insulin receptor, and the atrial natriuretic peptide receptor, as well as the organization and integration of cell signaling pathways and the action of G-protein-coupled receptors through G-protein-independent pathways.

Complete Support Package

For Students

Student Solutions Manual, Study Guide and Problems Book by David K. Jemiolo (Vassar College) and Steven M. Theg (University of California, Davis) includes summaries of the chapters, detailed solutions to all end-of-chapter problems, a guide to key points of each chapter, important definitions, and illustrations of major metabolic pathways. (0-495-11460-X)

Student Lecture Notebook Perfect for note taking during lecture, this convenient booklet consists of black and white reproductions of the PowerPoint slides. (0-495-11461-8)

CENGAGENOW™

CengageNOW at www.cengage.com/login CengageNOW's online self-assessment tool is developed specifically for this text, extending the "Essential Questions" framework. You can explore a variety of tutorials, exercises, and simulations (cross-referenced throughout the text with margin annotations). You can also take chapter-specific Pre-Tests and receive a Personalized Study plan that directs you to specific interactive materials that can help you master areas where you need additional work. Access to **CengageNOW** for two semesters may be included with new textbooks or may be purchased at www.ichapters.com using ISBN 0-495-60645-6. Instructors, please contact your Cengage Learning representative for bundling information.

For Professors

PowerLecture™

PowerLecture with ExamView

Instructor's Resource CD-ROM ISBN: 0-495-11459-6
PowerLecture is a one-stop digital library and presentation tool that includes:

- Prepared Microsoft® PowerPoint® Lecture Slides covering all key points from the text in a convenient format that you can enhance with your own materials or with additional interactive video and animations from the CD-ROM for personalized, media-enhanced lectures.
- Image Libraries in PowerPoint or in JPEG format that contain electronic files for all text art, most photographs, and all numbered tables in the text. These files can be used to print transparencies.
- Electronic files for the Test Bank.
- Sample chapters from the Student Solutions Manual, Study Guide, and Problems Book and the Lecture Notebook.
- ExamView® testing software, with all the test items from the Online Test Bank in electronic format, which enables you to create customized tests of up to 250 items in print or online.

OnlineTest Bank by Larry Jackson, Montana State University
Includes 25–40 multiple-choice questions per chapter for professors to use as tests, quizzes, or homework assignments. Electronic files for the Test Bank are available on the PowerLecture Instructor's CD-ROM. BlackBoard and WebCT formatted files for the Test Bank can be found on the faculty companion site for this book at www.cengage.com/chemistry/garrett, (0-495-11457-X)

Acknowledgments

We are indebted to the many experts in biochemistry and molecular biology who carefully reviewed this book at several stages for their outstanding and invaluable advice on how to construct an effective textbook.

Guillaume Chanfreau
University of California, Los Angeles

Jeffrey Cohlberg
California State University, Long Beach

Bansidhar Datta
Kent State University

Clyde Denis
University of New Hampshire

Gregg B. Fields
Florida Atlantic University

Eric Fisher
University of Illinois, Springfield

Nancy Gerber
San Francisco State University

Donavan Haines
University of Texas, Dallas

Nicole Horenstein
University of Florida

Gary Kunkel
Texas A&M University

Scott Lefler
Arizona State University

Susanne Nonekowski
University of Toledo

Wendy Pogozelski
State University of New York, Geneseo

Michael Reddy
University of Wisconsin

Mary Rigler
California Polytechnic State University

Huiping Zhou
Virginia Commonwealth University

Brent Znosko
St. Louis University

We also wish to warmly and gratefully acknowledge many other people who assisted and encouraged us in this endeavor. A special thank you to Scott Lefler, Arizona State University, who read page proofs with an eye for accuracy. This book remains a legacy of Publisher John Vondeling, who originally recruited us to its authorship. We sense his presence still nurturing our book and we are grateful for it. Lisa Lockwood, our new publisher, has brought enthusiasm and an unwavering emphasis on student learning as the fundamental purpose of our collective endeavor. Sandi Kiselica, Senior Developmental Editor, is a biochemist in her own right. Her fascination with our shared discipline has given her a particular interest in our book and a singular purpose: to keep us focused on the matters at hand, the urgencies of the schedule, and limits of scale in a textbook's dimensions. The dint of her efforts has been a major factor in the fruition of our writing projects. She is truly a colleague in these endeavors. We also applaud the unsung but absolutely indispensable contributions by those whose efforts transformed a rough manuscript into this final product: Teresa Trego, project manager; Carol O'Connell, production editor; Lisa Weber, media editor; and Ashley Summers, assistant editor. If this book has visual appeal and editorial grace, it is due to them. The beautiful illustrations that not only decorate this text, but explain its contents are a testament to the creative and tasteful work of Cindy Geiss, Director of Graphic World Illustration Studio, and to the legacy of John Woolsey and Patrick Lane at J/B Woolsey Associates. We are thankful to our many colleagues who provided original art and graphic images for this work, particularly Professor Jane Richardson of Duke University. We are eager to acknowledge the scientific and artistic contributions of Michal Sabat, Senior Scientist

in the Department of Chemistry at the University of Virginia. Michal was the creator of most of the PyMOL-based molecular graphics in this book. Much of the visual appeal that you will find in these pages gives testimony to his fine craftsmanship and his unflagging dedication to our purpose. We owe a very special thank-you to Rosemary Jurbala Grisham, devoted spouse of Charles and wonderfully tolerant friend of Reg. Also to be acknowledged with love and pride are Georgia Grant, to whom this book is also dedicated, and our children, Jeffrey, Randal, and Robert Garrett, and David, Emily, and Andrew Grisham. Also to be appreciated are Jatszi, Jazmine, and Jasper, three Hungarian Pulis whose unseen eyes view life with an energetic curiosity we all should emulate. Memories of Clancy, a Golden Retriever of epic patience and perspicuity, are companions to our best thoughts. We hope this fourth edition of our textbook has captured the growing sense of wonder and imagination that researchers, teachers, and students share as they explore the ever-changing world of biochemistry.

"Imagination is more important than knowledge. For while knowledge defines all we currently know and understand, imagination points to all we might yet discover and create."
—*Albert Einstein*

Reginald H. Garrett
Charlottesville, VA

Charles M. Grisham
Ivy, VA

December 2008