The Sixth 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 sixth 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

Chapter 10 The structure and chemistry of nucleotides and nucleic acids. New appreciation of cyclic dinucleotides as signaling molecules, including the role of cGAMP in triggering a program of gene expression aimed at halting infection. An updated introduction to the many roles of small RNAs in the regulation of gene expression: miRNAs and the long, noncoding RNAs (lincRNAs).

Chapter 11 The structure of nucleic acids and chromosomes. An overview of the next-generation DNA sequencing technologies, including emerging technologies to sequence single molecules of DNA. The techniques at the forefront of "personal genomics": the ability to carry out low-cost sequencing of an individual's genome and the implications of the information obtained on the diagnosis and treatment of disease. Also, creation of DNA molecules composed of not just two, but three, different base pairs opens up extraordinary potentials within synthetic biology. New structural models for chromatin at the level of its 30-nm fiber 'secondary structure' give insights into the long mysterious higher-order structure of chromosomes. A discussion of how new biological roles of RNA have come into sharper focus because of recent realizations that their three-dimensional architectures are conformationally dynamic, endowing these RNAs with functional abilities, such as ligand binding and even catalysis.

Chapter 12 The strategies of recombinant DNA technology and gene cloning. New features include a section devoted to high-throughput technologies that allow global study of millions of genes or proteins in a single experiment and a section devoted to the emerging field of synthetic biology, with special emphasis on the use of CRISPR/Cas9 to edit genes and genomes.

Chapter 13 The equations of enzyme kinetics. A new perspective on the response of enzyme reaction rate to increasing temperature is presented, wherein a temperature-dependent equilibrium between active enzyme and a catalytically inactive but not denatured state of the enzyme affords a deeper understanding of enzyme kinetics. Ribozymes, abzymes, and designer enzymes are featured here.

Chapter 14 Mechanisms of enzyme action. A new section on the role of quantum mechanical tunneling in electron and proton transfer reactions of enzymes. New Human Biochemistry box on antibiotic resistance by (carbapenem-resistant) superbugs. New Critical Developments in Biochemistry box on acceleration of enzyme reactions by electric fields.

Chapter 15 Enzyme regulation. This chapter highlights allosteric regulation and covalent modification of enzymes as important modes of metabolic regulation and includes discussion of reversible acetylation, a newly appreciated means to regulate metabolic enzymes. The relationship between quaternary structure and allosteric regulation is exemplified by a comparison of the oxygen-binding proteins myoglobin and hemoglobin.

Chapter 16 Motor proteins. A revised discussion of P-loop NTPases and their role in molecular motors and a revised section on the contraction cycle of skeletal muscle. New Human Biochemistry box on the "tubulin code" post-translational modifications that coordinate the functions of microtubules.

Chapter 17 An overview of metabolism, to prepare students for the ten chapters on metabolic pathways which follow. This edition highlights metabolomics, the study of all the metabolites in a cell at a particular moment, as the most accurate representation of what a cell is doing at any instant.

Chapter 18 Glycolysis. A Critical Developments in Biochemistry feature that describes a modern interpretation of the Warburg effect in cancer. Expanded coverage of glucokinase and its role as a glucose sensor that recognizes glucose and initiates a signaling pathway that results in glucose-induced insulin secretion. New information on protein kinase M2 (PK M2), including its newly-discovered protein kinase activity, its stimulation by SAICAR (an intermediate in the purine biosynthetic pathway), and its role in tumor proliferation. New coverage of the unregulated metabolism of dietary fructose in the liver, and its implications for insulin resistance, metabolic syndrome, and obesity.

Chapter 19 The citric acid cycle. A new discussion of the structure of pyruvate dehydrogenase comple; a new Deeper Look feature on the role of anaplerosis in insulin secretion; and a section on the regulation of TCA cycle enzymes by acetylation. A new Human Biochemistry box on the roles of citric acid cycle metabolites in post-translational modification of proteins, including acetylation, succinylation, and succination reactions. New information on the operation of the eight citric cycle enzymes as a supercomplex or metabolon.

Chapter 20 Electron transport and oxidative phosphorylation. Discussion of the new structure of Complex I and new information on supercomplexes in electron transport. New insights into the mechanism of action of the F_1F_0-ATP synthase. A new Human Biochemistry box describing mitochondrial dynamics and its role in cardiovascular, neurodegenerative, and endocrine diseases, as well as cancer. A new Human Biochemistry box on cardiolipin and its stabilization of respiratory supercomplexes, the biogenesis of mitochondrial proteins, and the fission and fusion processes of mitochondria.

Chapter 21 Photosynthesis—the most fundamental of all energy transduction systems in nature: the biochemistry of photosynthesis; the transformation of light energy into chemical energy. New information on species variability in the c-subunit stoichiometry of CF_1CF_0-ATP synthases and the implications of this variability for the energetic cost of ATP formation. The recently described structure of the Mn_4CaO_5 oxygen-evolving cluster at the heart of Photosystem II is presented. Emphasis on the pathway of carbon dioxide fixation that synthesizes organic molecules from CO_2, ultimately leading to cellulose and starch formation, the two significant polysaccharides produced by plants.

Chapter 22 Gluconeogenesis, glycogen metabolism, and the pentose phosphate pathway. A Deeper Look feature on TIGAR, a p53-induced enzyme that mimics fructose-2,6-bisphosphatase and responds to cellular stresses such as oncogenesis and DNA damage events; new information on O-GlcNAc signaling and the hexosamine biosynthetic pathway; and a new Critical Developments in Biochemistry feature describing how consumption of ATP promotes and supports the metabolism of cancer cells. The interplay of phosphorylation and O-GlcNAcylation in gluconeogenic gene transcription, particularly in the fasting state.

Chapter 23 Fatty acid oxidation. A new Deeper Look feature on the biochemistry of obesity describing the role of peroxisome proliferator-activated receptors in regulation of gene expression in

fatty acid oxidation and triglyceride metabolism. A new A Deeper Look box describing the trifunctional enzyme complex at the heart of the β-oxidation pathway and migration of its fatty acyl substrates along a negatively-charged substrate channel without diffusing into the bulk solvent. The role of β-hydroxybutyrate as a signaling metabolite that regulates gene expression, lipid metabolism, metabolic rate, and resistance to oxidative stress.

Chapter 24 Lipid biosynthesis. A Human Biochemistry box featuring the role of NPC1 and NPC2 proteins in cholesterol transport in lysosomes and Niemann-Pick type C disease. Four new Human Biochemistry boxes: Lipins—phosphatases essential for triglyceride synthesis and other functions; Lipoxins—anti-inflammatory eicosanoid products of transcellular metabolism; APOC3—an apolipoprotein that regulates plasma triglyceride levels; and new cholesterol-lowering drugs that target PCSK9, an LDL receptor chaperone.

Chapter 25 The assimilation of inorganic nitrogen into organic nitrogen metabolites and biosynthesis of the amino acids. Discussion of glutamine and its metabolic significance as the most abundant amino acid in human body fluids and tissues; glutamine and cancer. Further, tryptophan catabolism by the kynurenine pathway is presented, because this pathway has been implicated in human neurodegenerative disorders such as Parkinson's and Alzheimer's disease.

Chapter 26 Biosynthesis of purines and pyrimidines. Tetrahydrofolate and 1-carbon metabolism. Purinosomes as multi-enzyme assemblages of the purine biosynthetic enzymes. The purine pathway intermediate SAICAR as a key signal in reprogramming metabolism in cancer cells. The structure of human ribonucleotide reductase with its revelations regarding regulation by nucleotides are presented.

Chapter 27 Summing up metabolism and the metabolic roles of the various organs. AMP-kinase (AMPK) as the cell's energy charge sensor and the newly appreciated protection of AMPK by ADP are discussed. mTORC1 as the integrator of information about nutrient status and as the regulator of cellular synthesis is introduced. The regulation of eating behavior. The relationships between nutrient intake, AMPK, SIRT1 and protein acetylation and the consequences that these relationships have for caloric intake control and the development of metabolic syndrome. These interactions illuminate the underlying causes of the current obesity epidemic.

Chapter 28 DNA metabolism. The multiplicity of DNA polymerases. A new section to integrate DNA replication, recombination, and repair as interdependent aspects of DNA metabolism introduces this chapter. Another new feature is an illustration of how homologous recombination helps to prevent cancer. Genetic recombination, protein diversity, and immunology.

Chapter 29 Transcription; DNA-dependent RNA polymerases. Transcription regulation in bacteria and in eukaryotes. An update of eukaryotic translation initiation events in eukaryotes and the emerging science of miRNAs and lncRNAs as key regulators of post-transcriptional gene expression are presented, along with new structural and functional information about Mediator and its role as a bridge between enhancers of transcription and RNA polymerase II. The competing concepts of the histone code and histone crosstalk are discussed. The spliceosome.

Chapter 30 Protein synthesis. The genetic code. Aminoacyl-tRNA synthetases and the second genetic code. New features of the G-protein family members, Ef-Tu and EF-G, and their interactions with the ribosome, new structures for the ribosome RF-2 termination complex, and the more richly detailed appreciation of the events in eukaryotic translation initiation highlight this chapter. The ribosome as a ribozyme. Tethered ribosomes and new frontiers in synthetic biology.

Chapter 31 Completing the protein life cycle. Modes of post-transcriptional modification that control the functional protein pool, Protein folding and neurodegenerative protein folding diseases. A new Human Biochemistry box on chaperones that function by stress-induced protein unfolding. A Human Biochemistry highlight on autophagy, the process by which cells recycle their materials. Expanded coverage of Htr proteins.

Chapter 32 Cell signaling and neurotransmission. Intracellular responses to extracellular signals. Protein kinase cascades. Organization and integration of signaling pathways. Sensory systems. A Human Biochemistry feature on neurexins and neuroligins, which function as scaffolding proteins in the formation of synapses and the regulation of synaptic transmission, learning, and memory.

Supporting Materials

For the Instructor

Please visit http://www.cengage.com/chemistry/garrett/biochem6e for more information about instructor resources for this text.

For the Student

Please visit http://www.cengage.com/chemistry/garrett/biochem6e for more information about student resources for this text.

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Jazmine and Jatszi

Clancy

Jax and Jasper

"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

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