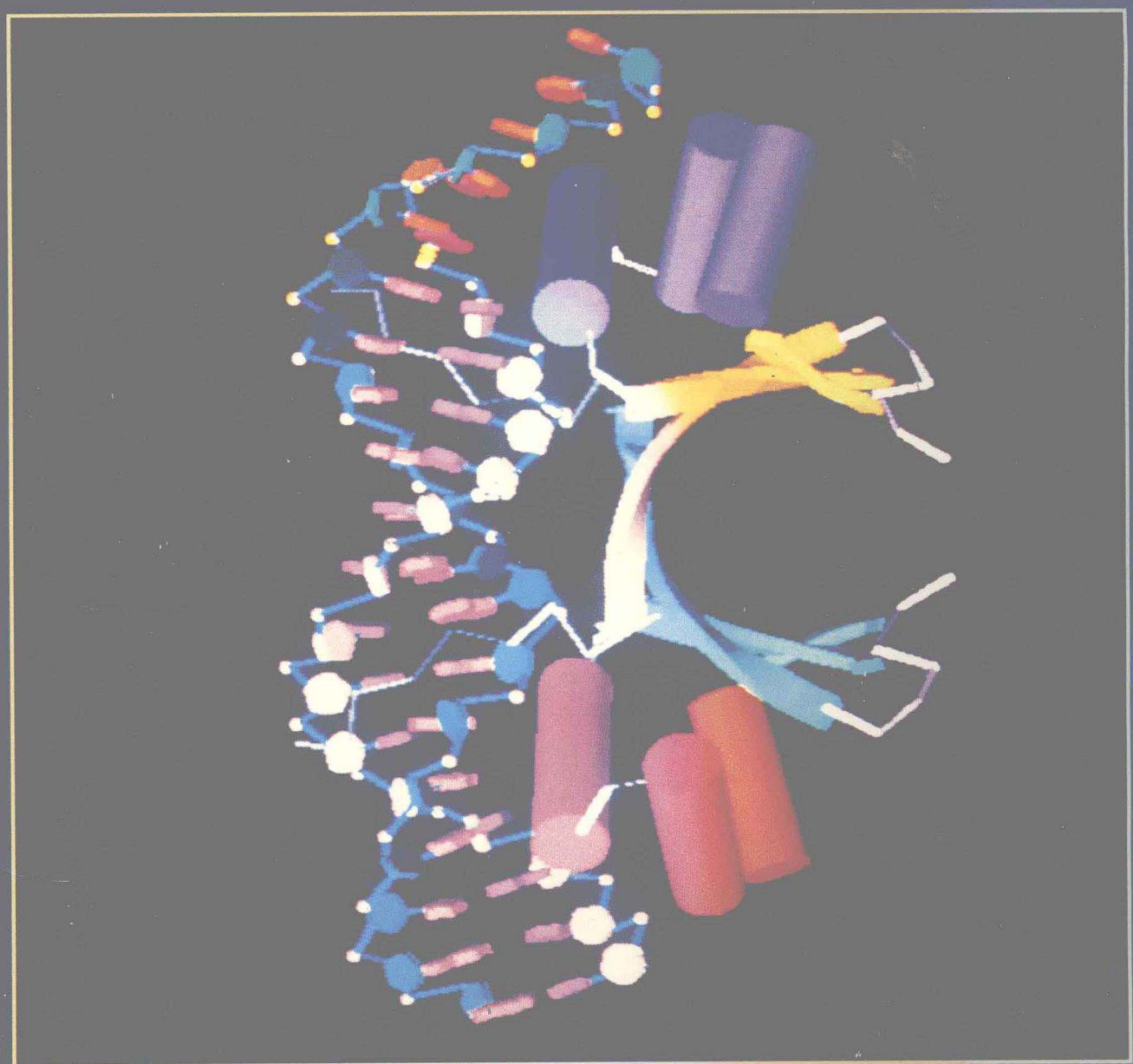
BIOCHEMISTRY

ZUBAY • THIRD EDITION

VOLUME THREE

GENETICS AND PHYSIOLOGY



BIOCHEMISTRY

THIRD EDITION

GEOFFREY ZUBAY

COLUMBIA UNIVERSITY

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This book is dedicated to Ed Jaffe, the late Editor-in-Chief of the William C. Brown Publishing Company.

Ed passed away suddenly just before this text went to press. I am deeply saddened by his passing and that he will not see the text he backed so strongly. He was a man of wisdom and integrity who maintained an excellent rapport with the WCB staff and with its authors.

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Guided Tour through the Biochemistry Learning System

A.

CHAPTER OUTLINES

Each chapter begins with an outline. These will allow students to tell at a glance how the chapter is organized and what major topics have been included in the chapter.

2
CHAPTER

Thermodynamics in Biochemistry

A.

The primary usefulness of thermodynamics to biochemists lies in predicting whether particular chemical reactions could occur spontaneously. A simple illustration is to predict what compounds could possibly serve as energy sources for an organism. You are aware from everyday experience that oxidation of organic molecules by molecular oxygen releases energy. For example, wood or coal burns with a large output of heat. Similarly, organisms can obtain energy by oxidizing carbohydrates, fats, or proteins. Some organisms oxidize hydrocarbons, some oxidize reduced forms of sulfur, and others oxidize iron. But no organisms live by oxidizing molecular nitrogen, and the explanation lies in thermodynamics. The reaction cannot occur spontaneously. This example illustrates the importance of thermodynamics in controlling all life. Because organisms live by extracting chemical energy from their surroundings, thermodynamics is not an esoteric subject. It is a matter of life or death.

We say that thermodynamics determines whether a process "could" occur, because thermodynamics tells us only whether the process is possible, not whether it actually will occur in a finite period of time. The rate at which a thermodynamically possible reaction occurs depends on the detailed mechanism of the process. For a biochemical process to occur rapidly, appropriate enzymes must be available. The distinction between spontaneity and speed is more critical for biochemists than it is for chemists, because if a chemical reaction does not proceed rapidly a chemist can change the pressure or temperature or increase the concentration of the reactants. A living organism is under more rigid constraints: It must function at a fixed temperature and pressure and within a limited range of concentrations of reactants.

In this chapter we will elaborate on the thermodynamic quantities that we introduced in chapter 1. We will then expand the discussion to show how the concept of free energy is used in predicting biochemical pathways, and we will explore the central role of ATP in providing energy for biochemical reactions.

Thermodynamic Quantities

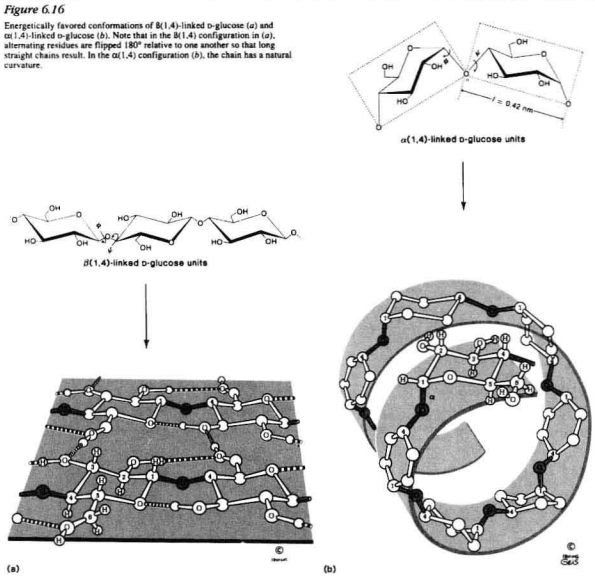
The properties of a substance can be classified as either intensive or extensive. Intensive properties, which include density, pressure, temperature, and concentration, do not depend on the amount of the material. Extensive properties, such as volume and weight, do depend on the amount. Most of the thermodynamic properties we will be discussing are extensive properties. These include energy (E), enthalpy (H), entropy (S), and free energy (G).

Energy, enthalpy, entropy, and free energy are all properties of the state of a substance. This means that they do not depend on how the substance was made or how it reached a particular state. In a chemical reaction, it is the difference between the initial and final states that is important; the pathway that is taken to get from the initial state to the final state has no bearing on whether the overall reaction releases or consumes energy (fig. 2.1).

B.

Figure 6.16

Energetically favored conformations of β(1,4)-linked D-glucose (*a*) and α(1,4)-linked D-glucose (*b*). Note that in the β(1,4) configuration in (*a*), alternating residues are flipped 180° relative to one another so that long straight chains result. In the α(1,4) configuration (*b*), the chain has a natural curvature.



to be discovered (1943) was the left-handed helix of amylose wound around molecules of iodine (fig. 6.17). This structure is responsible for the characteristic blue color of the amylose-iodine complex.

The extended-chain form of polyglucose has been exploited in nature for structural purposes, leaving by default the coiled form for use as an energy-storage macromolecule. Correlated with this functional difference is the omnipresence of degrading enzymes for glycogen and starch and the very limited phylogenetic distribution of comparable enzymes for cellulose. Cellulose is degraded in the gastrointestinal tract of herbivores, such as the cow, or in insects, such as termites, by a protozoan that synthesizes the enzyme cellulase. Humans do not possess this enzyme and hence cannot degrade cellulose.

148 Structure and Function of Major Components of the Cell

B.

DRAMATIC VISUALS PROGRAM

Colorful and informative photographs, illustrations, and tables enhance the learning program.

C.

3A BOX

Measurement of Ultraviolet Absorption in Solution

The general quantitative relationship that governs all absorption processes is called the Beer-Lambert law:

$$I = I_0\, 10^{-\epsilon c d}$$

where I_0 is the intensity of the incident radiation, I is the intensity of the radiation transmitted through a cell of thickness d (in centimeters) that contains a solution of concentration c (expressed either in moles per liter or in grams per 100 ml), and ϵ is the extinction coefficient, a characteristic of the substance being investigated (see fig. 3.7).

Light absorption is measured by a spectrophotometer as shown in the illustration. The spectrophotometer usually is capable of directly recording the absorbance A, which is related to I and I_0 by the equation

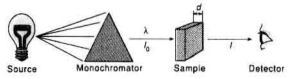
$$A = \log_{10}(I_0/I)$$

Hence $A = \epsilon cd$, and A is a direct measure of concentration. We can see from figure 3.7 that the ϵ values are largest for tryptophan and smallest for phenylalanine.

Since protein absorption maxima in the near ultraviolet (240–300 nm) are determined by the content of the aromatic amino acids and their respective values, most proteins have absorption maxima in the 280-nm region. By contrast, absorption in the far-ultraviolet (around 190 nm) is shown by all polypeptides regardless of their aromatic amino acid content. The reason is that absorption in this region is due primarily to the peptide linkage.

Figure 1

Schematic diagram of a spectrophotometer for measuring light absorption. Laboratory instruments for making measurements are much more complex than this, but they all contain the same basic components: a light source, a monochromator, a sample, and a detector. λ is the wavelength of the light, I_0 and I are the incident light intensity and the transmitted light intensity, respectively, and d is the thickness of the absorbing solution.



Another convention for referring to configurations is called the *R, S* convention. As the *R, S* convention is not as popular for amino acids or sugars as it is for other types of biomolecules, such as lipids, we will not discuss this notation until chapter 11 (see box 11A).

Peptides and Polypeptides

D.

Amino acids can link together by a covalent peptide bond between the α-carboxyl end of one amino acid and the α-amino end of another. Formally, this bond is formed by the loss of a water molecule, as shown in figure 3.9. The peptide bond has partial double-bond character owing to resonance effects; as a result, the C — N peptide linkage and all of the atoms directly connected to C and N lie in a planar configuration called the amide plane. In the following chapter we will see that this amide plane, by limiting the number of orientations available to the polypeptide chain, plays a major role in determining the three-dimensional structures of proteins.

Any number of amino acids can be joined by successive peptide linkages, forming a polypeptide chain. The polypeptide chain, like the dipeptide, has a directional sense. One end, called the N-terminal or amino-terminal end, has a free α-amino group, whereas the other end, the C-terminal or carboxyl-terminal end, has a free α-carboxyl group. The sequence of main-chain atoms from the N-terminal end to the C-terminal end is C_α—C—N—C_α, etc., and in the opposite direction it is C_α—N—C—C_α, etc. Short polypeptide chains, up to a length of about 20 amino acids, are called peptides or oligopeptides if they are fragments of whole polypeptide chains. A small protein molecule may contain a polypeptide chain of only 50 amino acids; a large protein may contain chains of 3,000 amino acids or more. One of the larger single polypeptide chains is that of the muscle protein myosin, which consists of approximately 1,750 amino acid residues. Figure 3.10 shows a section of a polypeptide chain as a linear array with α carbons and planar amides alternating as repeating units of the main chain. Different side chains are attached to each α carbon.

In addition to the covalent peptide bonds formed between adjacent amino acids within a polypeptide chain, covalent disulfide bonds can be formed within the same polypeptide chain or between different polypeptide chains (fig. 3.11). Such disulfide linkages have an important stabilizing influence on the structures formed by many proteins (see chapter 4).

C.

SUPPLEMENTARY BOX MATERIAL

Throughout the text, supplemental information on experimental procedures, mechanisms, and methods of evaluation are presented in boxes

D.

UNDERLINED KEY CONCEPTS

Important terms and concepts are highlighted by underlining.

E.

END-OF-CHAPTER SUMMARIES

Each summary offers a concise review of the material covered in the chapter. Students can use the summary to review the chapter or to preview the important topics.

F.

SELECTED READINGS

Each chapter concludes with carefully selected references that contain further information on the topics covered in that chapter.

G.

END-OF-CHAPTER PROBLEMS

These problems will challenge students' mastery of the chapter's basic concepts. Odd-numbered problems are answered briefly in the back of the text.

E.

Summary

In this chapter we have dealt with some of the fundamental properties of amino acids and polypeptide chains. The following points are especially important:

1. Nineteen of the twenty amino acids commonly found in proteins have a carboxyl group and an amino group attached to an α-carbon atom; they differ in the side chain attached to the same α carbon.
2. All amino acids have acidic and basic properties. The ratio of base to acid form at any given pH can be calculated from the pK with the help of the Henderson-Hasselbach equation.
3. All amino acids except glycine are asymmetric and therefore can exist in at least two different stereoisomeric forms.
4. Peptides are formed from amino acids by the reaction of the α-amino group from one amino acid with the α-carboxyl group of another amino acid.
5. Polypeptide formation involves a repetition of the process involved in peptide synthesis.
6. The amino acid composition of proteins can be discovered by first breaking down the protein into its component amino acids and then separating the amino acids in the mixture for quantitative estimation.
7. The amino acid sequences of proteins can be discovered by breaking down the protein into polypeptide chains and then partially degrading the polypeptide chains. For each polypeptide chain fragment, the sequence is determined by stepwise removal of amino acids from the amino terminal end of the polypeptide chain. Two different methods of forming polypeptide chain fragments are used so as to produce a map of overlapping fragments, from which the sequence of undegraded polypeptide chains in the proteins can be deduced.
8. Polypeptide chains with a predetermined amino acid sequence can be synthesized by chemical methods involving carboxyl-group activation.

F.

Selected Readings

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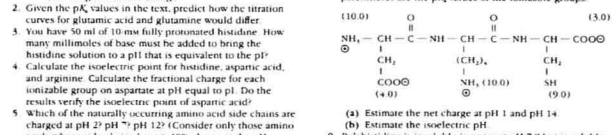
G.

Problems

1. (a) A 10-mM solution of a weak monocarboxylic acid has a pH of 3.00. Calculate K_a and pK_a for this carboxylic acid.
   (b) You add 0.06 g NaOH (M_r = 40) to 1,000 ml of the acid solution in part (a). Calculate the final pH, assuming no volume change.
2. Given the pK_a values in the text, predict how the titration curves for glutamic acid and glutamine would differ.
3. You have 50 ml of 10-mM fully protonated histidine. How many millimoles of base must be added to bring the histidine solution to a pH that is equivalent to the pI?
4. Calculate the isoelectric point for histidine, aspartic acid, and arginine. Calculate the fractional charge for each ionizable group on aspartate at pH equal to pI. Do the results verify the isoelectric point of aspartic acid?
5. Which of the naturally occurring amino acid side chains are charged at pH 2? pH 7? pH 12? (Consider only those amino acids whose side chains have >10% charge at the pH indicated.)
6. Amino acids are sometimes used as buffers. Indicate the appropriate pH value(s) of a buffer containing aspartic acid, histidine, and serine.
7. Ten ml of a 10-mM solution of lysine was adjusted to pH 11.20. Draw the structures of the principal ionized forms present in solution. Use the pK_a values shown in table 3.3 and calculate the concentration of each principal form.
8. For the tripeptide shown below, the numbers in parentheses are the pK_a values of the ionizable groups.



   (a) Estimate the net charge at pH 1 and pH 14.
   (b) Estimate the isoelectric pH.
9. Polyhistidine is insoluble in water at pH 7.8 but is soluble at pH 5.5. Explain the observation. Would you expect the polymer to be soluble at pH 10?

Preface

What makes biochemistry exciting? What makes biochemistry unique? What makes biochemistry so important? The answer to all three of these questions is virtually the same. Each and every reaction in biochemistry serves a function; that function is the maintenance and propagation of the living system. To understand biochemistry is to appreciate the place that each reaction occupies in the system.

Students of the previous generation discovered the principles that govern biochemistry, the basic reactions, and an immense body of facts consistent with these principles. Future biochemists to emerge from this generation of students will uncover the mysteries of developmental biology and physiology. They will find cures for cancers, cystic fibrosis, sickle cell anemia and many other diseases. My goal in putting this text together has been to convey my enthusiasm for this subject to this generation of students, to acquaint them with what is known and to prepare them for the discoveries of the future.

While the main principles of biochemistry are understood, the number of new facts that keep adding to the subject is immense. The field is becoming more and more subdivided as the volume of knowledge increases. No single person could directly cope with all the new information that is continuously appearing in the scientific literature. For the purpose of writing an authoritative up-to-date textbook on biochemistry, it would be ideal to involve a team of experts with hands-on experience. The contributing authors of this text are all research specialists who have made their mark in a specific area of biochemistry; they are teachers as well. Each contributing author could write an entire book on the chapter he/she has contributed to in this text. Recognizing that the primary goal of this text is to meet the needs of students facing the subject for the first time, each contributing author has had to pare down what he/she knows emphasizing principles, but not ignoring important facts. Each chapter has been carefully crafted with that goal in mind. My responsibility as coordinating author of this text has been to mold the contributions into a smooth reading, well integrated product.

This is the third edition of *Biochemistry*. Whereas I have had the same goal throughout this project, it is only with this edition, that the long-hoped-for product has finally emerged from our team approach. Reviewers tell us that this edition is not only consistently authoritative, it now reads like a cohesive, consistent single author textbook.

Each chapter emphasizes principles. Since the overriding principle is that every reaction serves a function, there is a strong emphasis on analysis of biochemical pathways and how different pathways are interrelated. In this pursuit balanced emphasis is given to chemistry and mechanisms, bioenergetics, metabolic regulation, and methods of biochemical analysis.

We have organized this text along conventional lines for teaching purposes. In Part 1 an overview is followed by an explanation of the importance of thermodynamics in biochemistry. In Part 2 we consider the structure and function of the major components of the cell. In Part 3 we discuss enzymes and coenzymes and the mechanisms of catalysis. Part 4 deals with energy producing catabolic processes, and Part 5 deals with energy consuming synthetic processes. In Part 6 we focus on nucleic acids and the way in which the biochemical information encoded in the chromosome is translated into the amino acid sequences found in proteins. Finally, in Part 7 we approach some of the applications of biochemistry to physiology.

Organizational Changes

The overall organization of the previous edition has been changed significantly:

- The chapter on methods for characterization and purification of proteins (formerly chapter 3) has been eliminated. Much of the material from this chapter has

been disseminated into other chapters, appearing at the points where it is most relevant. The same goes for the discussion of methods in general, and there is a special appendix indicating where specific methods are discussed.

- The chapter on nucleic acid structure (formerly chapter 7) has been moved to a later part of the text (chapter 25). This has been done because nucleic acids are not discussed in any depth until Part 6. The general significance of nucleic acids is adequately discussed in chapter 1 so this should create no problem for the rare student who has not encountered this subject already.
- The chapter on origin of life has been eliminated. A few points about this subject are now made in chapters 1 and 28. This is a delightful subject and very close to my major research interests. However, it simply is not mainstream biochemistry and space would not allow us to keep this chapter.
- After many years of agonizing appraisal I have decided to place thermodynamics as the second chapter. Bioenergetics is so central to everything in biochemistry that I thought it should be discussed as soon as possible. At the same time an esoteric chapter on this subject could easily turn off many students. To avoid this we have considerably simplified this chapter to make it as palatable as possible without losing any of the significance of a more esoteric chapter.
- A new chapter on functional diversity of proteins (chapter 5) has been added. This gives us an opportunity to dwell on the very important subject of the relationship between protein structure and function. In addition we have used this chapter as a location to discuss the subject of protein purification.
- The chapters on lipids and membrane structures have been combined into one chapter. Students are more attentive to a description of lipids if they can see the important role they play in membrane structure.
- The chapters on lipid catabolism and synthesis have been combined in this edition (chapter 17). This makes it easier to discuss regulation of lipid metabolism.
- At the end of the treatment of intermediary metabolism (chapter 24) we have added a chapter on the integration of metabolism. In this chapter we have included most of the coverage of hormone action that was presented much later in the second edition. It is more relevant here as hormones are the key to the integration of metabolism in multicellular organisms.
- Two short chapters have been added to Part 7; chapter 33, on immunobiology, and chapter 34 on carcinogenesis. These are two hot topics that are of great interest to students. The chapters are kept short and simple for those who would choose to use them in a two term course. It would be best to consider them after the core chapters of Part 6 (i.e., chapters 25, 26, 28 and 29).

Content Features of This Edition

The coverage of biochemistry in this text is determined by the consensus feedback that we have received as well as the limitations of the present state of our knowledge. Coverage of the biochemistry of bacteria and mammals is emphasized over plant biochemistry.

Part 1 is entitled "An Overview of Biochemistry and Energy Considerations." The first chapter "Overview of Biochemistry," is very similar to the introductory chapter in the second edition. It presents the basic principles in chemistry and biology that relate to biochemistry. The second chapter, "Thermodynamics in Biochemistry," has been considerably rewritten and simplified over the corresponding chapter in the second edition, which had appeared as chapter 12. Chapter 2 elaborates on the thermodynamic quantities introduced in chapter 1, to show how the concept of free energy is used to predict the possibility that given reactions can occur. It also describes the central role of ATP in providing energy for biochemical reactions.

Part 2, "Structure and Function of Major Components of the Cell," contains five chapters describing the structure and function of proteins, carbohydrates, and lipids. The contents of Part 2 are similar to the contents of Part 1 in the previous edition, except that the discussion of nucleic acids has been moved to Part 6, and a new chapter 5, "Functional Diversity of Proteins," has been introduced.

Chapters 3, 4, and 5 present the basic structural and chemical properties of proteins. Chapter 3, "The Building Blocks of Proteins: Amino Acids, Peptides, and Polypeptides," is very similar to the comparable chapter in the second edition. Chapter 4, "The Three-Dimensional Structure of Proteins," describes the secondary, tertiary, and quaternary structures of proteins, the rules for which govern the folding of polypeptide chains and the ways in which these structures are determined. In this edition there is more coverage of the relationship between symmetry and quaternary structures than in the second edition. Chapter 5, "Functional Diversity of Proteins," focuses on the question of how protein structure relates to function and describes techniques used to isolate proteins.

Chapter 6, "Carbohydrates, Glycoproteins, and Cell Walls," describes the structural properties of sugars, oligosaccharides, and polysaccharides, along with the various roles that these compounds play as energy-storage molecules, components of glycoproteins, and in cell walls. This chapter's segment on glycoproteins has been considerably updated. Finally, in chapter 7, "Lipids and Membranes," two chapters from the second edition have been fused into one cohesive chapter. In it, the structural properties of lipids are discussed with reference to the roles lipids play as energy-storage molecules and in membrane structures.

Part 3, "Catalysis," is divided into four chapters, the first three of which have been completely rewritten, while the last has been simplified considerably, with discussions of lipid-soluble vitamins and the role of metals as cofactors added.

Chapter 8, "Enzyme Kinetics," features a description of kinetic methods for analyzing enzyme-catalyzed reactions. Chapter 9, "Mechanisms of Enzyme Catalysis," focuses on the way in which the structure of the enzyme active site is related to enzyme activity under different conditions. In this chapter a general discussion of factors determining enzyme specificity is followed by several detailed examples. Chapter 10, "Regulation of Enzyme Activities," describes enzymes regulated by structural modifications or the binding of specific factors at allosteric sites, and chapter 11, "Vitamins, Coenzymes, and Metal Cofactors," covers the function of small molecules acting in conjunction with enzymes as cocatalysts.

Part 4 "Catabolism and the Generation of Chemical Energy," is divided into six chapters. Since both Parts 4 and 5 are concerned with intermediary metabolism, it's not easy, or even appropriate, to separate the subject into artificially tidy discussions of catabolism and anabolism. Suffice it to say that the emphasis in Part 4 is on catabolism and the generation of chemical energy, while in Part 5 the emphasis is on biosynthesis. Chapter 12, "Metabolic Strategies," which initiates Part 4, relates strongly to both Parts 4 and 5, as does chapter 24, "Integration of Metabolism and Hormone Action," which concludes Part 5.

Chapter 12, "Metabolic Strategies," deals with the general ways in which metabolism is organized and the ways in which it is regulated. Chapters 13, 14, and 15 are devoted to carbohydrate metabolism in relationship to the generation of ATP. Chapter 13, "Glycolysis, Gluconeogenesis, and the Pentose Phosphate Pathway," describes anabolic as well as catabolic processes—namely, the synthesis of simple sugars and simple sugar polymers, as well as their breakdown. Both synthesis and breakdown are covered in the same chapter in order to facilitate meaningful discussion of the regulation of these two processes, which are intimately related.

Chapter 14, "The Tricarboxylic Acid Cycle," describes the further catabolism of sugars possible under aerobic conditions. Chapter 15, "Electron Transport and Oxidative Phosphorylation," complements chapter 14 because it shows how electrons released by the aerobic oxidation of sugars are channeled down the electron-transport system, ultimately to synthesize ATP. Chapter 16, "Photosynthesis and Other Processes Involving Light," appears immediately after the chapter on electron transport and the production of ATP because both chapters describe energy-generating metabolism. The complex light-powered processes are explained so that a minimal background in physics and chemistry is needed.

Part 4 concludes with Chapter 17, "Metabolism of Fatty Acids," which represents a fusion of two chapters from the second edition. The reasons for discussing both synthesis and breakdown of lipids in the same chapter are exactly the same as the reasons for doing this with sugars (as in chapter 13).

In many schools a one-semester treatment of biochemistry would end with chapter 17. Even though the first half of the text is tightly structured, instructors may still wish to seek additional material or skip around. Two recommendations involve chapter 25 and chapter 32. Chapter 25, "Structures of Nucleic Acids and Nucleoproteins," could be treated as a chapter in Part 2. If this is done, instructors should make sure students read the opening pages of chapter 20, which deal with the structure of nucleotides. Likewise, some instructors may wish to assign readings from chapter 32, which deals with mechanisms of membrane transport, after they have assigned chapter 7 on lipids and membranes.

Part 5, "Biosynthesis of the Building Blocks," contains seven chapters, mainly describing the biosynthesis and utilization of amino acids, nucleotides, complex carbohydrates, and lipids. Although there is a great deal of useful information in these chapters, most of Part 5, except for chapter 24, can be skipped if there is a strong desire to get to Part 6 as quickly as possible.

Chapter 18, "Biosynthesis of Amino Acids," describes the biosynthesis of amino acids. Because twenty amino acids found in proteins are made in bacteria and plants (whereas only a few amino acids are synthesized *de novo* in mammals), and because these pathways are better understood in bacteria, most of this chapter focuses on biosynthesis in bacteria. Nonprotein amino acids are discussed briefly. Finally, the problem of nitrogen fixation in biological systems is examined.

Chapter 19 is entitled "The Metabolic Fate of Amino Acids." It discusses the way in which amino acids, when in excess or when present as the only available carbon or energy source, are reduced to carbohydrates, which can serve as a source of energy or carbon skeletons for the synthesis of other molecules. A few products derived from amino acid metabolism are also discussed in detail, including porphyrins, biological active amines, glutathione, and peptide antibiotics.

Chapter 20, "Nucleotides," deals with the structures, synthesis, and breakdown of nucleotides, with considerable attention devoted to the role of nucleotide derivatives as inhibitors of nucleic acid synthesis and the important role they play in the medical field. The biosynthesis of nucleotide-containing coenzymes is also discussed in this chapter.

Chapter 21, "Biosynthesis of Complex Carbohydrates," describes the synthesis of complex carbohydrates that serve structural roles and the synthesis of oligosaccharides that exist in combination with proteins. A great deal of new information on this subject appears in this chapter, as does a detailed discussion of bacterial cell-wall synthesis.

Chapter 22, "Biosynthesis of Membrane Lipids and Related Substances," describes the metabolism of complex lipids. Phospholipids and sphingolipids are viewed in terms of their important structural roles in membranes, while eicosanoids are described in terms of functioning local hormones.

Chapter 23, "Metabolism of Cholesterol," describes the biosynthesis of cholesterol and some of its derivatives—bile acids and steroids. The chapter devotes considerable attention to the transport of these compounds, along with the problems associated with defects in cholesterol metabolism.

Chapter 24, "Integration of Metabolism and Hormone Action," concludes the two parts on intermediary metabolism. This chapter emphasizes the way in which intermediary metabolism is regulated in multicellular organisms.

Part 6, "Storage and Utilization of Genetic Information," features seven chapters describing the metabolism of nucleic acids and proteins. The entire section has been updated to keep pace with this rapidly changing area. Where useful, key genetic phenomena have also been explained.

This part begins with chapter 25, "Structures of Nucleic Acids and Nucleoproteins," which describes structures and functions of DNA and deoxyribonucleoproteins. It has intentionally been placed after structures of nucleotides have been discussed (in chapter 20) and before the structures of RNA and ribonucleoproteins are discussed (in chapter 28).

In chapter 26, "DNA Replication, Repair, and Recombination," the emphasis is on the metabolism of replication. The treatment is equally balanced between replication in prokaryotes and eukaryotes including animal viruses.

Chapter 27, "DNA Manipulation and Its Applications," begins with a discussion of the procedures for determining DNA sequence, proceeds with a discussion of the techniques for manipulating DNA sequences, and concludes by describing two important applications of DNA manipulation—the mapping of the globin gene family and the mapping of a gene responsible for the dreaded disease cystic fibrosis.

Chapter 28, "RNA Synthesis and Processing," which describes RNA synthesis and processing equally, presents a considerable amount of new information on transcription factors in animals cells and a variety of ways in which RNA is processed.

Chapter 29, "Protein Synthesis, Targeting, and Turnover," has been significantly expanded over the corresponding chapter in the second edition, particularly in the area of targeting, where many new discoveries have been made recently.

Chapter 30, "Regulation of Gene Expression in Prokaryotes," includes a discussion of several well-characterized gene systems found in *E coli.* It also features a treatment of the sequence of regulatory events involving bacteriophage λ infection and lysogeny.

Chapter 31, "Regulation of Gene Expression in Eukaryotes," begins by discussing several different gene systems in the intensively studied unicellular eukaryote *Saccharomyces cerevisiae.* Then it shifts to multicellular eukaryotes, focusing on the complex assemblages of protein factors involved in regulating various genes. Both this chapter and the previous one cover in considerable detail the structures of proteins that regulate gene expression and the ways in which they interact with DNA. The chapter concludes with a special section on the ways in which gene expression is regulated during early development.

Part 7, "Physiological Biochemistry," contains five chapters: "Mechanisms of Membrane Transport" (chapter 32), "Immunobiology" (chapter 33), "Carcinogenesis and Oncogenes" (chapter 34), "Neurotransmission" (chapter 35), and "Vision" (chapter 36). Except for the first one, all of these chapters are intentionally short, so that it will be convenient to assign them at different points in the course, depending on the taste of the instructor. The titles of the chapters are self-explanatory.

Learning Aids

We have included a number of in-text learning aids to help both the professor and the student navigate their way through the text.

The goal of this edition is to stress, not merely the facts, but especially the principles of biochemistry. In as many cases as is practical, explanations are given for how certain facts have been revealed by scientific investigations. Biochemists are sleuths always devising new methods to discover Nature's secrets. We felt it best to integrate discussion of the methods of biochemistry directly in the text at points where the methods are actually employed in biochemical investigations. To aid in location of a particular method description, we have placed a section entitled *A Student's Guide to Methods of Biochemical Analysis* in the appendices.

Great care has been taken to make explanations clear and to inject the maximum significance into topical headings. *Key terms* are always explained the first time they are introduced and *Key concepts* are underlined . Nevertheless, it is easy to forget the meaning of a particular term on occasion. To overcome this frustration we have included a *glossary* just before the index and a list of *common biochemical abbreviations,* we have placed a list just inside the back book cover.

As an additional learning aid, a *brief introduction* to each of the book's seven parts is included. Furthermore, each chapter begins with an *outline of contents* and an *introduction.*

All chapters have *summaries* at the end, and the longer chapters have periodic summaries within them. For those who would like to know more about any specific topic, *extensive references* are included at the end of each chapter.

The *exercise problems* at the end of the chapters are intended to reinforce what has been learned by the reading. *Brief answers* to selected problems are given at the end of the book, and instructors can obtain a *Solutions Manual* that provides complete solutions to all of the problems in the text (see the following section on ancillary materials).

Ancillary Material

In choosing the order of our presentation, we have been strongly influenced by extensive feedback from instructors of biochemistry. As always, however, some instructors would have preferred a different ordering of the subject matter. For their benefit we have suggested alternative possibilities for using the text in an accompanying instructor's manual. This manual also includes additional problems and solutions not offered in the text.

As an aid to course presentations, a set of 100 overhead color transparencies and 200 black-and-white transparency masters is available upon adoption of the text. Also available upon request to professors is a solutions manual, including worked-out solutions to all of the end-of-chapter problems. This manual is available for sale to students, but only at the instructor's request.

Acknowledgments

This preface is full of "I"s. That's because I, the coordinating author, wrote it. By contrast, the text itself is the brainchild of some twenty biochemists, of which I was only one. Nevertheless, because the manuscripts submitted by the contributing authors were modified by me, I must take the blame for any errors. If you should find errors, please notify me so that I can make corrections in the second printing. I would be most grateful for your input.

I would like to make a special note that Chapters 12, 13, and 14 were written by me based on Dr. Daniel Atkinson's material from the second edition of *Biochemistry*. So again, any errors should be considered my responsibility.

My fellow authors and I consulted many experts during the writing of each specific chapter, largely on an informal, "over the phone" basis. Although the list of their names is too long to include here, we are indebted to all of them. In addition, we had the benefit of formal reviews of chapters and whole sections of the text. I am deeply grateful to each of the reviewers, whose aid we will certainly wish to solicit for future editions. The reviewers included:

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Last but not least I once again had the opportunity to benefit from the superb copy editing of Emily Arulpragasam, who smoothed out bumps in the prose and helped me spot errors before they could be set in type. Her understanding of the subject was a major asset in making changes in the text that were always scientifically accurate.

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