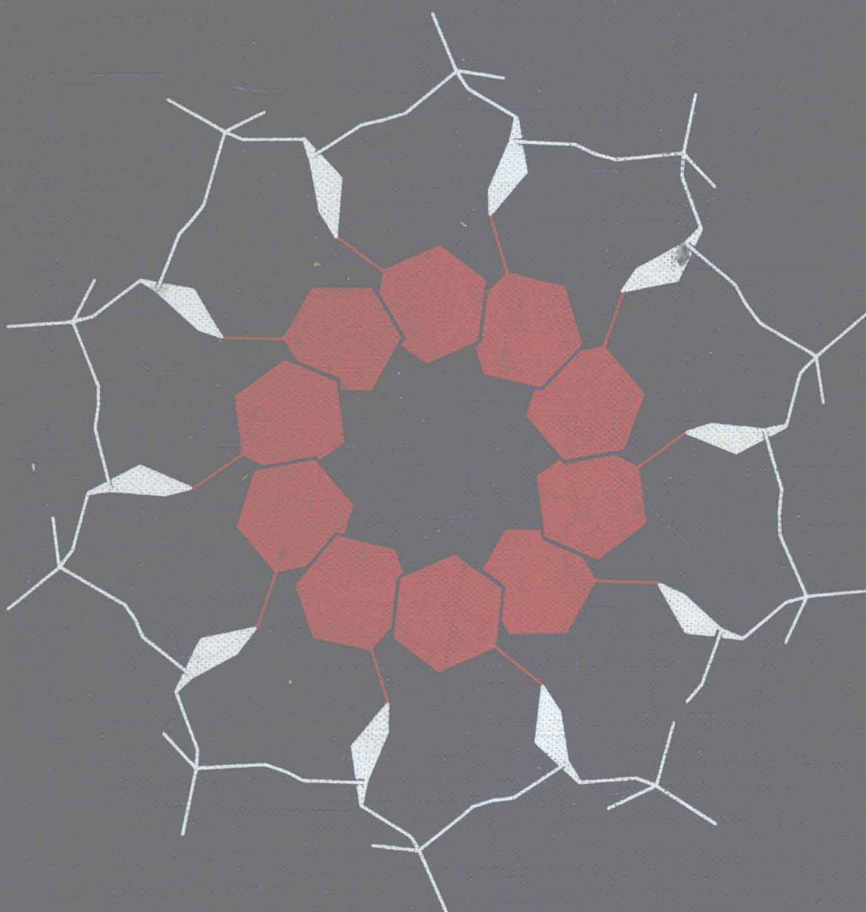
BIOCHEMISTRY

Lubert Stryer



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BIOCHEMISTRY

To my teachers

Paul F. Brandwein
Daniel L. Harris
Douglas E. Smith
Elkan R. Blout
Edward M. Purcell

PREFACE

This book is an outgrowth of my teaching of biochemistry to undergraduates, graduate students, and medical students at Yale and Stanford. My aim is to provide an introduction to the principles of biochemistry that gives the reader a command of its concepts and language. I also seek to give an appreciation of the process of discovery in biochemistry. My exposition of the principles of biochemistry is organized around several major themes:

1. Conformation—exemplified by the relationship between the three-dimensional structure of proteins and their biological activity
2. Generation and storage of metabolic energy
3. Biosynthesis of macromolecular precursors
4. Information—storage, transmission, and expression of genetic information
5. Molecular physiology—interaction of information, conformation, and metabolism in physiological processes

The elucidation of the three-dimensional structure of proteins, nucleic acids, and other biomolecules has contributed much in recent years to our understanding of the molecular basis of life. I have emphasized this aspect of biochemistry by making extensive use of molecular models to give a vivid picture of architecture and dynamics at the molecular level. Another stimulating and heartening aspect of contemporary biochemistry is its increasing interaction with medicine. I have presented many examples of this interplay. Discussions of molecular diseases such as sickle-cell anemia and of the mechanism of action of drugs such as penicillin enrich the teaching of biochemistry. Finally, I have tried to define several challenging areas of inquiry in biochemistry today, such as the molecular basis of excitability.

In writing this book, I have benefitted greatly from the advice, criticism, and encouragement of many colleagues and students. Leroy Hood, Arthur Kornberg, Jeffrey Sklar, and William Wood gave me invaluable counsel on its overall structure. Richard Caprioli, David Cole, Alexander Glazer, Robert Lehman, and Peter Lengyel read much of the manuscript and made many very helpful suggestions. I am indebted to Frederic Richards for sharing his thoughts on macromolecular conformation and for extensive advice on how to depict three-dimensional structures. Deric Bownds, Thomas Broker, Jack Griffith, Hugh Huxley, and George Palade made available to me many striking electron micrographs. I am also very thankful for the advice and criticism that were given at various times in the preparation of this book by Richard Dickerson, David Eisenberg, Moises Eisenberg, Joseph Fruton, Michel Goldberg, James Grisolia, Richard Henderson, Harvey Himel, David Hogness, Dale Kaiser, Samuel Latt, Susan Lowey, Vincent Marchesi, Peter Moore, Allan Oseroff, Jordan Pober, Russell Ross, Edward Reich, Mark Smith, James Spudich, Joan Steitz, Thomas Steitz, and Alan Waggoner.

I am grateful to the Commonwealth Fund for a grant that enabled me to initiate the writing of this book. The interest and support of Robert Glaser, Terrance Keenan, and Quigg Newton came at a critical time. One of my aims in writing this book has been to achieve a close integration of word and picture and to illustrate chemical transformations and three-dimensional structures vividly. I am especially grateful to Donna Salmon, John Foster, and Jean Foster for their work on the drawings, diagrams, and graphs. Many individuals at Yale helped to bring this project to fruition. I particularly wish to thank Margaret Banton and Sharen Westin for typing the manuscript and Martha Scarf for generating the computer drawings of molecular structures on which many of

the illustrations in this book are based. John Harrison and his staff at the Kline Science Library helped in many ways.

Much of this book was written in Aspen. I wish to thank the Aspen Center for Physics and the Given Institute of Pathobiology for their kind hospitality during several summers. I have warm memories of many stimulating discussions about biochemistry and molecular aspects of medicine that took place in the lovely garden of the Given Institute and while hiking in the surrounding wilderness areas. The concerts in Aspen were another source of delight, especially after an intensive day of writing.

I am deeply grateful to my wife, Andrea, and to my children, Michael and Daniel, for their encouragement, patience, and good spirit during the writing of this book. They have truly shared in its gestation, which was much longer than expected. Andrea offered advice on style and design and also called my attention to the remark of the thirteenth-century Chinese scholar Tai T'ung (*The Six Scripts: Principles of Chinese Writing*): "Were I to await perfection, my book would never be finished."

I welcome comments and criticisms from readers.

October 1974 *Lubert Stryer*

BIOCHEMISTRY

CONTENTS

CHAPTER 1. Molecules and Life 1

Part I CONFORMATION: exemplified by the relationship between the three-dimensional structure of proteins and their biological activity 9

CHAPTER 2. Introduction to Protein Structure and Function 11
3. Oxygen Transporters: Myoglobin and Hemoglobin 46
4. Hemoglobin: An Allosteric Protein 71
5. Molecular Disease: Sickle-Cell Anemia 95
6. Introduction to Enzymes 115
7. Mechanisms of Enzyme Action: Lysozyme and Carboxypeptidase 153
8. Zymogen Activation: Digestive Enzymes and Clotting Factors 178
9. Connective-Tissue Proteins: Collagen and Elastin 206
10. Introduction to Biological Membranes 227

Part II GENERATION AND STORAGE OF METABOLIC ENERGY 255

CHAPTER 11. Metabolism: Basic Concepts and Design 257
12. Glycolysis 277
13. Citric Acid Cycle 307
14. Oxidative Phosphorylation 331
15. Pentose Phosphate Pathway and Gluconeogenesis 356
16. Glycogen and Disaccharide Metabolism 378
17. Fatty Acid Metabolism 404
18. Amino Acid Degradation and the Urea Cycle 432
19. Photosynthesis 456

Part III BIOSYNTHESIS OF MACROMOLECULAR PRECURSORS 477

CHAPTER 20. Biosynthesis of Membrane Lipids and Steroid Hormones 479
21. Biosynthesis of Amino Acids and Heme 503
22. Biosynthesis of Nucleotides 528

Part IV INFORMATION: storage, transmission, and expression of genetic information 555

CHAPTER 23. DNA: Genetic Role, Structure, and Replication 557
24. Messenger RNA and Transcription 594
25. The Genetic Code and Gene-Protein Relationships 623
26. Protein Synthesis 645
27. Control of Gene Expression 679
28. Eucaryotic Chromosomes 693
29. Viruses 708

Part V MOLECULAR PHYSIOLOGY: interaction of information, conformation, and metabolism in physiological processes 729

CHAPTER 30. Immunoglobulins 731
31. Bacterial Cell Walls 754
32. Membrane Transport 767
33. Excitable Membranes 787
34. Hormone Action 807
35. Muscle Contraction and Cell Motility 826

Appendixes 843
Answers to Problems 847
Index 855

CHAPTER 1

MOLECULES AND LIFE

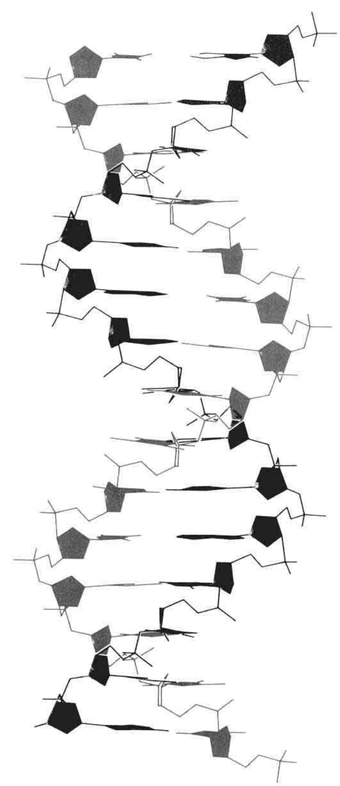

Figure 1-1
A model of the DNA double helix. The diameter of the helix is about 20 Å.

Biochemistry is the study of the molecular basis of life. There is much excitement and activity in biochemistry today for several reasons. *First, the chemical basis of some central processes in biology are now understood.* The discovery of the double-helical structure of DNA, the elucidation of the genetic code, the determination of the three-dimensional structure of some protein molecules, and the unraveling of the central metabolic pathways are some of the outstanding achievements of biochemistry. *Second, there are common molecular patterns and principles that underlie the diverse expressions of life.* Organisms as different as the bacterium *Escherichia coli* and man have many common features at the molecular level. They use the same building blocks to construct macromolecules. The flow of genetic information from DNA to RNA to protein is essentially the same in both species. Both use ATP as the currency of energy. *Third, biochemistry is making an increasing impact on medicine.* For example, assays for enzyme activity now play an important role in clinical diagnosis. The level of certain enzymes in the serum is a valuable criterion of whether a patient has recently had a myocardial infarction. Furthermore, biochemistry is beginning to provide a basis for the rational design of drugs. Most significant, the molecular mechanisms of diseases are being elucidated, as exemplified by sickle-cell anemia and the large number of inborn errors of metabolism that have been characterized. *Fourth, the rapid development of biochemistry in recent years has enabled investigators to tackle some of the most challenging and fundamental problems in biology and medicine.* How does a single cell give rise to cells as different as those in muscle, the brain, and the liver? How do cells find each other in forming a complex organ? How is the growth of cells controlled? What is the mechanism of memory? How does light elicit a nerve impulse in the retina? What are the causes of cancer? What are the causes of schizophrenia?

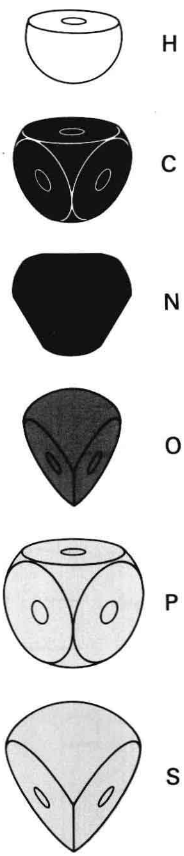

Figure 1-2
Space-filling models of hydrogen, carbon, nitrogen, oxygen, sulfur, and phosphorus atoms.

MOLECULAR MODELS

The interplay between the three-dimensional structure of biomolecules and their biological function is the unifying motif of this book. We will use three types of atomic models to depict molecular architecture: space-filling, ball-and-stick, and skeletal. The *space-filling* models are the most realistic. The size and configuration of an atom in a space-filling model are determined by its bonding properties and van der Waals radius (Figure 1-2). The colors of the atoms are set by convention.

Hydrogen: white	Oxygen: red
Carbon: black	Sulfur: yellow
Nitrogen: blue	Phosphorus: yellow

Space-filling models of several simple molecules are shown in Figure 1-3.

Ball-and-stick models will be used frequently. They are not as realistic as space-filling models because the atoms are depicted as spheres of smaller radius than the van der Waals radius. However, the bonding arrangement is easier to see than in space-filling models because the bonds are explicitly represented by sticks. The taper of a stick tells whether the bond is directed in front of or behind the plane of the page. More of a complex structure can be seen in ball-and-stick models than in space-filling models. An even simpler image is achieved with *skeletal models,* which show only the molecular framework. In these models, atoms are not explicitly shown. Rather, their position is implied by the junctions of bonds and their termini. Skeletal models are frequently used to depict

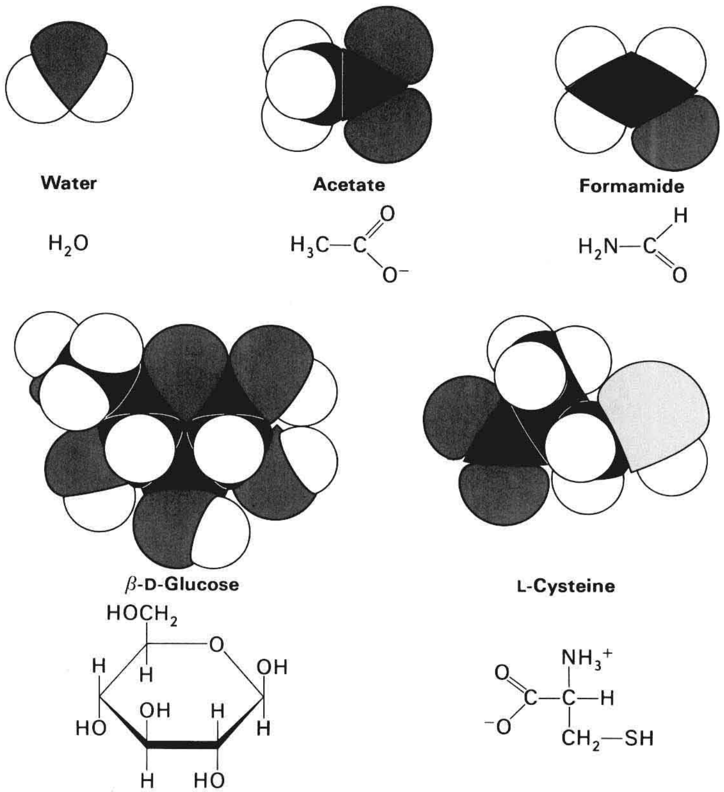

Figure 1-3
Space-filling models of water, acetate, formamide, glucose, and cysteine.

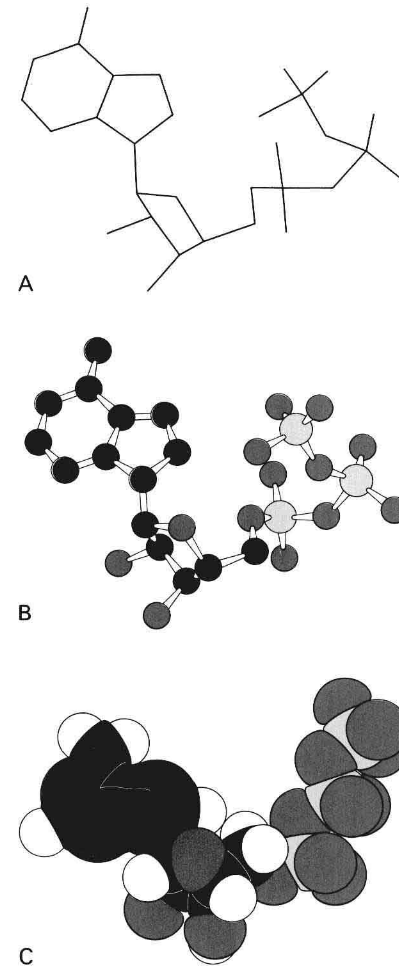

Figure 1-4
A comparison of (A) skeletal, (B) ball-and-stick, and (C) space-filling models of ATP. Hydrogen atoms are not shown in models A and B.

large biological macromolecules, such as protein molecules having several thousand atoms. Space-filling, ball-and-stick, and skeletal models of ATP are compared in Figure 1-4.

DESIGN OF THIS BOOK

This book has five parts, each centered on a major theme:

- I: Conformation
- II: Generation and Storage of Metabolic Energy
- III: Biosynthesis of Macromolecular Precursors
- IV: Information
- V: Molecular Physiology

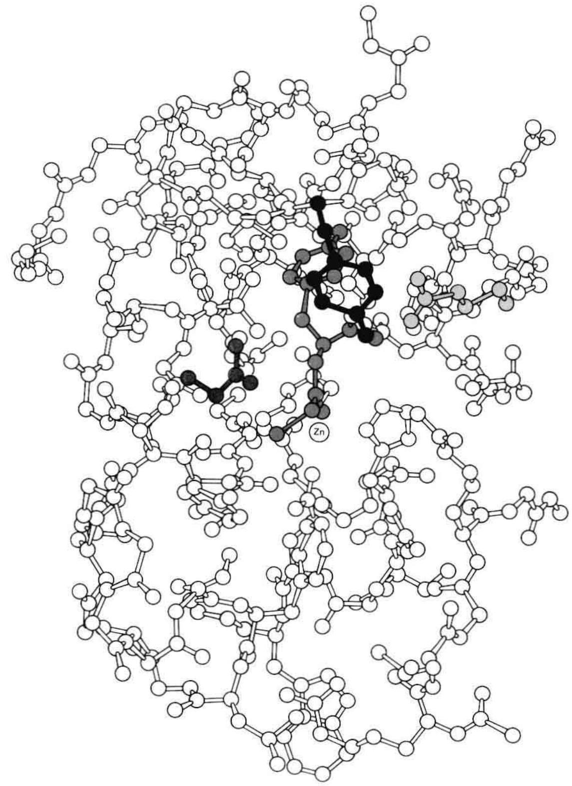

Figure 1-5
Structure of an enzyme-substrate complex. Glycyltyrosine (shown in red) is bound to carboxypeptidase A, a digestive enzyme. Only a quarter of the enzyme is shown. [Based on W. N. Lipscomb. *Proc. Robert A. Welch Found. Conf. Chem. Res.* 15(1971):141.]

The interplay of three-dimensional structure and biological activity as exemplified in proteins is the major theme of Part I. The structure and function of myoglobin and hemoglobin, the oxygen-carrying proteins in vertebrates, are presented in detail because these proteins illustrate some general principles. Hemoglobin is especially interesting because its binding of O_2 is regulated by specific molecules in its environment. The molecular pathology of hemoglobin, particularly sickle-cell anemia, is also presented. We then turn to enzymes and consider how they recognize substrates and enhance reaction rates by factors of a million or more. The enzymes lysozyme, carboxypeptidase A, and chymotrypsin are examined in detail because they provide insight into many general principles of catalysis. Rather different facets of the theme of conformation emerge in the chapter on collagen and elastin, two connective-tissue proteins. The final chapter in Part I is an introduction to biological membranes, which are organized assemblies of lipids and proteins. One of the major functions of membranes in biological systems is to create compartments.

Part II deals with the generation and storage of metabolic energy. First, the overall strategy of metabolism is presented. Cells convert energy from fuel molecules into ATP. In turn, ATP drives most energy-requiring processes in cells. In addition, reducing power in the form of NADPH is generated for use in biosyntheses. The metabolic pathways that carry out these reactions are then presented in detail. For example, the generation of ATP from glucose involves a sequence of three series of reactions—glycolysis, the citric acid cycle, and oxidative phosphorylation. The latter two are also common to the generation of ATP from the oxidation of fats and some amino acids, the other major fuels. We see here an illustration of molecular economy. Two storage forms of fuel molecules, glycogen and triacylglycerols (neutral fats), are also discussed in Part II. The concluding topic of this section is photosynthesis, in which the primary event is the light-activated transfer of an electron from one substance to another against a chemical potential gradient.

Part III deals with the biosynthesis of macromolecular precursors, starting with the synthesis of membrane lipids and steroids. The pathway for the synthesis of cholesterol, a 27-carbon steroid, is of particular interest because all of its carbon atoms come from a 2-carbon precursor. The reactions leading to the synthesis of selected amino acids and the heme group are discussed in the next chapter. The control mechanisms in these pathways are of general significance. The final chapter in this part is concerned with the biosynthesis of nucleotides, the activated precursors of DNA and RNA.

The storage, transmission, and expression of genetic information is the central theme of Part IV. The experiments that revealed that DNA is the genetic material and the discovery of the DNA double helix are discussed first, followed by a presentation of the enzymatic mechanism of DNA replication. We then turn to the expression

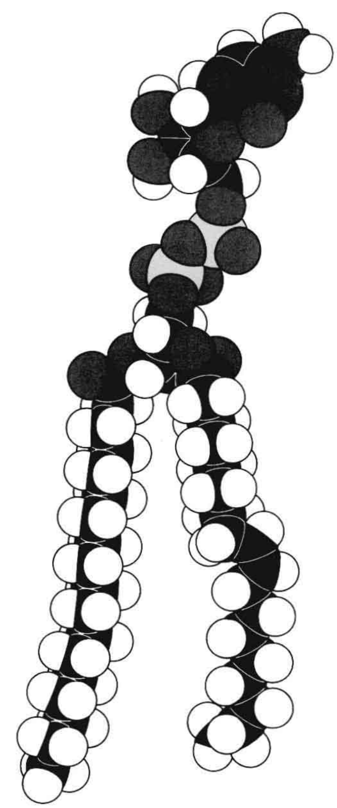

Figure 1-6
Model of CDP-diacylglycerol, an activated intermediate in the synthesis of some membrane lipids.

Figure 1-7
Electron micrograph of a DNA molecule. [Courtesy of Dr. Thomas Broker.]

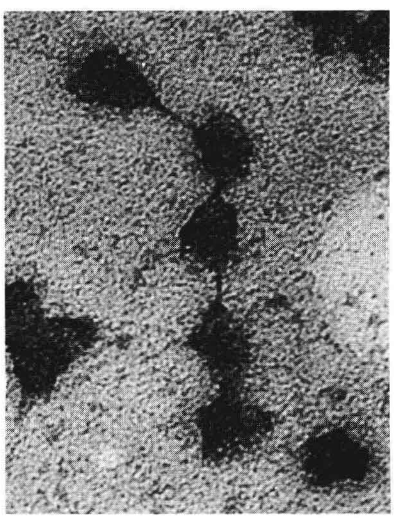

Figure 1-8
Electron micrograph of several ribosomes bound to a messenger RNA molecule. [Courtesy of Dr. Henry Slayter.]

of genetic information in DNA, starting with the evidence that showed that messenger RNA is the information-carrying intermediate in protein synthesis. The process of transcription, which is the synthesis of RNA according to instructions given by a DNA template, is then considered. This brings us to the genetic code, which is the relationship between the sequence of bases in DNA (or its messenger RNA transcript) and the sequence of amino acids in a protein. The code, which is the same in all organisms, is beautiful in its simplicity. Three bases constitute a codon, the unit that specifies one amino acid. Codons on messenger RNA are read sequentially by transfer RNA molecules, which are the adaptors in protein synthesis. We then examine the mechanism of protein synthesis, a process called translation because it converts the four base-pairing letters of nucleic acids into the twenty-letter alphabet of proteins. Translation is carried out by the coordinated interplay of more than 100 kinds of macromolecules, centered on ribosomes. The next chapter deals with the control of gene expression in bacteria. The focus here is on the lactose operon of *E. coli,* which is now understood in detail. Recent research on the chromosomes of higher organisms, which are much larger and more complex than those of bacteria, is then presented. Part IV concludes with a discussion of viral multiplication and assembly. The assembly of viruses exemplifies some general principles of how biological macromolecules form highly ordered structures. Some viruses that cause cancers in experimental animals are also considered here.

Part V, entitled Molecular Physiology, is a transition from biochemistry to physiology. Here we use many of the concepts that were developed in the preceding parts of the book, since physiology involves the interplay of information, conformation, and metabolism. We start with the molecular basis of the immune response. How does an organism recognize a foreign substance? Bacterial cell walls are considered next. Here the mechanism of action of penicillin is described. Several subsequent chapters deal with aspects of membrane structure and dynamics. How do cells transport ions such as Na^+, K^+, and Ca^{2+} and molecules across their membranes? What is the molecular basis of action potentials in nerve cells? How does acetylcholine trigger receptors in the postsynaptic membrane? How is a retinal rod cell triggered by a single photon? What are some unifying principles of hormone action? The final chapter deals with the problem of how chemical bond