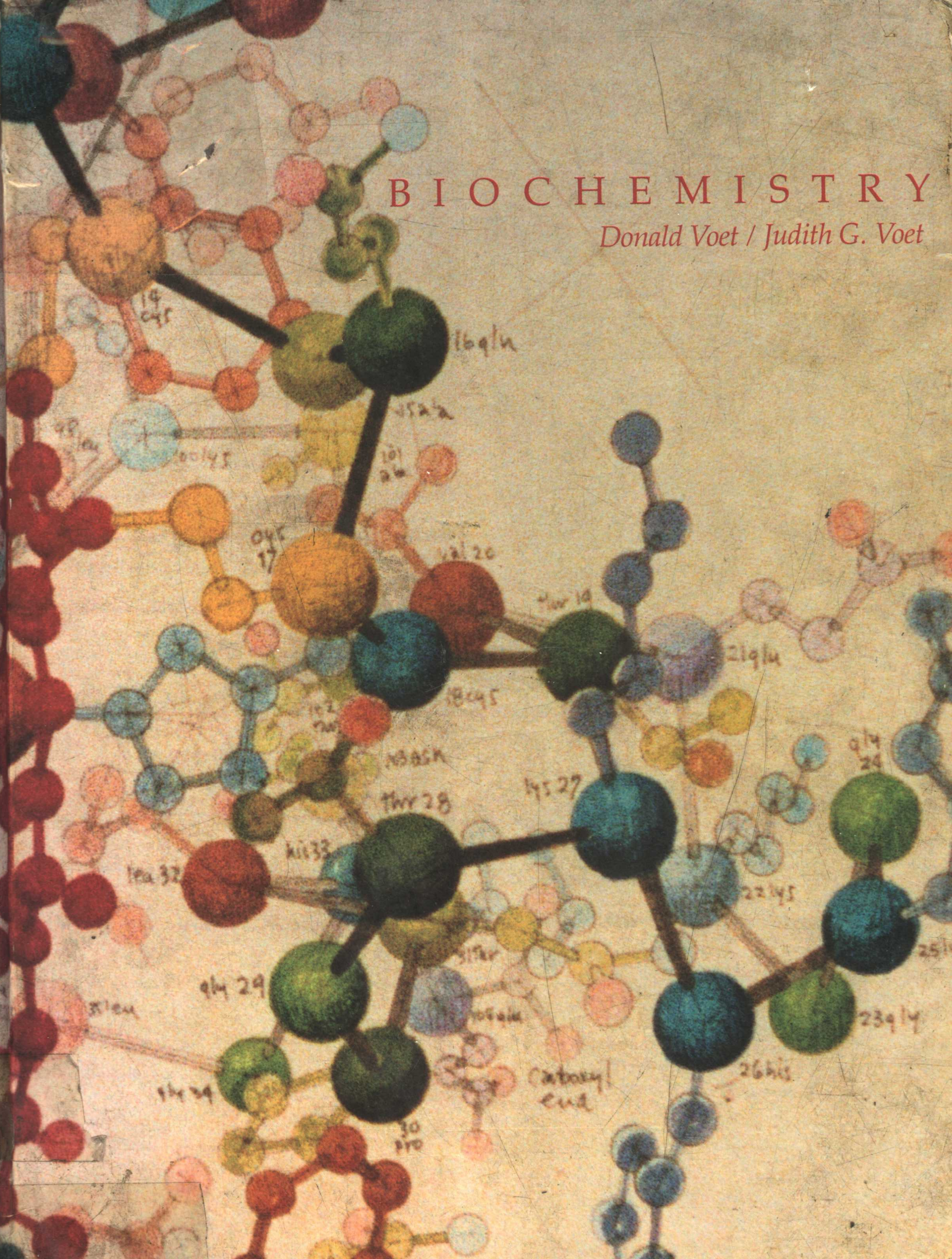
BIOCHEMISTRY

Donald Voet / Judith G. Voet



BIOCHEMISTRY

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To:

Our parents, who encouraged us,
Our teachers, who enabled us, and
Our children, who put up with us.

Cover Art: One of a series of color studies of horse heart cytochrome *c* designed to show the influence of amino acid side chains on the protein's three-dimensional folding pattern. We have selected this study to symbolize the discipline of biochemistry: Both are beautiful but still in process and hence have numerous "rough edges." Drawing by Irving Geis in collaboration with Richard E. Dickerson.

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FOREWORD

Contrary to what I once thought, scientific progress did not consist simply in observing, in accumulating experimental facts and drawing up a theory from them. It began with the invention of a possible world, or a fragment thereof, which was then compared by experimentation with the real world. And it was this constant dialogue between imagination and experiment that allowed one to form an increasingly fine-grained conception of what is called reality.
François Jacob, The Statue Within, *Basic Books, 1988.*

This text is a grand synthesis of biochemical science for the 1990s. It incorporates traditional intermediary metabolism along with the most recent advances in molecular genetics and macromolecular structure.

There have been other inspirational grand syntheses of science in the past. In 1543, Andreas Vesalius produced his great work, *De Humani Corporis Fabrica* (Fabric of the Human Body), an elaborately illustrated compendium of anatomy that laid the foundation for the science of modern medicine. Closer to our time, in the 1970s, Albert Lehninger produced a classic biochemistry text that eloquently summarized metabolism and bioenergetics. Although he also described macromolecular structure and function along with aspects of molecular biology, these descriptions could only point to the great advances yet to come.

The flood of new ideas and experiments in the late 1970s and 1980s — recombinant DNA techniques, site-directed mutagenesis, highly mechanized DNA sequencing, spectacular advances in genetic engineering and vivid new methods for visualizing complex molecular structures — all of these advances demanded a fresh, comprehensive and coherent presentation of current biochemical science. The new complexities revealed by recent experimental data have, paradoxically, made the science easier to comprehend. The new data have uncovered new organizing principles. New methods of presentation have made it possible to dramatically visualize the three-dimensional structure of complex macromolecules by artistic rendition and advanced computer graphics. These advances are incorporated into the communications system of this book. The authors begin each chapter with succinct statements of relevant principles, followed by the ideas and experimental evidence that generated these principles. Presentations of structural chemical formulas, renditions of macromolecular structures and schematic portrayals of processes are all woven into the fabric of the text, helping to make evident the connection between structure and function. The two thousand illustrations along with the clarity of the writing make this book a contemporary classic.

Myoglobin, the first protein structure to be determined, provides an illuminating case history demonstrating how a knowledge of function can be a key to understanding structure. The complete visualization of myoglobins's 153 amino acids seems at first bewilderingly complex. The structure, even at low resolution, proved to be daunting. Max Perutz, who pioneered protein structure determination, remarked on first seeing myoglobin:

> *Could the search for ultimate truth really have revealed so hideous and visceral-looking an object? Was the nugget of gold a lump of lead? Fortunately, like many other things in nature, myoglobin gains in beauty the more you look at it.*
> (Scientific American, *November, 1964.)*

Not only in beauty, but also in logical structure. It can now be seen to assume a simple folding pattern, whose very clear function is to provide a watertight pocket for the oxygen-binding iron atom.

Nature cherishes successful designs and tends to preserve them over aeons of evolutionary time. Cytochrome *c* shows remarkably similar three-dimensional folding patterns for species as different as mammals and bacteria, although their amino acid sequences may differ widely. Families of enzymes, such as the serine proteases, share recognizably similar folding patterns, even though there are differences in their active sites. Connectivity is rampant in Nature, as is reflected in this book. The separate disciplines of cell biology, enzyme kinetics electron microscopy, x-ray crystallography, NMR spectroscopy, DNA sequencing, and gene splicing—all share a common goal, to understand the structure and function of the machinery of life on the molecular level. Living systems maintain their steady state (homeostasis), through the control of metabolic pathways. These, in turn, are monitored by regulatory enzymes. Elucidation of complex regulatory enzyme structure is now beginning to explain how their specific motions exercise feedback control at the molecular level. The Germans have a picturesque word for this kind of coherence, *zusammenhängen,* (literally, "hanging together"). This classic text is comprehensive, clear and concise, but above all, it has *coherence.*

Concise summaries and clear illustrations are of great help in teaching—but biochemistry is, in essence, an experimental science. Ideas generated in the mind must be tested in the laboratory. Marshall McLuhan, a popular sociologist of the 1960s, explained the wide influence of television by coining the phrase, "The Medium is the Message." In a sense, the laboratory is the *message center* where questions are asked in terms of laboratory procedure and answered in coded machine language: that is, in numbers, graphs, spots of differing intensity on film, recordings of spectra, and tracings of polypeptide chains on computer screens. Students must learn to read and interpret these coded signs. Furthermore, they must be able to read the special languages of the research papers in which experiments are recorded. The authors are well aware of the necessity of mastering the skills and codes of the laboratory and the literature. They have provided concise overviews of laboratory practices by describing, for example, the variety of methods for purifying proteins and nucleic acids and determining their sequences. Each chapter has copious references, and there is a valuable guide on how to read a research paper. The student learns to read codes (among others, the three-letter and one-letter codes for amino acids), numerical recordings, spots and tracings on film, arcane jargon for antibodies and newly discovered genes—all with the purpose of seeing life on the molecular level.

Biochemistry in the 1990s may be a mature science, but it is far from a finished one. Imaginative concepts, tested by experiment, and organized into working principles, lead to more concepts. The upward spiral of research continues, but much remains mysterious. Science marches on. This book gives the student and the professional the equipment to understand state of the art biochemistry. It is also preparation for comprehending investigations yet to come. To this end, the authors and the publisher plan to issue periodic updates so that the seeds that have been planted will take root, grow, blossom, and bear fruit.

IRVING GEIS

New York City
August 1989

PREFACE

Biochemistry is a field of enormous fascination and utility, arising, no doubt, from our own self-interest. Human welfare, particularly its medical and nutritional aspects, has been vastly improved by our rapidly growing understanding of biochemistry. Indeed, scarcely a day passes without the report of a biomedical discovery that benefits a significant portion of humanity. Further advances in this expanding field of knowledge will no doubt lead to even more spectacular gains in our ability to understand nature and to control our destinies. It is therefore of utmost importance that individuals embarking on a career in biomedical sciences be well versed in biochemistry.

This textbook is a distillation of our experiences in teaching undergraduate and graduate students at the University of Pennsylvania and Swarthmore College and is intended to provide such students with a thorough grounding in biochemistry. In writing this text we have emphasized several themes. First, biochemistry is a body of knowledge compiled by people through experimentation. In presenting what is known, we therefore stress how we have come to know it. The extra effort the student must make in following such a treatment, we believe, is handsomely repaid, since it engenders the critical attitudes required for success in any scientific endeavor. Although science is widely portrayed as an impersonal subject, it is, in fact, a discipline shaped through the often idiosyncratic efforts of individual scientists. We therefore identify some of the major contributors to biochemistry (the majority of whom are still professionally active) and, in many instances, consider the approaches they have taken to solve particular biochemical puzzles. The student should realize, however, that most of the work described could not have been done without the dedicated and often indispensable efforts of numerous co-workers.

The unity of life and its variation through evolution is a second dominant theme running through the book. Certainly one of the most striking characteristics of life on earth is its enormous variety and adaptability. Yet, biochemical research has amply demonstrated that all living things are closely related at the molecular level. As a consequence, the molecular differences among the various species have provided intriguing insights into how organisms have evolved from one another and have helped to delineate the functionally significant portions of their molecular machinery.

A third major theme is that biological processes are organized into elaborate and interdependent control networks. Such systems permit organisms to maintain relatively constant internal environments, to respond rapidly to external stimuli, and to grow and to differentiate. A fourth theme is that biochemistry has important medical consequences. We therefore frequently illustrate biochemical principles by examples of normal and abnormal human physiology.

We assume that students who use this text have had the equivalent of one year of college chemistry and at least one semester of organic chemistry (perhaps being taken concurrently) so that they are familiar with both general chemistry and the basic principles and nomenclature of organic chemistry. We also assume that students have taken a one-year college course in general biology in which elementary biochemical concepts were discussed. Students who lack these prerequisites are advised to consult the appropriate introductory textbooks in these subjects.

This book is organized into five parts:

I. **Introduction and Background:** An introductory chapter followed by chapters that review the properties of aqueous solutions and the elements of thermodynamics.

II. **Biomolecules:** A description of the structures and functions of proteins, carbohydrates, and lipids.

III. **Mechanisms of Enzyme Action:** An introduction to the properties, reaction kinetics, and catalytic mechanisms of enzymes.

- **IV. Metabolism:** A discussion of how living things synthesize and degrade carbohydrates, lipids, amino acids, and nucleotides with emphasis on energy generation and consumption.
- **V. The Expression and Transmission of Genetic Information:** An exposition of nucleic acid structures and both prokaryotic and eukaryotic molecular biology.

This organization permits us to cover the major areas of biochemistry in a logical and coherent fashion. Yet, modern biochemistry is a subject of such enormous scope that to maintain a relatively even depth of coverage throughout the text, we include more material than most one-year biochemistry courses will cover in detail. This depth of coverage, we believe, is one of the strengths of this book; it permits the instructor to teach a course of his/her own design and still provide the student with a resource on biochemical subjects not emphasized in the course.

The order in which the subject matter of the book is presented more or less parallels that of most biochemistry courses. However, several aspects of the book's organization deserve comment:

1. We present nucleic acid structures (Chapter 28) as part of molecular biology (Part V) rather than in our discussions of structural biochemistry (Part II) because nucleic acids are not mentioned in any substantive way until Part V. Instructors who, nevertheless, prefer to consider nucleic acid structures in a sequence different from that in the text can easily do so because Chapter 28 requires no familiarity with enzymology or metabolism.

2. We have split our presentation of thermodynamics between two chapters. Basic thermodynamic principles—enthalpy, entropy, free energy, and equilibrium—are discussed in Chapter 3 because these subjects are prerequisite for understanding structural biochemistry, enzyme mechanisms, and kinetics. Metabolic aspects of thermodynamics—the thermodynamics of phosphate compounds and oxidation–reduction reactions—are presented in Chapter 15, since knowledge of these subjects is not required until the chapters that follow.

3. Techniques of protein purification are described in a separate chapter (Chapter 5) that precedes the discussion of protein structure and function. We have chosen this order so that students will not feel that proteins are somehow "pulled out of a hat." Nevertheless, Chapter 5 has been written as a resource chapter to be consulted repeatedly as the need arises.

4. Chapter 9 describes the properties of hemoglobin in detail so as to illustrate concretely the preceding discussions of protein structure and function. This chapter introduces allosteric theory to explain the cooperative nature of hemoglobin oxygen binding. The subsequent extension of allosteric theory to enzymology (Chapter 12) is a relatively simple matter.

5. Concepts of metabolic control are presented in the chapters on glycolysis (Chapter 16) and glycogen metabolism (Chapter 17) through discussions of flux generation, allosteric regulation, substrate cycles, covalent enzyme modification, and cyclic cascades. We believe that these concepts are best understood when they are studied in metabolic context rather than as independent topics.

6. There is no separate chapter on coenzymes. These substances, we feel, are more logically studied in the context of the enzymatic reactions in which they participate.

7. Glycolysis (Chapter 16), glycogen metabolism (Chapter 17), the citric acid cycle (Chapter 19), and oxidative phosphorylation (Chapter 20) are detailed as models of general metabolic pathways with the emphasis placed on many of the catalytic and control mechanisms of the enzymes involved. The principles illustrated in these chapters are reiterated in somewhat less detail in the other chapters of Part IV.

8. Consideration of membrane transport (Chapter 18) precedes that of mitochondrially based metabolic pathways, including the citric acid cycle and oxidative phosphorylation. In this manner, the idea of the compartmentalization of biological processes can be easily assimilated.

9. Discussions of both the synthesis and the degradation of lipids have been placed in a single chapter (Chapter 23) as have the analogous discussions of amino acids (Chapter 24) and nucleotides (Chapter 26).

10. Energy metabolism is summarized and integrated in terms of organ specialization in Chapter 25, following the descriptions of carbohydrate, lipid, and amino acid metabolism.

11. The basic principles of both prokaryotic and eukaryotic molecular biology are introduced in sequential chapters on transcription (Chapter 29), translation (Chapter 30), and DNA replication, repair and recombination (Chapter 31). Viruses (Chapter 32) are the considered as paradigms of more complex cellular functions followed by discussions of newly emerging concepts of eukaryotic gene expression (Chapter 33).

12. Chapter 34, the final chapter, is a series of minichapters that describe the biochemistry of a variety

of well-characterized human physiological processes: blood clotting, the immune response, muscle contraction, hormonal communication, and neurotransmission.

The old adage that you learn a subject best by teaching it simply indicates that learning is an active rather than a passive process. The problems we provide at the end of each chapter are therefore designed to make students think rather than to merely regurgitate poorly assimilated and rapidly forgotten information. Few of the problems are trivial and some of them (particularly those marked with an asterisk) are quite difficult. Yet, successfully working out such problems can be one of the most rewarding aspects of the learning process. Only by thinking long and hard for themselves can students make a body of knowledge truly their own. The answers to the problems are worked out in detail in the Solutions Manual that accompanies this text. This manual, however, can only be an effective learning tool if the student makes a serious effort to solve a problem before looking up its answer.

We have included lists of references at the end of every chapter to provide students with starting points for independent biochemical explorations. The enormity of the biochemical research literature precludes us from giving all but a few of the most important research reports. Hence, we list what we have found to be the most useful reviews and monographs on the various subjects covered in each chapter.

Biomedical research is advancing at such an astonishing pace that a seminal discovery often leads to the development of a mature subdiscipline within the period of a year or so. Consequently, a textbook on biochemistry can never be truly up to date. To alleviate this problem, we shall periodically bring out supplements to this textbook that review the recent biochemical literature and list some of its most important reviews and research reports. Nevertheless, students should be encouraged to peruse the current biochemical literature for only then will they acquire a feeling for the scope and excitement of modern biochemistry.

Finally, although we have made every effort to make this text error free, we are under no illusions that we have done so. We therefore request that readers provide us with their comments and criticisms.

DONALD VOET
JUDITH G. VOET

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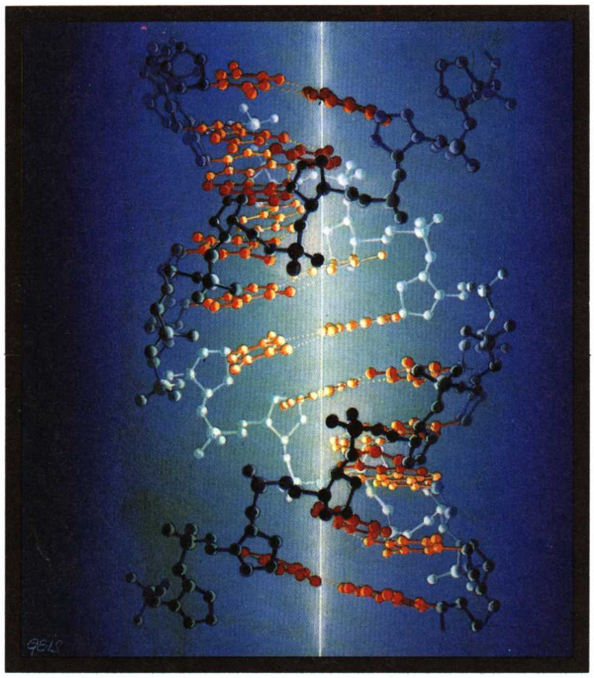

"Hot wire" A-DNA illuminated by its vertical axis.

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   B. Reading a Research Article

It is usually easy to decide whether or not something is alive. This is because living things share many common attributes such as the capacity to extract energy from nutrients to drive their various functions, the power to actively respond to changes in their environment, and the ability to grow, differentiate and perhaps most telling of all, to reproduce. Of course, a given organism may not have all of these traits. For example, mules, which are obviously alive, rarely reproduce. Conversely, inanimate matter may exhibit some lifelike properties. For instance, crystals may grow larger when immersed in a supersaturated solution of the crystalline material. Therefore, life, as are many other complex phenomena, is perhaps impossible to define in a precise fashion. Norman Horowitz, however, has proposed a useful set of criteria for living systems: *Life possesses the properties of replication, catalysis, and mutability.* Much of this text is concerned with the manner in which living organisms exhibit these properties.

Biochemistry is the study of life on the molecular level. The significance of such studies are greatly enhanced if they are related to the biology of the corresponding organisms or even communities of such organisms. This introductory chapter therefore begins with a synopsis of the biological realm. This is followed by an outline of biochemistry, a discussion of the origin of life, and finally, an introduction to the biochemical literature.