

Preface

In 1975 I was introduced to the pleasures and agonies of writing a textbook. When I finished that book, I vowed never to undertake another one; but somehow five other books were conceived and then brought to fruition in the next five years. In 1980 I acceded to the insistence of my undergraduate students, who for several years had been asking me why I did not write an undergraduate molecular biology text, and decided to do just that.

Molecular Biology, A Comprehensive Introduction to Prokaryotes and Eukaryotes is the result of this most recent effort. A multipurpose college textbook in molecular biology, it is based, in part, on a course that I taught for many years at Brandeis University. Its primary use will be in undergraduate courses emphasizing basic molecular processes (such as the synthesis of DNA, RNA, and protein) and genetic phenomena in both prokaryotic and eukaryotic cells. Students who wish to make full use of the text should have knowledge of basic biology and general chemistry and have completed or be enrolled in a course in organic chemistry.

Because of the variety of subjects treated and the detailed presentation in some chapters, the book can also be used in other courses. For example, fairly complete coverage of the structure of macromolecules enables the book to serve as a text for a short course in structural biology. (An advanced course in this subject would require an additional book on physical biochemistry.) The material contained in the

rather lengthy chapters on the chemical and physical properties of DNA and on nucleic acid synthesis has been used in a one-semester course in nucleic acids that I taught several years ago. Classical genetics, microbial genetics, and general features of genetic recombination are likewise treated in detail; my experience has been that when supplemented with sets of problems these topics can serve as a core for a molecular genetics course. (A separate problems book is available to make this application possible.) I expect that the book will be useful in advanced genetics courses, also. Finally, reviewers of the text who teach in medical schools have pointed out to me that the text can be used as a component of medical biochemistry and cell biology courses, in keeping with the current trend of emphasizing molecular processes in such courses. Before writing my text, I made a survey to determine the college year in which molecular biology and molecular genetics are usually taught. This was found to range from the sophomore year to the first year of graduate school. Thus, in an effort to accommodate various curricula, I have included in each chapter of my book basic information (sometimes in the form of a review or an overview), advanced topics, and discussion of many specific systems.

Molecular Biology differs in organization from other molecular biology texts: it follows my philosophy that molecular biology must emphasize both molecules and biology, and that to be molecular, it must also be chemical and physical—quite a tall order for a single book. With this goal in mind, I chose to present a biological introduction to the subject first (Chapter 1) before getting into the complexity of molecular detail, so that the student will know the phenomena that molecular biologists would at present like to explain and will be familiar with the biological systems used in research. A second introductory discussion, Chapter 2, reviews those aspects of organic chemistry needed by the reader and provides some basic biochemical concepts. The first major discussion following the introductory material is concerned with physical biochemistry; hence, there is extensive early coverage of the properties of macromolecules; this is a notable feature of the organization of this book. Early presentation of this material is based on my teaching experience, in which I have concluded that students have an easier time understanding the great variety of phenomena in which macromolecular interactions play a role if they have first acquired a thorough understanding of macromolecular structure. For example, the student should have a clear understanding of the significance of molecular shape and the interactions that give rise to the shape of a particular molecule; how, otherwise, can the concepts of templates, active sites, specificity of binding, and mutation be understood?

Following the treatment of macromolecules, the text turns to what is traditionally thought of as molecular biology—namely, DNA, RNA, and protein synthesis. In each case, both prokaryotic and eukaryotic

systems are described in the same chapter; the prokaryotic systems are given in greater detail, as more is understood about these systems, and the similarities and differences between prokaryotes and eukaryotes are pointed out.

The next major unit of the book is concerned with how the basic synthetic processes are integrated to enable a prokaryotic cell or particle to function efficiently and to respond to a changing environment; here, the text examines in some detail metabolic regulation in bacteria and phages, stressing the notion of efficiency.

Features of genetic exchange—natural systems such as plasmids, transposons, and homologous recombination, and the artificial process of genetic engineering—form the next unit; parts of each chapter are presented as a survey, for a beginning course, but discussions of particular models are provided for use in courses of greater depth.

The final unit of the book is concerned exclusively with eukaryotic systems. It is divided into two parts, the first on animal and plant viruses—their basic biology and how they are regulated—the second on regulation in numerous eukaryotic systems, in both unicells and animal tissue.

A problems book (*Problems for Molecular Biology*, Science Books International/Van Nostrand Reinhold Company, 1983), containing more than 800 problems with complete and detailed solutions, is also available as a supplement to this text and is matched to the text chapter by chapter. Drill questions to test a student's mastery of facts are given for each major topic and many problems of a more substantive and sometimes difficult nature are also included. These problems have all been used in prior courses and have been extensively checked for ambiguities and correctness of solutions by undergraduate students at Brandeis University and graduate students and faculty at the University of California, Berkeley.

Inasmuch as *Molecular Biology* can be used in its entirety in either a condensed one-semester course, such as I have taught, or a more relaxed full-year course, instructors will have to be selective of the material for one-semester courses. To aid in this selection, summaries of the chapters—and especially of the points of view taken in the chapters—are presented in the following paragraphs.

Since the *modus operandi* of molecular biologists requires knowledge of phage biology, bacteriology, cell biology, and classical and microbial genetics, these topics are presented in Chapter 1 in a phenomenological way. Commonly used genetic tools such as recombinational mapping and complementation are reviewed. A brief discussion is also given of the logical approach taken in molecular biology that distinguishes it from the biology of the earlier part of the century. The basic life cycles of particular biological systems used by molecular biologists—namely, *E. coli*, phage, viruses, yeasts, and animal cells—

and the means for handling these systems—liquid culture, growth on agar, colony and plaque counting, and eukaryotic cell culture—are described in some detail. Chapter 2 provides a parallel review of elementary organic chemistry (e.g., functional groups) and introduces the molecules commonly found in biological systems. Since in many schools the study of molecular biology precedes that of biochemistry and cell biology, such biochemical topics as carbohydrate metabolism, the role of ATP in biochemical reactions, and the concept of the metabolic pathway are also included. A discussion of growth media for various organisms is also provided. To some students, little of the introductory material will be new, but my experience as a teacher has demonstrated to me that most college students have forgotten a great deal of what they learned in previous courses and profit from such a review. Instructors for advanced courses may choose to omit Chapters 1 and 2, but I advise having the student read these chapters quickly and reflect on possibly forgotten topics.

The text then turns to a study of macromolecules. Chapter 3 presents the general properties of macromolecules and some of the more common techniques used in their study. Chapters 4 and 5 treat nucleic acids and proteins, respectively, in considerable detail, with respect to both their chemistry and physical properties; structure is related to function whenever possible. A goal in the treatment of nucleic acids is to provide the student with the information needed to understand the mechanisms of replication and transcription, which are examined in later chapters. Furthermore, the reader will examine in some detail the properties of nucleic acids that researchers utilize when designing experiments investigating fundamental biochemical mechanisms. Chapter 5 has three goals—to give the student an appreciation of the variety of possible protein structures, to relate protein structure to biological function, and to indicate how a single amino acid change in a mutant can have a profound effect on protein function. In recent years knowledge of macromolecular structure has reached the point where examination of complex systems of macromolecules—for example, antibodies, chromatin, membranes, nuclear bodies, cell walls, and so forth—is profitable; these and other topics are included in Chapter 6. Some of these topics may be omitted from a short course, but the sections on immunoglobulins and chromatin should be included, for knowledge of these structures will be required in later chapters of the book.

To keep their science courses contemporary, most instructors cannot afford to spend much time on the story of how molecular biology evolved as a science; indeed, I believe many students find the topic less interesting nowadays than instructors do. (An instructor's interest is often derived from acquaintance with the personages involved, but increasingly the material must be considered history.) Accordingly,

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very little history is given in this book; however, I have included a brief presentation of the discovery of the genetic nature of DNA, for it still seems worth while to me to give beginning students some idea of the foundation of the field of study on which they are embarking. This historical interlude is presented in Chapter 7 but is given as part of a more general discussion of those properties that enable nucleic acids to serve as the repository of genetic information.

The treatment of what is traditionally thought of as molecular biology begins in Chapter 8 with DNA replication—an uncommon starting point. I have chosen this organization for five reasons: (1) the essential concepts of a template and of chemical polarity are easily introduced with this approach; (2) DNA replication exemplifies, in a simple way, the kinds of geometric problems faced by many biochemical systems; (3) this topic shows how complicated a “simple” process can be; (4) the concepts of both variability of genetic material (for example, mutational changes) and protection of existing information (for example, repair processes) are more obvious here than in other topics; (5) the notion of regulation (that is, when DNA synthesis begins in a cell) can be introduced. The chapter on DNA replication is very lengthy because I have chosen to present examples of almost every known mode of replication in both prokaryotes and eukaryotes. The instructor will probably have to be selective and may choose to delay certain topics—for example, phage DNA replication—to later chapters.

Chapter 9, the subject of which is DNA repair, and Chapter 10, which is concerned with mutations, follow logically from a treatment of DNA replication, for in these chapters I have discussed the imperfections of biological systems and how cells deal with the problem of damage to their DNA by many environmental agents and reagents. Most of the material in these chapters consists of well-understood subjects; the main exception is SOS repair, a subject still actively being investigated.

By the time the reader has completed Chapter 10, he or she will have become familiar with the structure of the important intracellular molecules and will have examined systems for synthesis of one type of macromolecule. In so doing, the foundation will have been laid for understanding how a cell manages to do what it has to do at the appropriate time and how it responds to environmental factors. Thus, the reader is ready to be presented with the mechanisms of RNA synthesis and protein synthesis in prokaryotes and eukaryotes, which is done in Chapters 11–13. Chapter 11 deals with transcription; as in Chapter 8, the basic phenomenon is described first; then this is elaborated on in considerable detail. Special attention has been paid to essential features (such as recognition sites) of the macromolecules required for transcription, and the value of understanding the complete nucleotide sequence is made evident. Chapters 12 and 13 are concerned with pro-

tein synthesis. This immense topic has been divided into two parts—namely, the information problem, which is presented in Chapter 12, and the chemistry, which is given in Chapter 13. The structures of the relevant molecules (tRNA and the aminoacyl synthetases) and particles (ribosomes) are described twice—first in a simple way and then in considerable detail. The chemistry of protein synthesis is presented fairly completely and, in some cases, as somewhat advanced material, but chapter sections have been arranged in such a way that more detailed sections may be omitted, if desired. For example, a student can learn about protein synthesis by reading an overview consisting of a few pages, but if detail is wanted, a sequence of sections consisting of nearly twenty pages can be used.

Having completed all units on macromolecular synthesis, the reader is then ready to study how such synthesis is regulated. Chapter 14 is concerned with regulation in prokaryotes and presents the operon concept. (Regulation in eukaryotic cells is delayed to Chapter 22 because of its complexity, but it may be covered after Chapter 14.) The *lac* operon serves as the basis for the chapter because most of the features and concepts of regulation were developed by investigating this system. Discussion of the *lac* operon is rather lengthy, though, and some instructors may wish to omit certain subsections. In the early days of molecular biological research, when the *lac* operon was first being studied, it appeared that a general mechanism of regulation—namely, via operons—had been uncovered and that the *lac* system was the prototype. However, work from numerous laboratories has shown that though operons are indeed a general phenomenon in prokaryotes, a great many different regulatory programs exist for different metabolic systems; furthermore, the *lac* system has been found to be considerably more complex than was earlier thought. In Chapter 14 the reader is exposed to a wide variety of systems—the negatively regulated, the positively regulated, those with one promoter or with more than one promoter, degradative systems and biosynthetic systems, and so forth. The chapter is rather long and I assume that instructors will pick and choose among the systems. (Although a large number of operons are presented, selectivity has nonetheless been necessary and no doubt some instructors will find that a favorite system has been omitted.)