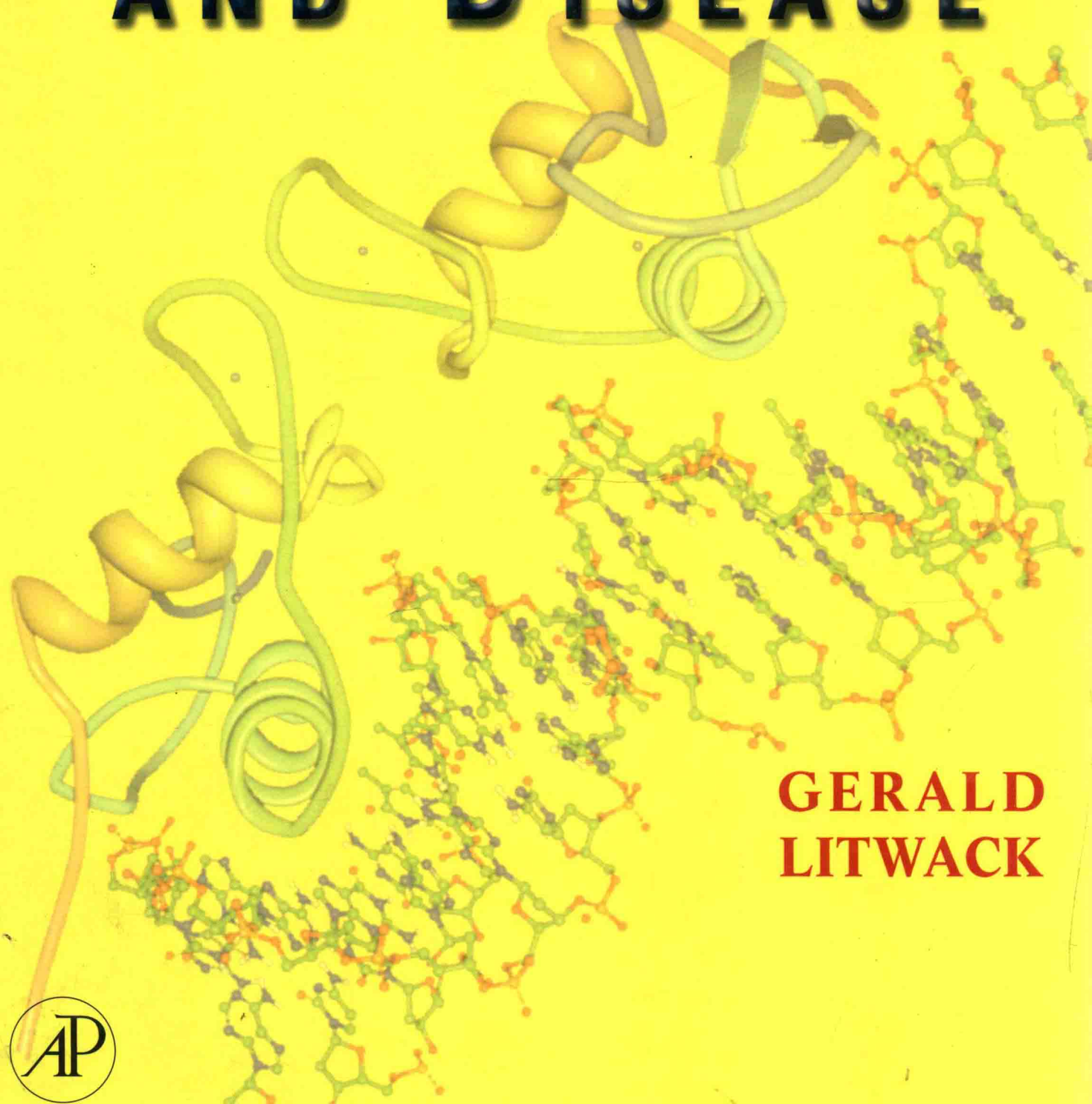
Human Biochemistry and Disease



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Preface

This is a different kind of a biochemistry textbook. The book is centered on human biochemistry and does not dwell on comparative biochemistry, except in a few cases to enhance meaning. This text is directed to medical students, graduate students, and undergraduate students, particularly those majoring in biochemistry or biology and those who are pre-medical students. The content is fairly concentrated, but there are many figures, making this a satisfying experience for visual learners. I have always felt that a picture to support the word is the best way to learn. Since I love to set ideas down in pictures, I have slanted the entire book in this direction. In addition, there are several pictures of structures, especially of proteins. Because so much information is now available on protein structure, students should become used to looking at three-dimensional structures that may resemble the actual protein in solution. Sometimes, little will be conveyed through the structure about its function; other times, especially when there is another macromolecule or small molecule with which the protein is reacting, the picture will impart a great feeling for how the protein is working, surpassing the verbal explanation. Also, there are no distinctions made between biochemistry, molecular biology, and cell biology; in my view, they are related seamlessly.

The impetus for creating this book came from many years of experience in planning for and teaching biochemistry to medical students. The majority of medical students, in my opinion, found biochemistry to be a grueling experience because they had a difficult time understanding how biochemistry relates to medicine or to disease. Part of this perception came from the way in which biochemistry is taught. Biochemists usually know rather little about disease, and clinicians know little about biochemistry. I have tried to make the relationship of biochemistry to medicine evident by introducing each biochemical topic with a study of a disease that represents the biochemical principles to be conveyed. For example, the subject of carbohydrate biochemistry is introduced by a discussion of diabetes, proteins by a discussion of prion disease, microbial biochemistry, by a discussion of HIV, and so on, with an introductory discussion of a relevant disease or clinical relationship in each chapter. This should make the study of biochemistry more meaningful for the medical student and not something to be avoided by the undergraduate or graduate student. After all, in many cases disease stems from abnormal biochemistry, and normalizing it may be the way to treat the disease. One needs to understand aberrant

biochemistry and certainly normal biochemistry because this is the way in which cells in the body function.

Figures and tables are, for the most part, taken from the literature. Many citations to the sources for the data shown appear and these references will be useful to those readers who wish to pursue the literature beyond what is presented. For this reason, I have not appended a list of published papers at the end of each chapter, as is the usual custom, but rather I mention one or more specialized books for further reading.

Ten years ago, it might have taken me twice the time it actually took to prepare this book. Now with powerful search engines and availability of the literature on the Internet, writing this book was a pleasant experience. In particular, I need to give credit to the search engines and people who have helped me. Google search engine and to a lesser extent Google Scholar were very powerful tools. PubMed was especially helpful. Academic Press/Elsevier, through the courtesy of Jeremy Hayhurst, provided Science Direct, which allowed my entry into the current literature in many journals. Two university libraries were made available to me online: Dr. Thomas Nasca made it possible for me to utilize the Thomas Jefferson University library of my former institution. Dr. Elizabeth Neufeld, Chair of the Department of Biological Chemistry, David Geffen School of Medicine at UCLA, invited me to be a Visiting Scholar and at the same time made the library of the institution available to me. Because of this kind of assistance, I was able to generate most of the information I needed directly from my computer.

The Publisher, Academic Press/Elsevier, is one I have been associated with for many years. The Publishing Editor, Jeremy Hayhurst, was helpful and very supportive during the process and agreed with my idea for this text from the beginning. In the later stages of the completion of the book and its publication, Tari Broderick and Renske Van Dijk of Academic Press facilitated the final steps and production.

Gerald Litwack

For the people who worked with me in research over the years

Technicians, graduate students, post-doctoral fellows, and sabbatical visitors. A few of a great many are: Ann Trowbridge, Kris Morey, Nora Lichtash, Peter Bodine, Emad Alnemri, Sandy Singer, George Tryfiates, Tom Diamondstone, Emerich Fiala, Teresa Fernandes, Ilga Winicov, Tom Schmidt, Noreen Robertson, Sonia Lobo Planey, Andrea Miller, Violet Daniel, Costas Sekeris, Bob Baldridge, Gary Smith, Max Cake, Virginia Ohl, and David Phelps.

For the teachers, mentors, collaborators, and friends who inspired me or helped in some way

Kathryn Cook, Conrad Elvehjem, Jesse (Jerry) Williams, Jr., Edwin Bret Hart, Moe Cleland, Joe Nielands, Mavis Brandt, Charity Crocker, Roger Monier, Vern Schramm, Gordon Tomkins, Carlo Croce, Kay Huebner, Gary Stein, Brian Ketterer, Joe Gonnella, Tom Nasca, Sidney Weinhouse, Mannie Rubin, Marge Foti, Alan Kelly, Darwin and Ellie Prockop, Tony and Helen Norman, and many others.

For my family

Ellie, Geoff, Kate, Claudia, Debbie, and David.

Contents

CHAPTER 1

Introduction and General Considerations

Introduction

This is a text of human biochemistry interwoven with clinical aspects. It is a text that can be used by medical students, graduate students, undergraduate biochemistry majors, and other undergraduate majors interested in the interplay between biochemistry and disease.

Over the years, through my experience in teaching freshman medical students, it became clear to me that most students were eager to obtain relevant clinical experience, their reason for coming to medical school. As the increasing detail of biochemistry was presented, they lost sight of the role that biochemistry plays in medicine. Standing back and inspecting the scientific disciplines, it becomes obvious that medicine is based largely in biochemistry and physiology. One problem in making a basic science relevant is that most scientists are absorbed in their fields of endeavor and know little about medicine. On the other hand, few physicians know enough about basic science to make the coupling. My purpose here is to begin each chapter with the presentation of a disease illustrative of a biochemical subject. If I successfully start with a disease process, describing the molecular basis of the disease in biochemical terms, the relevance factor should be satisfied. Knowing the abnormal biochemistry explaining the disease process automatically leads to a discussion of the normal processes; thus, human biochemistry can be introduced in the context of disease. This should peak the interest of the medical student and illustrate the roles of biochemistry in clinical problems.

Most biochemistry graduate students know little about disease. This approach should be an interesting introduction to aspects of medicine. The material presented here can be mastered easily by the instructor in biochemistry and will allow biochemistry graduate students to learn more about disease processes.

Undergraduates, especially those contemplating a career in medicine or in medically related research, will find this a useful book. The instructor who wants to base a course on this book will undoubtedly attract an excited body of students. The text is not daunting; any interested instructor should be able to organize lectures of interest to undergraduates.

Integration of Biochemistry with Clinical Medicine

In general, each case of a disease is an example of a disruption of a normal biochemical process. So, I begin each biochemical topic with a disease that represents an abnormality of that process. Thus, the subject of proteins, for example, can be launched with the introduction of prion disease, an abnormal process of protein conformation. The medical explanation of the disease will be made first, progressing to the molecular events. This should raise the question, If this process is abnormal, what is the normal process? This automatically leads into the basic human biochemistry of proteins.

Usually, biochemistry textbooks start with proteins or carbohydrates. I chose to begin with proteins because virtually all enzymes are proteins, which make it possible to achieve complex chemical reactions under the restricted conditions of temperature, pressure, and so on, imposed by the human body. Thus, the reactions in carbohydrate metabolism, lipid metabolism, and those of proteins, nucleic acids, and so on, are all catalyzed by enzyme proteins. Then the study of enzymology becomes important to understand biological catalysis. And although the basic information is provided on the principles of enzymology, the chapter in this book discusses clinical enzymology to illustrate the usefulness of the basic information as it applies to the diagnosis of disease. In selecting disease entities to reflect specific biochemical topics, I tried to choose examples that medical students may eventually see in the hospital or in their practice or those of importance in world health. In a few cases, I resorted to a disease that may not be widely prevalent but may be the best representative of the biochemical topic under discussion. In some cases, there are prevalent diseases about which the biochemical and molecular understanding may be rudimentary still. I avoided their discussion, but they are mentioned in some context, although this is not meant to be a textbook on the introduction to medicine.

There are many figures in this book, which are rendered for the purpose of explaining pathways and to give an overall picture of what is happening. Some figures are highly simplified to serve as an introduction and to provide a snapshot of the "forest," introducing the concept before proceeding to the discussion of individual steps in a pathway or process. Sometimes detailed figures tie together a lot of information and give it some perspective. These figures may serve the research-oriented student.

General Considerations

The Human Body and Organ Systems

Figure 1-1 shows Leonardo da Vinci's famous Vitruvian man drawn in 1492. It would seem difficult to improve much on this drawing. From here we can break down the human organism into organ systems. The human body is extremely complex when we consider the one-celled