PRINCIPLES OF BIOCHEMISTRY

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TO OUR WIVES

PREFACE

Biochemistry, also designated frequently either as physiological or biological chemistry, has developed as a result of the application of the principles and methods of chemistry to the fields of physiology and biology. The growth of biochemistry has paralleled the advances in knowledge in chemistry and biology, and more recently in physics as well.

As a result of its use of the tools and information derived from a variety of fundamental sciences, biochemistry now permeates every field of biological thinking. The emphasis on animal biochemistry and, to a lesser degree, on plant biochemistry has been matched in more recent years by the newer interest in the biochemistry of microorganisms, stimulated by the recognition that fundamentally similar metabolic processes occur in all organisms, as well as by practical developments in the study of pathogens and in the production of antibiotics.

The increasing importance of biochemistry in the medical curriculum may be attributed in large part to the great progress being made in the biochemical research laboratories. As a consequence of the growing understanding by the biochemist of fundamental cellular processes, medicine has looked to an increasing degree to contributions by biochemistry to the understanding of disease processes, to diagnostic methods, and to more rational therapeutic measures. Although the traditional place of biochemistry is in the first year of the medical school curriculum, there is a trend in some institutions toward supplemental instruction in this subject in the years generally devoted to the clinical disciplines. Various departments of medical schools have found it desirable to have laboratories which are concerned with the application of biochemical principles to problems in medicine, pediatrics, pharmacology, pathology, etc. In addition to this expanded interest in biochemistry in the program of medical schools, there has continued one of the fundamentally important functions of biochemistry departments in these institutions, namely, the training of graduate students for teaching and research careers in biochemistry.

As biochemistry has grown increasingly broad in its scope, it has become more difficult to achieve success in providing in a single course or textbook the principles of biochemistry for all types of students. This book attempts to present an introduction to biochemistry for medical students and others who are concerned primarily with mammalian biochemistry. As a result, the biochemical principles are illustrated chiefly with examples chosen from studies of man and of other mammals. However, many illustrations have been cited, from comparative biochemistry, of the chemical and metabolic differences which occur among various species.

The organization of this book is based upon the teaching experience of the authors. The subject matter is divided into parts which appear logical both in sequence and content. The initial part, on the composition of living matter, presents the chemical nature of the diverse substances with which the biochemist is concerned. The second part encompasses the concepts of catalysis, including the chemical nature of the important biocatalysts, the enzymes, and the basic knowledge regarding the physical and chemical laws of enzyme action. The third part, metabolism, then deals with the reactions in the organism in which the chemical components of cells participate and with the enzymes which catalyze these reactions. The fourth part is concerned with body fluids, the composition of these fluids, and their contributions to the manifold reactions characteristic of living organisms. The fifth part, on the biochemistry of specialized tissues, provides the opportunity to treat of the chemistry and physiology of certain tissues and organs which, by virtue of either their unique composition or their manufacture of a highly specialized product, reflect a structural localization of an unusual type of bodily function. The sixth part, the biochemistry of the endocrine glands, presents from a biochemical point of view the nature and function of a group of physiological regulators of prime importance in the homeostasis of the mammal. The final part, on nutrition, not only includes the chemistry of, and optimal requirements for, particular dietary components but interprets these requirements in the light of the known functions of these substances in cellular phenomena.

It has been assumed that the beginning student of biochemistry has had little or no formal training in physical chemistry. The necessary concepts of this discipline are presented in the framework of the above parts rather than in a separate introductory section. It has been the experience of the authors that the interest of the student is much greater when particular chemical concepts are illustrated with a biological or biochemical principle close at hand. Adopting this point of view, the book has not included the classical chapter on digestion. Rather, this aspect of biochemistry has been integrated into the chapters dealing with the metabolism of the major foodstuffs.

In the preparation of this book, it has been difficult in many instances to distinguish between what constitutes biochemistry and what should more properly belong in a textbook of physiology. For example, the present text includes a discussion of energy metabolism, water and electrolyte metabolism, and endocrinology. Although much of the information in these chapters may also belong in the province of physiology, an effort has been made to emphasize chemistry and to present the material from a biochemical point of view.

Literature references have been provided at the end of the chapters in the form of key references to books, review articles, and current journal articles. It has seemed undesirable to attempt to cover the literature completely in a basic textbook or to document each statement with a suitable literature reference. Rather, by the use of a selected list of references, the student will be able to broaden his knowledge of any particular topic. Numerous cross references from one chapter to another will be found throughout the book. By this method, an effort has been made to correlate the material of the various parts and at the same time to avoid unnecessary duplication.

It will be noted that an unusual degree of emphasis has been placed upon those parts of the book which treat of the dynamic aspects of biochemistry, *e.g.*, catalysis, biological oxidations, and metabolism. This emphasis appears justified in view of the fundamental contributions which these segments of biochemistry have made to an understanding of living phenomena.

A few comments are in order regarding the method used in writing this book. The preparation of the first draft of each of the chapters was assigned to one of the four authors. Each complete first draft was then subjected to the criticisms and suggestions of each of the other authors. In addition, the authors were able to convene at intervals for meetings of several days' duration, at which sessions criticisms, suggestions, and discussions of the manuscripts took place. In certain instances material written by one author was rewritten by another. In effect, this led to each chapter being contributed to by all four authors.

Grateful acknowledgment is made to the many friends and colleagues who have read, criticized, and made suggestions for the improvement of the various chapters of the book.

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INTRODUCTION

The field of study or discipline with which this textbook is concerned is designated as biochemistry; it can also be described as biological chemistry and as physiological chemistry. These various names are synonomous and encompass the knowledge derived from the application of chemistry and physics to the study of biological phenomena. The fundamental importance of biochemistry in the medical sciences, as well as in those studies concerned with any form of living matter, stems from the early recognition that every manifestation of biological activity in all cells results from an underlying chemical process or processes. It is this concept which, from the beginning of the study of biochemistry, and continuing to the present time, has channeled the teaching and research in this subject along two major lines of endeavor. These are, first, the qualitative and quantitative characterization of the chemical components of cells and, second, the elucidation of the nature and mechanism of the reactions in which these components participate.

Biochemistry is a relatively young science, approximately 100 years old. Its beginning is often dated from the year 1866, when Felix von Hoppe-Seyler became the first to receive the title of professor of physiological chemistry, bestowed upon him by the University of Tübingen. However, for many years prior to that time analytical and organic chemists had been prying into living organisms in an effort to determine the nature and quantities of the substances which comprise these structures. In the middle eighteenth century, Scheele, a Swedish pharmacist generally known for his discovery of chlorine and of oxygen, had also identified lactic acid in sour milk, citric acid in the juice of lime, malic acid in apples, and uric acid in urine. Somewhat later, the Swedish chemist Berzelius proposed a system of chemical notation in which the chemical elements were designated by their present-day letters (symbols) or combinations of letters. The suggestions of Berzelius also provided a means of expression of chemical proportions, showing clearly the number of atoms of each element present in a compound. Thus, the writing of formulas for compounds, indicating the atomic proportions which constitute molecules, evolved concomitantly with the initial isolation and description of substances from living tissues.

Approximately 25 years after many of Scheele's observations, Lavoisier in France demonstrated the utilization of oxygen by living organisms for the combustion of foodstuffs and the production of heat. With the aid of the physicist Laplace, Lavoisier was able to show that the *quantity* of heat produced by the animal organism during the combustion of a foodstuff was equivalent to that obtained when the same material was burned in a laboratory calorimeter.

In the nineteenth century, there occurred the rise of the organic chemists, striving to elucidate the structure of biologically important substances, and the investigations of the physiologists, who sought to unravel the nature of the processes by means of which these compounds participate in cellular reactions. Frequently, the chemists conducted both chemical and physiological studies of living materials. In 1840, the German chemist Justus von Liebig pointed out that plants do not subsist merely on the water and carbon dioxide which they abstract from the air and the soil but that they have to be fed with the variety of chemical elements necessary for the building of the plant structures. Liebig was also the first to show that two compounds with markedly different properties may have the same elemental composition, and for this phenomenon Berzelius suggested the name *isomerism*.

Particular mention should also be made of the organic chemist, Emil Fischer, whose brilliant investigations spanned the latter half of the nineteenth and the beginning of the twentieth centuries. Fischer examined in detail the structure of naturally occurring organic compounds, notably carbohydrates, proteins, amino acids, and purines, and provided fundamental information regarding these primary constituents of living cells.

Thus the early biochemists employed the tools of the analytical and organic chemists in conjunction with the techniques of the physiological laboratory. Physical chemistry, which began to develop late in the last century, contributed significantly to the growth and differential development of organic and analytical chemistry, thereby simultaneously imparting a significant impetus to the advancement of biochemistry. As the various other branches of the basic sciences developed, *e.g.*, physics, an increasing number of more complex and applicable techniques were made available for the study of the fundamental problems concerned with the nature of living processes.

Parallel with these stirring events in the natural sciences were the far-reaching developments in immunology and bacteriology, as a consequence of which there were formulated the subjects of immunology and bacterial biochemistry, or microbiology. More recently, the theoretical and technical advances in physics have been of prime importance for biochemistry. Electron microscopy, x-ray diffraction analysis, mass spectrometry, ultraviolet and infrared spectroscopy, radioactivity measurements, and ultrasonic methods for the lysing of cells represent a few of the practical contributions of physics to biochemistry and to biological problems. The significance of this development is attested to by the creation in universities of divisions of research and teaching designated as biophysics and medical physics. The lines of demarcation among and between the various disciplines contributing to biochemistry and, indeed, within biochemistry itself are dimly perceived and artificial. For example, biophysics and biochemistry have merged as a single field of science in many problems, *e.g.*, the use of isotopes for the study of metabolic phenomena.

From the foregoing, it is evident that biochemistry is a broad discipline which has adapted and utilized the advances that have been made in all the basic sciences. For this reason, and as its growth and expansion continues, biochemistry will be in a position to apply an increasing number of techniques and facts to the solution of the fundamental problem of biology, *viz.*, the nature and the mechanisms of the normal and the abnormal physiology of living organisms. The biochemist continues to examine the nature and quantity of cellular constituents and to attempt to elucidate the regulatory factors, *e.g.*, the enzymes and the hormones, which control the rates of cellular reactions, and the mechanisms by which these catalytic forces exert their influence.

The form of life with which this book is chiefly concerned is man. Broadly speaking, the study of medicine involves examination of knowledge in four general fields, all of which are capable of intimate integration. These are (1) the structure of the human organism, (2) its normal physiology, (3) its abnormal physiology, and (4) therapeutics, or treatment of the abnormal condition. To all these, biochemistry has made significant contributions in terms of understanding and explaining what is observed in the laboratory and in the clinic. In those instances in which the abnormal physiology can be understood in terms of derangements of biochemical processes, the institution of therapy with the view of restoring the normal, or healthy, condition may often find a more rational basis.

Although this book will give emphasis to the study of the principles of biochemistry as a basis for the understanding of, and application to, medicine, attention should be directed to a point of perhaps obvious importance, but which is not infrequently disregarded. Biochemistry as related to forms other than man or even mammalian structures is of fundamental importance and too much neglected. Indeed, from the field of what might be termed comparative biochemistry have come observations and discoveries of far-reaching importance and significance for medicine. The advances in knowledge and understanding of disease and its treatment are dependent on continuing laboratory research, and this is in large part conducted not only on mammals but on other forms as well. Until more recent times, observations in non-mammalian species were not considered to have a fundamental significance for medicine. However, the modern investigations in plant and bacterial biochemistry have served to emphasize that information derived from studies in comparative biochemistry may have practical applications to medicine. Perhaps more than any other factor contributing to this enlightened point of view was the development and growth of the field of antibiotics. Studies of bacterial metabolism are now recognized as contributing as much to the knowledge of certain diseases as laboratory work with the white rat has aided in understanding human nutrition. While it is obvious that data obtained in the laboratory in studies with species other than the human cannot be transferred unreservedly to the explanation of processes in man, the pages which follow will contain many examples of the advances made in knowledge of human biology as a consequence of biochemical studies with plants, bacteria, and laboratory animals.

It has been pointed out that biochemistry is based upon the use of the basic knowledge and tools of chemistry, physics, and biology. Therefore, it is assumed that the reader and student of this book will have completed, as a minimum, fundamental courses in inorganic, organic, and analytical chemistry, in physics, and in general biology. At the end of each chapter there will be found selected references which should be useful for both augmenting and explaining in somewhat more detail certain aspects of the topics which have been presented in that chapter. This type of reference to the extensive literature has been chosen as that which is most desirable and useful for the student.

PART ONE

Chemical Composition of Cells