Biochemistry
for Medical Sciences

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To my wife, Madeleine,
our son, Kenneth,
and daughter, Avis

Preface

The primary goal of this book is to present the biochemical foundation necessary to students of medicine and related fields. More specifically, the aim is to introduce the reader to the basic aspects of normal metabolism that are required for an understanding of the causes and consequences of various disorders. As such, this text should also be useful to biologists and clinicians who wish to keep abreast of ongoing developments and current hypotheses.

A major portion of the book deals with intermediary metabolism and its relationship to the overall functioning of mammalian organisms. In order to maintain the emphasis on these subjects, digressions into historical developments are avoided, and descriptions of experimental methodologies are kept to a minimum. In conformance with the primary objective, attention is centered on the reactions or pathways that regulate metabolism and the disorders that result from disturbances or deficiencies in those processes.

The basic principles and the structural chemistry required for the description of intermediary metabolism are discussed in the first two chapters. More specific details of molecular structures and enzyme characteristics are presented in conjunction with their application to metabolism. For example, only the general aspects of lipid structure are described in Chapter 1, whereas the individual structures are given when lipid metabolism is discussed in Chapters 3 and 5. Similarly, the principles of enzyme catalysis are described in Chapter 2, but the features of allosteric enzymes are defined in connection with isocitrate dehydrogenase (Chapter 3) and aspartate transcarbamoylase (Chapter 9).

Chapters 3, 4, and 5 deal with the metabolism of lipids and carbohydrates. The interrelationships of the metabolism of these materials, their transport in the circulatory system, and their disposition in different tissues are discussed in Chapter 6. Various control mechanisms and disorders of lipid and carbohydrate metabolism are also outlined in this chapter.

Chapter 7 discusses the reactions that are common to most amino acids and their relationship to carbohydrate and lipid metabolism. This discussion is followed by an outline of the metabolism of each amino acid (Chapter 8). The biosynthesis and degradation of nucleotides and porphyrins are then described in Chapters 9 and 10, respectively. Chapter 11 focuses on the general field of molecular biology, i.e., synthesis of nucleic acids and proteins. If one desires, the material covered in Chapter 11 may be inserted in the teaching sequence before the discussions of intermediary metabolism.

Blood, respiration, and electrolyte balance are the subjects of Chapters 12 and 13. Although some material introduced in those chapters overlaps topics that are treated in physiology courses, the chemical aspects are extremely important to medical students and are, therefore, covered in this text.

Chapter 14 is concerned with the structure and function of specialized tissues, and Chapter 15 deals with various aspects of nutrition. In addition to the basic importance of nutrition, discussions of this subject also serve to integrate various aspects of metabolism described in earlier chapters.

The Suggested Reading lists include articles that expand on the subject matter in each chapter, as well as papers involving clinical applications.

As a research science, the field of biochemistry has become so vast and diverse that its specific boundaries cannot always be defined. Therefore, in writing a book on this subject, one is faced with the prospect of preparing an encyclopedic compendium but still not including all the important topics. In this textbook I have attempted to restrict myself to material that can be covered within the amount of time assigned to biochemistry in most medical schools. It includes the core subject matter required for clinical medicine and for comprehension of the current literature. Conceivably, there will be some objections regarding subjects that were omitted. It is hoped there will not be too many.

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I. D.

Contents

1. Fundamentals

1.1. Scope of Biochemistry

The aim of biochemistry is to define the chemical or molecular properties of living entities. This involves characterization of the structural components of cells as well as elucidation of the chemical reactions that occur within the organism. Living systems are unique in several respects. Cells can utilize materials from the environment to maintain their functional capabilities and structural integrity. They also contain the machinery for self-repair and reproduction. Additionally, higher organisms undergo regulated growth and develop tissues with specialized functions. Biochemistry deals with the molecular structures and transformations that give rise to these distinctive manifestations of life.

The maintenance of life involves numerous dynamic systems of sequential and concurrent reactions. Most of the subject matter of biochemistry is concerned with these processes. Before this material can be considered, however, it is necessary to describe some of the structural features and chemical properties of the principal cellular and tissue components. This chapter deals with the basic concepts and structures required for understanding biochemistry. Details of some of the more complex molecular structures will be described in conjunction with discussions of their metabolism.

1.2. Chemistry of Cellular Components

A. WATER AND ELECTROLYTES

Water constitutes about 80% of the weight of animal tissues. It also serves as the medium in which tissue components are dissolved or suspended. Substances that dissociate in water to yield ions are called *electrolytes*. These include acids, bases, and salts. *Acids* are defined as electrolytes that release hydrogen ions, or protons. *Bases* are substances that combine with hydrogen ions. Acids are classified further according to their degree of ionization or dissociation: those that are completely dissociated (or ionized) are termed *strong acids*, and those that are partially dissociated (or ionized) are called *weak acids*.

When a weak acid is dissolved in water, the solution contains a mixture of undissociated acid, hydrogen ions, and anions. Thus, for such an acid

(HA), the dissociation can be expressed as a reversible reaction:*

$$HA \rightleftharpoons H^+ + A^-$$

The concentrations of these components when the process reaches equilibrium are governed by the equation:

$$K_a = \frac{[H^+][A^-]}{[HA]} \qquad (1\text{-}1)$$

In this relationship, the square brackets indicate that the concentrations of H^+, A^-, and HA are in moles per liter. The term K_a is the *ionization constant*, or the dissociation constant, of the acid, and it has a specific value for a given temperature. The ionization constant for acetic acid (CH_3COOH) at 25°C, for example, is 1.86×10^{-5}. From the relatively low value of this ionization constant, we know that only a very small fraction of acetic acid is dissociated.

Water itself dissociates to a minute but significant extent, and this process can also be defined by an equilibrium constant:

$$H_2O \rightleftharpoons H^+ + OH^-$$

$$K_a = \frac{[H^+][OH^-]}{[H_2O]} = 1.8 \times 10^{-16} \quad \text{at} \quad 25°C$$

Since the molar concentration of undissociated water (1000/18) is not affected significantly by the amount that is ionized, this equation may be written as:

$$K_a = \frac{[H^+][OH^-]}{55.5} = 1.8 \times 10^{-16}$$

A new constant, K_w, the *ion-product of water*, is thus obtained:

$$K_w = [H^+][OH^-] = 1 \times 10^{-14} \qquad (1\text{-}2)$$

In pure water, $[H^+]$ is equal to $[OH^-]$, and the concentrations of the hydrogen ions and of the hydroxyl ions are equal to 10^{-7} molar.

Upon addition of acid to water, the hydrogen-ion concentration is in-

* The dissociation of acids in aqueous solutions yields hydronium ions rather than protons:

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

However, since this does not affect the ensuing discussions or calculations, H^+ will be employed for simplification.

Table 1-1. Relationship Between $[H^+]$, $[OH^-]$, and pH

Molarity of H^+	Molarity of OH^-	pH
1.0	10^{-14}	0
0.01 (10^{-2})	10^{-12}	2
10^{-4}	10^{-10}	4
10^{-6}	10^{-8}	6
10^{-7}	10^{-7}	7
10^{-8}	10^{-6}	8
10^{-10}	10^{-4}	10
10^{-12}	10^{-2}	12

creased. However, since the ion-product of water is a constant, the hydroxyl-ion concentration must be decreased to a value less than 10^{-7} M. The hydrogen-ion concentration of an aqueous solution can be expressed in terms of pH. The *pH* is defined as the negative logarithm of the hydrogen-ion concentration:

$$pH = -\log[H^+] = \log\frac{1}{[H^+]} \tag{1-3}$$

Thus, for neutral solutions, when $[H^+]$ is 10^{-7}, the pH is 7. Acidic solutions have a hydrogen-ion concentration greater than 10^{-7}; hence, their pH is below 7. The relationship between pH and hydrogen-ion concentration is shown in Table 1-1.

The ionization constants of acids can also be expressed in a manner analogous to the pH scale. Thus, the pK_a of an acid is the negative logarithm of the ionization constant of the acid:

$$pK_a = -\log K_a = \log\frac{1}{K_a} \tag{1-4}$$

In this system, an acid with an ionization constant of 10^{-6} has a pK_a of 6, one with K_a of 10^{-3} has a pK_a of 3, and so on. From this consideration, it should be obvious that the magnitude of the pK_a is related inversely to the strength of the acid, i.e., a strong acid will have a low pK_a value and a weak acid a high one.

Problem 1 If the hydrogen-ion concentration of a solution is 3.2×10^{-5} moles per liter, what is the pH?

Answer
$$\begin{aligned} pH = -\log[H^+] &= -\log(3.2 \times 10^{-5}) \\ &= -\log 3.2 + 5 \\ &= -0.505 + 5 = 4.49 \end{aligned}$$