SODEMAN'S

PATHOLOGIC PHYSIOLOGY

MECHANISMS OF DISEASE

WILLIAM A. SODEMAN, JR., M.D., F.A.C.P.

THOMAS M. SODEMAN, M.D., F.C.A.P., F.A.C.P.

SEVENTH EDITION

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PREFACE

Thirty-five years ago the first edition of *Pathologic Physiology* was released. Truman was President, the Korean War began, Tennessee Williams published *The Rose Tattoo,* Charles Schultz began drawing Peanuts, and the Nobel Prize in Medicine went to Hench, Kendall, and Reichstein for their work on cortisone. The available medical texts focused on signs, symptoms, differential diagnosis, and therapy. The pathology texts focused on gross and microscopic characteristics. Each was an encyclopedic assemblage of known facts. *Pathologic Physiology* was to serve as a bridge between the technologically maturing basic sciences and the clinical encyclopedias. Since that time the science of medicine has, with increasing success, illuminated the art in a continuum, which this text has both participated in and recorded.

This edition strives to maintain this continuum. We are indebted to the contributors who made this edition possible. Its successes are theirs, while the defects are the editors' responsibility. We are grateful to Mr. John Hanley, the former president of the W. B. Saunders Company, for his continued support and are particularly indebted to Mr. John Dyson, our editor at the W. B. Saunders Company, for his patient counsel through two editions. Our families have been more than tolerant, for revision of a large text is a thief of family time and its publication a family triumph. Their patience and support should not go unrecognized. Dr. William A. Sodeman, Sr., as editor emeritus, has had an equally unsung, but essential, influence which we acknowledge.

Last, our special thanks to Mrs. Alison Goins, who catalogued each manuscript page, illustration, galley, and page proof.

William A. Sodeman, Jr., M.D.
Thomas Sodeman, M.D.

CONTENTS

Section I

SCIENTIFIC FOUNDATIONS

Metabolic Biochemistry

1

Thomas M. Sodeman

Characterization of the normal state and of the complex changes wrought by disease formulates the goal of biochemical research. Locked in the intricate interlinking pathways toward that goal are the sources of the structural elements of cells, their physiology, and their metabolic regulation. The protoplasm of the cell, contained by the cell wall and holding numerous organelles, consists of a mixture of water, minerals, and organic macromolecules. From these mixtures stem the physiologic characteristics of life. The study of these chemical mixtures in terms of their components, synthesis, storage, interaction, and degradation is the foundation of biochemistry, of which a clear understanding is essential. Most, if not all, of the pathologic processes to be discussed in this text involve either primary defects or secondary alterations in biochemical processes.

The biochemical processes of the body occur at a subcellular level and involve synthesis and catabolism of organic material, regulation of exchange of material, and conversion of chemical energy into usable forms. The chemical composition and ratio of compounds of cells are complex and vary among cell types. Oxygen, carbon, hydrogen, nitrogen, phosphorus, and sulfur contribute most of the structural mass of the cell and provide the elements for its intrinsic chemical physiology. Additional elements—for example, the metals sodium and magnesium—are essential to life. Of known elements, only 19 appear to be absolutely necessary. The task of unraveling the chemical nature of cell function and structure is formidable and is certain to lead to change in the understanding of even the most well-established biochemical mechanisms.

The intent of this chapter is to review biochemical principles that govern biologic processes. It is assumed that basic organic chemical concepts of covalent bonds, bond angles, and the spatial relationships between atoms are familiar. The chemical and physical properties of biochemical compounds in most situations reflect the nature of the functional groups.

TABLE 1–1 FUNCTIONAL GROUPS

Alcohol	R—CH_2—OH
Aldehyde	R—C(=O)—H
Ketone	R—C(=O)—R
Amines	R—NH_2
Carboxylic acid	R—COOH

Fundamental groups of alcohols, aldehydes, ketones, amines and carboxylic acids are encountered throughout carbohydrate, lipid, and protein metabolism (Table 1–1). Alcohols are hydroxylated hydrocarbons and alkyl derivatives of water. In polyhydric form they represent sugars and, as cyclic or ring forms, steroids. Aldehydes and ketones are composed of a carbonyl group (—C=O) with one or two alkyl groups attached. These organic configurations are also present in the polyhydric alcohols of sugars and other organic compounds. Amines are alkyl derivatives of ammonia and, as will be discussed, are essential elements in proteins. The carboxylic functional group consists of a carbonyl and hydroxyl group on the same atom. Functionally, they form weak acids.

These functional groups and their activity in oxidation, esterification, reduction, and other reaction modes provide many of the characteristics of organic compounds.

EQUILIBRIUM

Equilibrium is the process in which a forward reaction is equal to the reverse reaction. Although there is no net change in reactants and products, turnover is occurring on either side of the reaction through equal change. A better term for the equilibrium in biologic processes is "steady state." This implies that a concentration of a substance can be held constant. The equilibrium, or steady state, is nonproductive in the biologic system with regard to the thermodynamics of the system. No free energy is made available by the system. Biologic studies are more concerned with the initial state, routes, and rate of conversion in which energy changes occur. This is, essentially, the study of the kinetics of the reaction. Isolation of a single reaction in an in-vitro system permits an understanding of interaction of the components and the thermodynamics that occur. In-vivo study is more difficult because the components of a reaction, either reactants or products, are influenced by the complex pathways that yield or utilize them in the continuous biologic system. Under these circumstances, equilibrium becomes less important. The concentrations of many substances are held at rigid levels within the body. This steady state is controlled by reactions producing or utilizing the

components. Feedback mechanisms that control enzymes and enzyme substrate induction represent some of the controls that assure availability of reactants and energy necessary for biologic processes. All chemical reactions to some degree are reversible; however, in biochemical pathways, the products of a reaction are usually utilized in the next step. This forces the reaction one way, resulting in irreversibility and nonequilibrium of reaction.

The reaction kinetics and steady state can be expressed mathematically, and the influence of component concentrations, temperature, and pressure can be analyzed to determine the dynamics of the reaction and interacting systems. The environmental demands on in-vivo reactions are difficult to comprehend at the subcellular level. For this reason, reaction characteristics are more commonly thought of in terms of the changing concentrations of intermediates and the effects these may have in regulation of distant but indirectly coupled reactions. A pathologic state may be derived from or result in the inability of regulatory influences to compensate for changes in biochemical interactions. Changes in the immediate kinetics of a reaction or distal reactions can result in the development of new steady states with accumulations or depletions of pathway components. Such effects can be seen in storage diseases, the inability to maintain sufficient glucose levels, and the failure of normal trigger mechanisms to initiate the coagulation cascade in the absence or depression of key factors.

THERMODYNAMICS

Thermodynamics is the study of quantitative changes in energy as biologic reactions pass to equilibrium. It is not concerned with processes at equilibrium, as that is a terminal state in which free energy is zero. The energy produced within a system may take the form of thermal, osmotic, mechanical, chemical, or electrical energy. Transformation of energy from one form to another may be completed in biologic systems.

In the biologic system, energy is primarily obtained by chemical linkage to oxidative reactions. The energy of a system can be considered in two parts. Entropic energy is that energy required internally by the system to maintain its molecular configuration. Enthalpic energy is the energy available externally for work (free energy). In the conversion of glucose in the presence of oxygen to yield carbon dioxide and water, 673,000 cal/mole of free energy are produced that may be transferred by chemical means to reactions requiring energy. In a reaction process, some energy is lost as heat and may not be utilized in chemical reactions.

The difference in energy states of a substrate versus the product is a measure of the extent to which a reaction will proceed. Exergonic reactions (i.e., those that yield energy) may proceed spontaneously. Whether an exergonic reaction will spontaneously occur depends on the energy of activation of the reactants. Each molecule has an average level of energy that maintains its molecular configuration. For a reaction to occur spontaneously, a critical energy level or barrier must be reached so that bonding or exchange may occur between elements. When two atomic orbits merge, a more stable configuration occurs that will require less energy. Enzymes, through the formation of an enzyme-reactant complex, reduce the energy of activation and thus accelerate a reaction. Endergonic reactions, however, require large amounts of energy to proceed.

The energy requirement of reactions plays an important role in determining the availability of products and, therefore, in controlling subsequent reactions. In biologic systems, there is both compartmentalization and linkage of reactions to ensure the efficient availability of reaction products and energy necessary to activate, or drive, a reaction. Energy is usually supplied by chemical means and under strictly controlled mechanisms. The energy released in a reaction may contribute to further activation of the initial substrate or may provide energy for closely associated reactions. The product of the reaction may be sufficiently activated to reduce the energy requirements for the next step.

In the metabolic process, the mechanism of free energy transfer relies heavily on intermediate energy absorbers, for example, the nucleotide *adenosine triphosphate (ATP)*. The advantage of energy absorbers lies in their universal activity, which permits energy transfer in a wide variety of reactions. Throughout the biochemical pathways, ATP has an essential role in providing energy to endergonic processes. ATP is composed of a purine, a ribose, and three phosphate groups. It carries a central position in relation to other organophosphates in its ability to yield and accept high-energy phosphate. ATP has the stability necessary to function as an energy storehouse. The source for the high-energy bond is provided in the respiratory chain oxidation in mitochondria, in the catabolism of substrates (as in the Embden-Meyerhof pathway of glycolysis), and in high-energy storage depots, such as creatine phosphate in muscle. Upon hydrolysis ATP liberates 8.8 cal/mole of free energy. Three factors are involved in this release: (1) a change in resonance energy, (2) ionization-released energy, and (3) relief of electrostatic repulses. The prime reservoir of energy is in the body's macromolecules, which, through metabolic processes, provide high-energy phosphates. Lipids are particularly effective in this process and provide the added advantage of osmotic stability in the cell.

TABLE 1–2 ENZYME CLASSIFICATION

Oxidoreductases
Transferases
Hydrolases
Lyases
Isomerases
Ligases

ENZYMES

Enzymes are protein biocatalysts that reduce the necessary chemical energy for activation of a reaction. They are not consumed, and, therefore, only small quantities are required. In contrast to catalysts, they tend to be reaction-specific. Six functional classes of enzymes have been established and are outlined in Table 1–2.

Almost all biochemical reactions are enzyme-catalyzed. Many enzymes require nonprotein cofactors or coenzymes in their reactions. Coenzymes are important in transferring groups between reactants and, unlike enzymes, are not re-formed in the reaction. B-vitamins are a common structural part of coenzymes.

The three-dimensional structure of enzymes plays an important role in their function and stability. An enzyme, a relatively large molecule in comparison with the substrate, combines with a substrate, altering the enzyme configuration to bring functional or catalytic groups into place.

Enzyme aggregates resulting from association of subunits form a series of multiple molecular forms with similar enzymatic activity but structural differences. One form may dominate over others in a tissue. Clinically, multiple molecular forms are expressed in isoenzymes of dehydrogenases, phosphatases, transaminases, and proteolytic enzymes.

Measurements of circulating enzymes have become routine in the practice of medicine as an indicator of cellular damage or genetic defects. Because of the small quantities present, enzymes are measured by their activity. This has given rise to a number of arbitrary units. Many of the enzymes in plasma have no physiologic function in the blood but represent release from cells and normal cellular degradation. Other enzymes exist in proenzyme forms, for example, coagulation factors and lipoprotein lipase, which, upon activation, play critical roles in the body's homeostatic processes.

METABOLIC REGULATION

The regulation of metabolic processes is particularly controlled by enzyme activity. Control may be based on the amount of enzyme synthesized, enzyme inhibition, activation, degradation, and covalent modification of protein structure. Regulatory mechanisms also include the availability of substrates or cofactors, transport systems, and compartmentalization of reactions. Compartmentalization permits localization of reaction and independence from potentially influencing processes. It provides an orderly sequence for controlled enzymatic processes linking reactants and assures energy transfer. Compartmentalization does pose problems when reactants must be moved from one compartment to another. Translocation may require a converting process to change a metabolite to a permeable state or form for passage across a membrane and then similar processes for reconversion. Such a process would require two forms of enzymes physically separated.

Metabolic processes tend to maintain a steady state within cells despite short-term changes within the environment. Chemical processes must occur at the right time and rate to meet the coordinated processes in a cell. Enzymes play a key role in this regulation. Many factors are involved in enzyme control. Among those not yet mentioned is control of synthesis by substrate induction, by product repression or feedback repression, by regulated enzyme degradation, and by hormonal and dietary influences. Secondary enzyme activation provides one method of regulation. In this process, a proenzyme is converted to an active form by a second enzyme. This provides a mechanism for concentrating an enzyme at an appropriate site ready for its physiologic demand. Examples can be seen in the coagulation process and in digestive enzymes. Knowledge of these regulatory processes is limited, but they are important in understanding the pathologic physiology of disease and the possible approaches to therapy. The ability to control enzymes may in the future open new avenues for therapeutics.

BIOLOGIC OXIDATION

Free energy in the cell ultimately lies in the oxidative reaction. In biologic systems, this mostly involves the transfer of hydrogen and formation of water. The loss of electrons is known as *chemical oxidation;* a gain in electrons is called *reduction.* The energy released in biologic oxidation may be chemically conserved in high-energy phosphates. This process of coupling of oxidation to high-energy carriers is referred to as *oxidative phosphorylation.* When a coenzyme (e.g., ATP or NAD) is reduced, a mechanism for reoxidation and regeneration, the respiratory chain, is available in the cell. This system provides an assemblage of enzymes in coupled reactions that can transport electrons and provide high-energy bonds. It is compartmentalized in the mitochondria. These high-energy bonds provide a mechanism for storing energy formed in biologic oxidation.

The energy from oxidation of fatty acids, amino acids, and carbohydrates is made available

in the mitochondria through the respiratory chain. Numerous enzymes are involved in the oxidative process. Among these are oxidases, aerobic and anaerobic dehydrogenases, hydroperoxidases, and oxygenases. The respiratory chain transports reducing equivalents, hydrogen or electrons, for reaction with oxygen to form water. The order is arranged sequentially, with increasing tendency for free-energy exchange or redox potential. The main mitochondrial chain (Fig. 1–1) is initiated by a NAD-linked dehydrogenase system and proceeds through flavoprotein and cytochrome systems to molecular oxygen. Metabolic pathways feed reducing equivalents (NAD or $FADH_2$) into the system. The terminal cytochrome system possesses many elements, starting with coenzyme Q, which links flavoprotein to cytochrome, and extending through cytochromes C_1, C, A, and A_3. The respiratory chain provides three sites at which energy change is sufficient to permit coupling with ADP to form ATP. Each mole of NADH that enters the chain produces three moles of high-energy phosphate, and each mole of $FADH_2$ yields two moles of this high-energy product. The control of the respiratory process depends on the availability of substrate, ADP, and oxygen.

High-energy bonds are not produced solely in the respiratory chain. Substrate phosphorylation involving the production of high-energy bonds during metabolic oxidation sequences of glucose, lipids, and amino acids will be reviewed later in this chapter during specific discussions. Mechanisms are available to transfer to the mitochondria the NADH produced by glycolysis in the cytosol with substrate-pair translocation systems.

The impact of both mitochondrial and substrate phosphorylation is provision of energy. With oxidation of glucose in the glycolytic process and citric acid cycle, six high-energy phosphate bonds are produced and two are used. These represent phosphorylation at the substrate level. Linkage with the respiratory chain, with reoxidation of reduced coenzymes, yields 34 high-energy bonds per cycle of glucose. Through these processes it is possible to account for 46 per cent of the free energy of glucose metabolism. Under anaerobic conditions, two high-energy phosphate bonds are produced.

CARBOHYDRATE METABOLISM

CARBOHYDRATE STRUCTURE

Carbohydrates may be defined as aldehyde or ketone derivatives or polyhydric alcohols and are divided into four major groups. Monosaccharides, including trioses, tetroses, pentoses, hexoses, and heptoses, are physiologically important carbohydrates. The hexose sugars glucose, fructose, galactose, and mannose are common dietary components and provide a major energy source. D-ribose, a pentose sugar, is an essential component of nucleic acid. Disaccharides such as sucrose, maltose, and lactose are composed of two monosaccharides united by a glycosidic linkage and are common elements of the daily diet. Polysaccharides occur in the forms of starches, glycogen, and dextrins. Polysaccharides in the form of glycosaminoglycans (mucopolysaccharides) and glycoproteins (mucoproteins) are important structural components of the body. Glycoproteins are elements of blood groups and certain hormones.

GLYCOLYSIS

This process, the Embden-Meyerhof pathway, is a complex sequence in which glucose and other carbohydrates are metabolized to pyruvate or lactate. It is an extramitochondrial function, occurring in the cytosols of cells. A schematic outline of the glycolytic process is included in Figure 1–2. In step 1, glucose is phosphorylated to glucose 6-phosphate by hexokinase or, in the liver, by glucokinase. The reaction is irreversible and is associated with an extensive heat loss. Glucose 6-phosphate is a major pivotal compound in carbohydrate metabolism. Processes involving synthesis and degradation of glycogen, from either glucose or citric acid components, and entry into the hexose monophosphate shunt involve this critical component. Step 3 involves an irreversible phosphorylation reaction that is followed by a splitting of the hexose molecule into two triose phosphate molecules. These trioses are interconvertible. The glycolysis pathway continues with oxidation of glyceraldehyde 3-phosphate and the

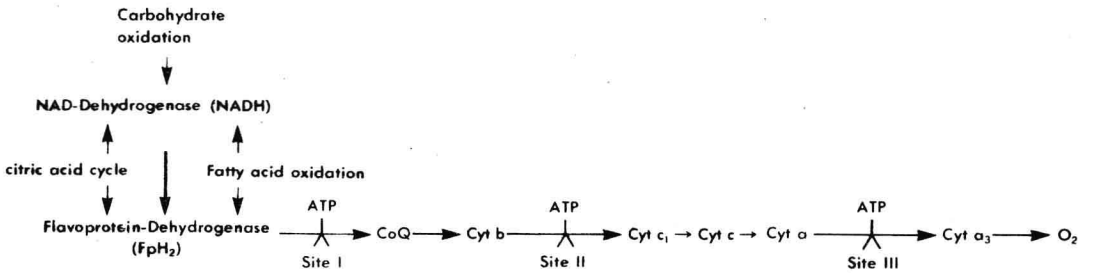

Figure 1–1 Mitochondrial respiratory chain for transport of reducing equivalents.