fifth edition

PATHOLOGIC PHYSIOLOGY

MECHANISMS OF DISEASE

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PREFACE TO THE FIFTH EDITION

This edition of *Pathologic Physiology*, the fifth, represents a complete rewriting of the text. This restructuring coincides with an extensive turnover in the list of contributors. It is in the spirit of the dramatic changes and staggering advances in medical science that the editors accepted the fact that many of the contributors who had remained with the book since the First Edition in 1950 should now give way to a younger group. Thus, the text has undergone a complete rewriting and reorientation of approach, especially in fields such as immunology, genetics, and molecular biology. Importantly, these new contributors have joined with us in capturing the concept presented in the First Edition, the goal of the text being to present and interpret the clinical picture of disease and the genesis of symptoms and signs as physiologic dysfunctions.

The W. B. Saunders Company and its staff have been more than patient and cooperative as the work has progressed. We are grateful and thank them. The Editors also wish to thank their wives, Marjorie Christian Sodeman and Mary Agnes Sodeman, for their support and tolerance as the work on the text and the reading of manuscripts progressed.

WILLIAM A. SODEMAN, JR., M.D.
WILLIAM A. SODEMAN, SR., M.D.

PREFACE TO THE FIRST EDITION

This volume, a collaborative effort by 25 authors, approaches problems of disease in the field of internal medicine from the standpoint of disturbed physiology. Unlike the usual text, which is devoted to discussions of etiology, pathology, symptoms and treatment, this work analyzes symptoms and signs and the mechanisms of their development. The monograph is not intended to take the place of standard texts on physiology or textbooks of medicine. It does not aim at the completeness of either, but does try to bridge the gap between them by presenting a clinical picture of disease seen as physiologic dysfunction. An attempt is made to promote understanding of how and why symptoms appear, so that the student or physician may have a reasonable explanation for the findings he elicits. Neurologic problems are considered only as they are related to the various disease groups. The same is true of metabolic disturbances and disorders of acid-base balance.

The Editor thanks the contributors for their ready cooperation in covering certain aspects of disease in which presentation of material is at times most difficult. He thanks the Saunders Company for their help and guidance, and also Miss Brent S. Robertson for her long hours of hard work and patience in reading and checking manuscripts.

WILLIAM A. SODEMAN, M.D.

CONTENTS

SECTION I

SCIENTIFIC FOUNDATIONS

CHAPTER 1

METABOLIC BIOCHEMISTRY

MILTON TOPOREK
PAUL H. MAURER

The ultimate goal of metabolic biochemistry or intermediary metabolism is to determine all the reactions undergone by the various molecules which enter the body, by normal or other means, from the time they enter until they or their derivatives leave the body. Although much has been accomplished in this field in the last 25 years since radioactive isotopes became available, much more remains to be learned. However, much of the information available has already provided the medical profession with many useful procedures for diagnosis and therapy based on objective criteria of clinical laboratory determinations which, when compared to normal metabolic patterns, can indicate the health status of the patient. It is therefore the purpose of this chapter to review, in limited form, the major metabolic pathways, with some examples of abnormal changes correlated with clinical conditions.

CARBOHYDRATE METABOLISM

A general summary of carbohydrate metabolism is presented in Figure 1-1. This diagram shows the possible uses of glucose in the liver and muscle to be as follows:

Liver	*Muscle*
Storage as glycogen	Storage as glycogen
Oxidation for energy purposes	Oxidation for energy purposes
Conversion to other metabolites:	
Fat	
Amino Acids	
Other carbohydrates	

USES OF GLUCOSE

Storage as Glycogen (Glycogenesis)

Glucose not used for other purposes as listed below may be converted to glycogen and deposited in the liver or muscle tissues in relatively small and limited amounts. Remaining available glucose is disposed of in pathways discussed below.

Oxidation for Energy Purposes

Complete oxidation of glucose to CO_2 and H_2O can furnish energy for the body as required. This is accomplished in two stages: (1) glycolysis (Embden-Meyerhof pathway), taking glucose to the 3-carbon pyruvate or lactate point; and (2) the tricarboxylic acid cycle (Krebs, or citric acid cycle), which converts the 3-carbon pyruvate to CO_2 and H_2O. Under anaerobic conditions, as in muscle after prolonged or strenuous exercise, glycolysis produces lactic acid, a reduction product of pyruvic acid. By way of the blood, the lactic acid reaches the liver for reprocessing or further oxidation. Under aerobic conditions, lactate is converted back to pyruvate, and the oxidation of pyruvate is completed in liver and muscle by way of the tricarboxylic acid cycle.

Liver and adipose tissue can also degrade glucose by the pentose phosphate pathway (pentose shunt), a pathway which is relatively unimportant in skeletal muscle.

Conversion to Other Metabolites

Fat. Excess glucose may be converted to fatty acids and glycerol and deposited as triglycerides

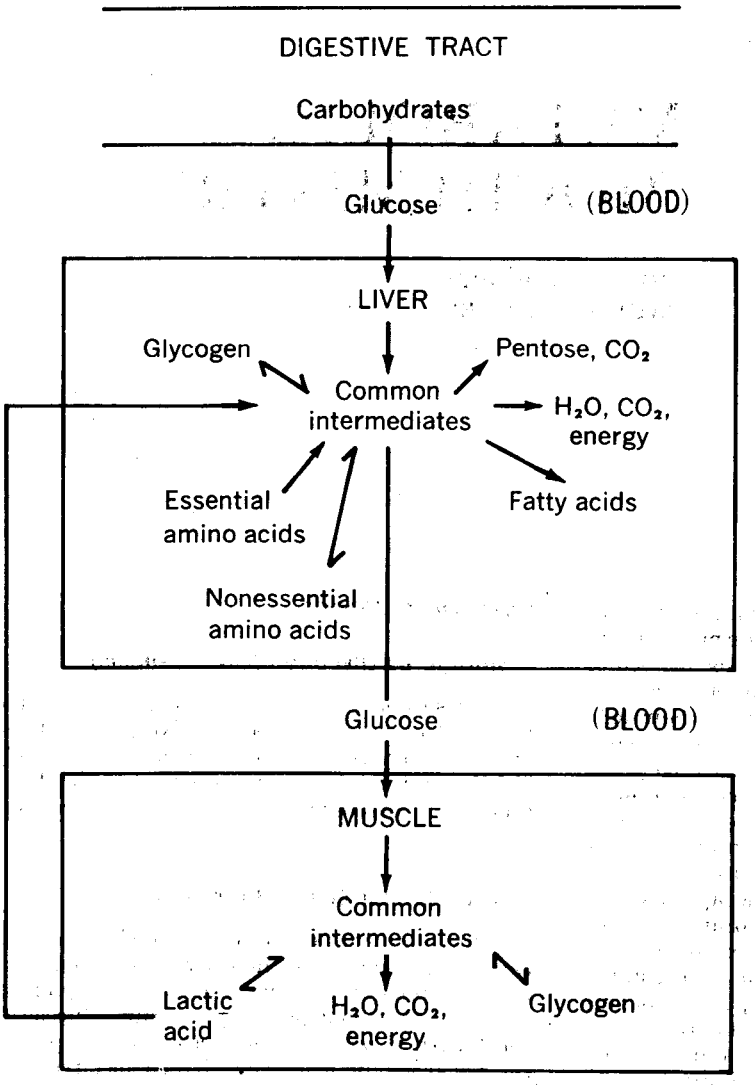

Figure 1–1 General summary of carbohydrate metabolism. (From Toporek: Basic Chemistry of Life, 1968. Courtesy of Appleton-Century-Crofts, Inc.)

in adipose tissue, a process which, to the sorrow of many, is unlimited except by restrictions on intake of carbohydrates. As will be noted later, there are certain features common to the metabolic pathways of glucose and the fatty acids, but the conversion of glucose to fatty acids is irreversible on the basis of energy accounting, i.e., it would require a net expenditure of energy to convert fatty acids to glucose.

Amino Acids. The carbon skeletons of the nonessential amino acids may be derived from glucose in a reversible process. The essential amino acids can also contribute to the carbon skeleton of glucose, but the reverse is not possible in this case.

Other Carbohydrates. Some glucose is used for the synthesis of other important sugars such as ribose and deoxyribose, components of the nucleic acids, and galactose, a component of cerebrosides, gangliosides, and glycolipids.

OXIDATION OF GLUCOSE

The complete oxidation of glucose is divided into two major phases: (1) glycolysis (Embden-Meyerhof pathway), an anaerobic pathway (does not require oxygen but can occur in its presence) which includes glycogenesis and glycogenolysis, interconversions of galactose, fructose, and glucose, and ends with the production of pyruvate (under aerobic conditions) or lactate (under

anaerobic conditions) and a small amount of energy; and (2) the tricarboxylic acid cycle (Krebs cycle, citric acid cycle), an aerobic pathway which completes the oxidation of glucose to H_2O and CO_2, with the production of a much larger amount of energy.

Glycolysis

The metabolic reactions of glycolysis are outlined in Figure 1-2. The solid line arrows indicate the reactions in the direction of glycogenesis and the anaerobic metabolism of glucose to the pyruvate or lactate stage (glycolysis). A single-headed arrow (⟶) indicates a reaction which is irreversible as written. A double-headed arrow (⟷) indicates a reversible reaction. A broken arrow (⇢) indicates a reaction which has the effect of reversing an irreversible reaction by a reaction which is different from the forward reaction. Thus, there is complete *biologic reversibility*, but it occurs at the price of a loss of energy, i.e., since the reactions in the direction of glucose to pyruvate generate energy, the reactions in reverse must require an input of energy. The individual reactions are listed below by numbers corresponding to those in Figure 1-2.

Reactions to Glycolysis

Reaction 1 – Glucose is converted to glucose-6-phosphate (G-6-P) under the influence of hexokinase and adenosine triphosphate (ATP). This is an irreversible reaction because a high-energy phosphate group in ATP is used to form a low-energy ester phosphate bond in G-6-P.

Reaction 2 – G-6-P is converted back to glucose in the liver by glucose-6-phosphatase, not by reversal of reaction 1. Muscle does not have this phosphatase.

Reaction 3 – G-6-P is converted to glucose-1-phosphate (G-1-P) by phosphoglucomutase.

Reaction 4 – This summarizes a series of reactions resulting in the formation of glycogen, as follows:

$$\text{G-1-P} + \text{UTP} \xrightarrow{\text{Pyrophosphorylase}} \text{UDPG} + \text{pyrophosphate}$$

$$\text{UDPG} \xrightarrow[\text{Branching enzyme}]{\text{Glycogen synthetase}} \text{Glycogen} + \text{UDP}$$

$$\text{UDP} + \text{ATP} \xrightarrow{\text{Phosphokinase}} \text{UTP} + \text{ADP}$$

UTP = uridine triphosphate
UDP = uridine diphosphate
UDPG = uridine diphosphate-glucose
Glycogen synthetase: forms 1,4-linkages between glucose moieties, making straight chains
Branching enzyme: forms 1,6-linkages between glucose moieties, making branches between straight chains

Reaction 5 – Glycogen is broken down to G-1-P in the presence of a debranching enzyme (breaks 1,6-linkages) and phosphorylase (breaks 1,4-linkages). Reaction 3 converts G-1-P to G-6-P. If required for blood sugar, G-6-P can be converted back to glucose by reaction 2.

Reaction 6 – G-6-P is converted to fructose-6-phosphate (F-6-P) in a reversible reaction catalyzed by phosphohexose isomerase.

Reaction 7 – F-6-P is phosphorylated to fructose-1,6-diphosphate (F-1,6-P_2) in an irreversible kinase reaction in the presence of phosphofructokinase.

Reaction 8 – Reaction 7 can be biologically reversed by way of a phosphatase reaction.

Reaction 9 – F-1,6-P_2 is split into two triose phosphate molecules, glyceraldehyde-3-phosphate (glycerald-3-P) and dihydroxyacetone phosphate [$(OH)_2$-acetone-P], in a reversible reaction catalyzed by fructose diphosphate aldolase.

Reaction 10 – The triose phosphates, glycerald-3-P and $(OH)_2$-acetone-P, are in equilibrium with each other in the presence of an isomerase. Thus, both halves of the original glucose molecule are available for subsequent reactions.

Reaction 11 – The conversion of glycerald-3-P to 1,3-diphosphoglycerate (1,3-P_2-glycerate) is catalyzed by glycerald-3-P-dehydrogenase in a reversible reaction. The carboxyl phosphate bond is a high-energy bond, the energy coming from the oxidation of the aldehyde to a carboxyl group.

Reaction 12 – In the conversion of 1,3-P_2-glycerate to 3-phosphoglycerate (3-P-glycerate) under the influence of phosphoglycerate kinase, the energy of the carboxyl phosphate bond is captured in the concomitant conversion of ADP to ATP.

Reaction 13 – 3-P-glycerate forms 2-P-glycerate in the presence of phosphoglyceromutase in a reversible reaction.

Reaction 14 – The dehydration of 2-P-glycerate to phosphoenolpyruvate (P-E-pyr) with the production of a high-energy phosphate bond is catalyzed by enolase.

Reaction 15 – The high energy in P-E-pyr is captured in the formation of ATP from ADP in an irreversible reaction in the presence of pyruvate kinase, resulting in the formation of pyruvate.

Reaction 16 – Under anaerobic conditions, pyruvate is converted to lactate in the presence of lactate dehydrogenase in a reaction which reverses itself under aerobic conditions. This concludes the glycolysis reactions.

Reaction 17 – In the liver, reaction 15 can be

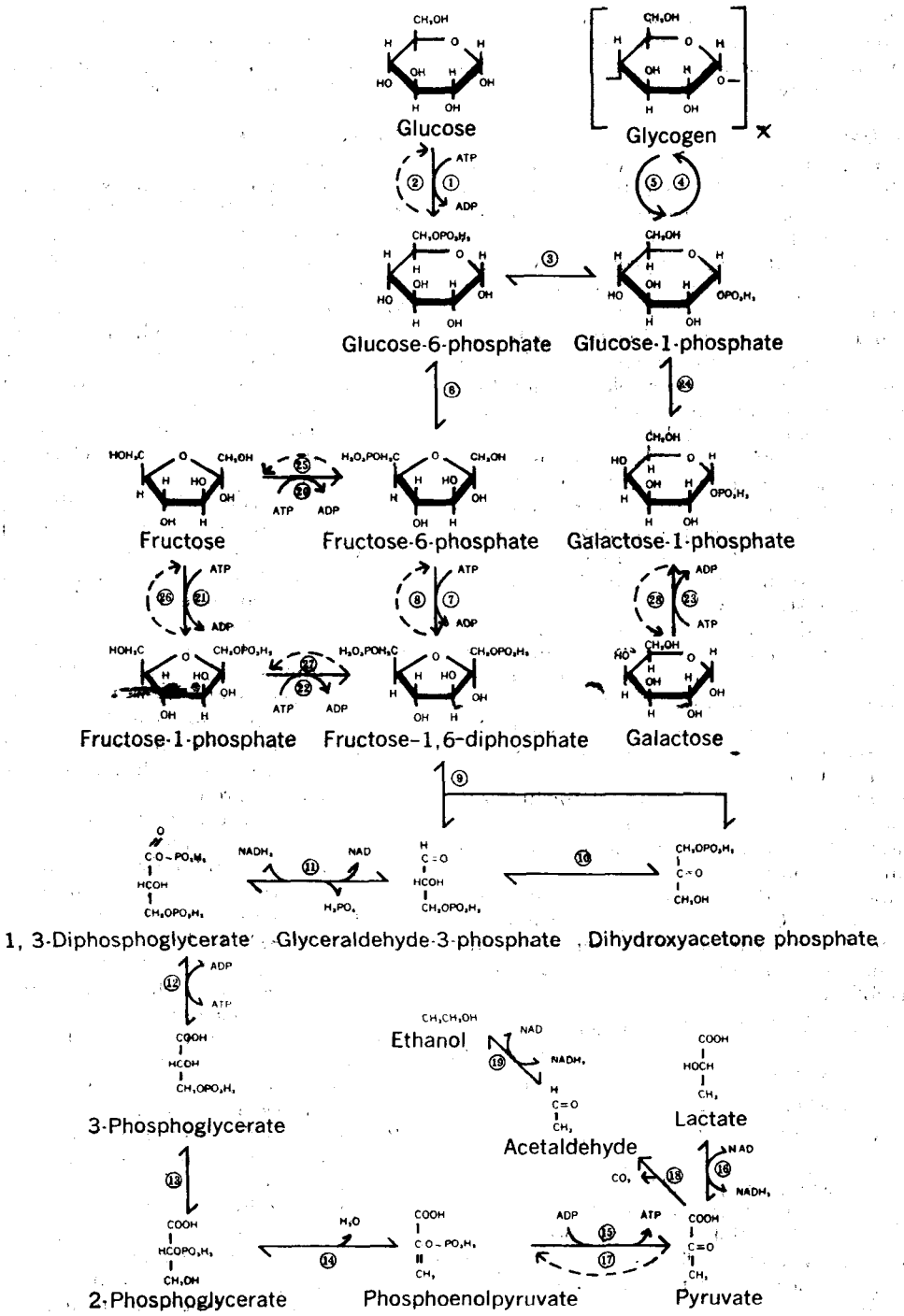

Figure 1–2 Anaerobic metabolism of glucose (glycolysis) and related hexoses. (~ = high energy bond.) (From Toporek: Basic Chemistry of Life, 1968. Courtesy of Appleton-Century-Crofts, Inc.)