EDITORIAL

INTERRELATIONSHIP OF GLUCOSE AND LIPID METABOLISM

Since 1948 evidence has accumulated which indicates that the synthesis of fatty acid requires the concomitant utilization of glucose. Within the past two years additional information about the relationship between glucose metabolism and fatty acid synthesis has given a better understanding of the defect in lipid metabolism in the diabetic animal. It has long been recognized that the oxidation of fatty acids is accelerated in the uncontrolled diabetic. This resulted in the investigative emphasis on ketone formation as the major defect in lipid metabolism of the diabetic patient. It was not until the work of Drury[1] and of Stetten and Boxer[2] that a marked depression in fatty acid synthesis was demonstrated. Thus, when normal glucose utilization is restricted, as in diabetes, the synthesis of fatty acids is depressed while oxidation continues unchecked.

The classic work of Lynen[3] has elucidated the steps by which long-chain fatty acids are oxidized in a stepwise fashion to form acetyl Coenzyme-A (acetyl Co-A). This so-called fatty acid cycle includes two oxido-reductive reactions which require flavin adenine dinucleotide (FAD) and diphosphopyridine nucleotide (DPN) as cofactors. It was believed that the synthesis of fatty acids resulted from the reversal of the steps of oxidation and that these same two cofactors were involved. Shaw, Dituri and Gurin[4] demonstrated that the failure of cell-free systems prepared from the livers of alloxan diabetic rats to synthesize fatty acids was due to an inability to convert acetyl Co-A to butyryl Co-A. Their work localized a possible block in fatty acid synthesis in the diabetic to the reaction in which crotonyl Coenzyme-A is converted to butyryl Coenzyme-A. Langdon[5] demonstrated that in the synthesis of fatty acids from acetate, the reduction of crotonyl Coenzyme-A to form butyryl Coenzyme-A requires reduced triphosphopyridine nucleotide (TPNH). Thus, when this reaction proceeds in the direction of the synthesis of fatty acids it requires TPNH but when this same reaction proceeds in the oxidative direction it requires FAD. This has led to the conclusion that the pathways of fatty acid synthesis and oxidation may be different.

The demonstration that fatty acid synthesis requires TPNH has aroused interest in TPNH production and its relationship to lipogenesis. Two pathways for glucose utilization exist in liver and adipose tissue, major sites of fatty acid synthesis. One pathway is the Embden-Meyerhof pathway which produces DPNH but no TPNH. The other is the phosphogluconate oxidative pathway (PGO) in which the first two reactions produce TPNH. The following evidence has led to the conclusion that the utilization of glucose via the PGO pathway is important in fatty acid synthesis. Felts et al.[6] first noted a decreased glucose utilization via the PGO pathway in liver slices prepared from alloxan diabetic rats. Siperstein[7] demonstrated in liver homogenates that the stimulation of glucose metabolism via the Embden-Meyerhof pathway by the addition of DPN to the medium results in little or no increase in fatty acid synthesis. However, when glucose utilization via the PGO pathway is stimulated by the addition of TPN, there is a marked increase in fatty acid synthesis. He also showed that the defect in fatty acid synthesis in homogenates prepared from the livers of alloxan diabetic rats can be corrected by the stimulation of glucose utilization via the PGO pathway.

Milstein[8] has also observed a decrease in the utilization of glucose via the PGO pathway as estimated from carbon dioxide production by the epididymal fat pad obtained from the alloxan diabetic rat. Winegrad and Renold[9,10] studied the relationship between glucose metabolism and fatty acid synthesis in the epididymal fat pad of the normal rat. The addition of insulin in vitro results in an increased synthesis of fatty acids from glucose at the same time that there is an increased utilization of glucose via both the Embden-Meyerhof and PGO pathways. They also showed that the stimulation of fatty acid synthesis from other precursors of acetyl Co-A (acetate and pyruvate) which results from the addition of insulin in vitro, is dependent upon the concomitant utilization of glucose. Insulin added in vitro to the fat pads of alloxan diabetic rats will correct the defect in fatty acid synthesis. Winegrad, Shaw and Renold[11] employed the in vitro effect of growth hormone in the epididymal fat pad to elucidate the relationship between a specific pathway of glucose utilization and fatty acid synthesis. When growth hormone is added in vitro to this tissue, there is an increased oxidation of glucose to carbon dioxide but no increase in fatty acid synthesis. Studies with differentially labeled glucose (glucose-1-C^{14} and glucose-6-C^{14}) indicate that growth hormone produces a marked decrease in the utilization of glucose via the PGO pathway. The increase in the carbon dioxide formation from glu-

cose makes it apparent that there is adequate formation of acetyl Co-A under these circumstances; thus a deficiency of acetyl Co-A cannot be used to explain the depressed fatty acid synthesis.

Thus, the present evidence suggests that fatty acid synthesis is dependent upon normal glucose metabolism for the production of three substances: (a) acetyl Co-A, the structural unit from which fatty acid synthesis proceeds; (b) reduced diphosphopyridine nucleotide (DPNH) which is required for most of the reductive steps in the synthesis of fatty acids; and (c) TPNH which is necessary for the reduction of crotonyl Co-A to butyryl Co-A. In diabetes, the abundant production of acetoacetic and β-hydroxybutyric acids indicates no deficiency of acetyl Co-A formation or the production of DPNH. The defect in fatty acid synthesis in the diabetic can best be explained in the following manner. Because of the insulin deficiency, glucose available for metabolism within the cell is greatly reduced and the fraction of glucose utilized via the PGO pathway is particularly depressed. Under these circumstances fatty acid synthesis from acetyl Co-A is limited by the availability of TPNH formed in the PGO pathway. It would appear that the synthesis of fatty acid is regulated by glucose utilization via the PGO pathway.

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WALTER N. SHAW, PH.D.
ALBERT I. WINEGRAD, M.D.
Philadelphia

BOOK REVIEWS

THE CLINICAL APPLICATION OF HORMONE ASSAY. *By John A. Loraine, M.B., Ph.D., M.R.C.P.* (Ed.). *$7.00, pp. 368, The Williams & Wilkins Co., Baltimore, 1958.*

This is an exceptionally valuable book. It is indeed a major undertaking to review and winnow the extensive literature pertaining to hormone assays. However, the author brings to the subject unique qualifications—a broad personal experience in hormone research, sound critical judgment and a most pleasing clarity of presentation.

In the initial chapter the general principles of hormone assay are discussed—criteria of reliability, practicability, factors entering into bio-assays and calculation of errors in bio-assays. Subsequent chapters are devoted to the individual hormones. In each chapter the several bio-assay and/or chemical assay procedures that have been published are outlined and discussed critically. In addition, the author reviews the results of assays made under normal and abnormal circumstances, a feature of particular interest to the clinician. The greatest amount of space is devoted to the gonadotropins, estrogens and progesterone, reflecting, no doubt, the author's particular interests. The discussions of the other hormones are less extensive; however, with the single exception of the chapter on insulin, which is brief (only seven pages) and less complete than one might wish, these other chapters are highly satisfactory.

In summary, this book is a most welcome addition to the book shelf, not only of the investigator interested in hormone research, but of the clinician as well.

THE NURSE AND THE DIABETIC. *By Joan B. Walker, M.D., M.R.C.S., L.R.C.P. $1.47 net (by post $1.57), pp. 128, fourteen photographs and a number of line drawings, Iliffe & Sons Ltd., London, 1958.*

This is a very well organized discussion of the management of the diabetic, with particular emphasis on the role played by the nurse. It seems quite appropriate that the discussion includes an explanation of the nature of diabetes, a description of the more routine laboratory tests, and a review of the diets and their importance. As nurses are now getting better technical training and are becoming responsible for simple laboratory tests, it is indeed fitting that this should have been discussed.

The management of the outpatient diabetic clinic is excellent and brings out the importance of having the patients seen by the staffs of other departments, such as the Eye Department, the Dental Department and the Chiropodist. A chapter also covers the diabetic emergencies that bring the patient into the hospital, and a discussion of the diabetic in the home. There is ample information on directions for taking insulin and a short discussion of the new sulfonylurea hypoglycemic drugs. This book can be recommended to nurses and to diabetic patients.