Brief Notes and Comments

L-xylulose Concentrations in Sera of Diabetic Patients

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L-xylulose is a non-phosphorylated intermediate of the glucuronic acid pathway of glucose metabolism. Burns,[1] Strominger,[2] Hollmann,[3] and Touster[4] have reviewed the reactions of this newly recognized cycle which was first proposed as the result of studies of the biosynthesis of L-ascorbic acid and L-xylulose from glucose. Interest in L-xylulose metabolism in man has largely centered about the fact that patients with hereditary essential pentosuria excrete large and relatively constant amounts of L-xylulose in the urine. Hiatt[5,6] has provided evidence that the missing or inhibited enzyme in patients with hereditary pentosuria is NADP-xylitol dehydrogenase which catalyzes the reduction of L-xylulose to xylitol, and he and his co-workers have demonstrated that the fasting serum concentration of L-xylulose is elevated in these patients.[6]

Recent studies in this laboratory have suggested that the relative contribution of the glucuronic acid pathway to total CO_2 production from glucose is greater in adipose tissue from starved or alloxan diabetic rats than in tissue from normal fed animals.[7] The relative contribution of the glucuronic acid pathway to total CO_2 production from glucose appears to be increased by growth hormone in vitro or in vivo in adipose tissue from normal fed animals and to be decreased when insulin is added to tissue from starved rats.[7] These observations led us to speculate that the utilization of glucose by way of the glucuronic acid pathway may be unimpaired or increased in the diabetic state.

Interest in the possibility that unimpaired or increased glucose utilization by way of the glucuronic acid pathway may occur in human diabetics derives in part from the relationship between the early steps of the glucuronic acid pathway and those postulated for the synthesis of various polysaccharides from glucose.[8,9] Increased glucose utilization by pathways which normally account for only a small fraction of total glucose utilization might help to clarify the paradox that in diabetes mellitus, which is characterized by impaired glucose utilization in its clinically recognizable form, the specific vascular lesions contain increased quantities of glycoprotein whose polysaccharide moiety has presumably been synthesized from glucose.[10]

Since L-xylulose is a non-phosphorylated sugar, it was thought that increased glucose utilization by way of the glucuronic acid pathway might be reflected in an elevated serum concentration of L-xylulose even in the absence of a block in its further utilization such as that present in essential pentosuria. The fasting serum concentration of L-xylulose has been measured in an initial series of thirty-nine diabetic and thirty-six nondiabetic patients, using NADP-xylitol dehydrogenase prepared from acetone powder of guinea pig liver by the fractionation procedure of Hickman and Ashwell.[11]

Blood samples were obtained from hospital patients after an overnight fast and before the administration of the morning dose of insulin or arylsulfonylurea, if the patient was receiving such therapy. Since essential pentosuria has been described almost exclusively in Jews,[5] patients with Jewish ancestry were excluded from the study. Dr. Gilbert Ashwell generously provided samples of chemically synthesized L-xylulose and D-xylulose to check the enzyme fractionation. The ammonium sulfate fraction used gave no significant reaction with D-xylulose, D-glucuronolactone, or D-glucuronic acid. The zero values referred to herein do not exclude the presence of L-xylulose in the samples tested, for the lower limit of the sensitivity of this method under the conditions employed in these studies was of the order of 0.05 to 0.08 mg. per cent.

In nineteen of the thirty-six nondiabetic patients the fasting serum level of L-xylulose was so low as to be immeasurable by this technic; in the remaining seventeen nondiabetic patients the levels ranged from 0.05 to 0.51 mg. per cent. The fasting serum L-xylulose levels could not be correlated with age, sex, fasting blood sugar, or BUN. Kumahara et al.[6] in Hiatt's laboratory found that the fasting L-xylulose concentration was immeasurably low in nine of their eleven non-Jewish controls, and ob-

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served levels of 0.14 and 0.18 mg. per cent in the other two subjects. The control subjects in that study included normal laboratory personnel in addition to hospital patients.[6]

In contrast to the nondiabetic patients, all of the diabetic patients in our series had measurable fasting levels of L-xylulose in their sera with a range of 0.17 to 2.30 mg. per cent, and the mean fasting L-xylulose concentration was significantly higher in the diabetic group than in the nondiabetic group (table 1). There was no apparent relationship between the fasting levels of serum L-xylulose and blood sugar in the diabetic group.

TABLE 1

L-xylulose concentrations in sera from fasting nondiabetic and diabetic patients

Group	No.	Mean L-xylulose mg. per cent ± S.E.
Nondiabetic	36	0.14±0.03
Diabetic	39	0.57±0.06
Diabetic — excluding two patients with liver disease	37	0.56±0.06

The observation that L-xylulose levels are elevated in the sera of diabetic patients suggests either that L-xylulose production from glucose is increased or that its metabolism or excretion is decreased. Studies designed to evaluate these possibilities are in progress. Mehnert et al.[12] have recently reported that there is no significant difference in the rate of disappearance of intravenously infused xylitol from the blood of normal subjects and patients with diabetes mellitus, suggesting that the utilization of xylitol, which is one step removed from L-xylulose in the glucuronic acid pathway, is unimpaired in patients with diabetes mellitus. This observation and the poor correlation between serum L-xylulose levels and BUN in our studies make the authors tend toward the view that the elevated levels of L-xylulose in the sera of diabetic patients results from increased production by way of the glucuronic acid pathway. This view is supported by the observation of Stroumfjord and West[13] that the synthesis of ascorbic acid, which is derived from a precursor of L-xylulose in the glucuronic acid pathway, is four to five times greater in alloxan diabetic rats than in normal animals.

No nondiabetic with gross evidence of liver disease was included in the present study, and whether or not the two diabetic patients with liver disease (hemochromatosis 0.90 mg. per cent, and Hodgkin's disease with hepatic infiltration 0.63 mg. per cent) are excluded from the calculations the mean fasting level of L-xylulose in the sera of the diabetic patients is significantly higher than that of the nondiabetic patients (table 1). The stimulatory effect of numerous drugs on glucose and galactose utilization by way of the glucuronic acid pathway is well recognized and has been extensively studied by Burns and co-workers,[14] and Salomon and Stubbs.[15] There was no apparent relationship between the prior administration of hypnotics, sedatives, or analgesics in their usual therapeutic dosage and the fasting serum concentration of L-xylulose in the patients studied. It is of interest, however, that one of the nondiabetic patients with a very high fasting level of L-xylulose (0.49 mg. per cent) was recovering from an overdose of phenobarbital taken in an attempt at suicide.

The poor correlation between fasting blood sugar and serum L-xylulose concentrations suggests that studies of glucuronic acid pathway activity in human diabetics may provide an insight into a disturbance of carbohydrate metabolism that is not directly reflected in the usual clinical measurements of blood glucose concentration or urinary glucose excretion.

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BOOK REVIEWS

HOW DIABETICS CAN EAT WISELY. *By Dorothy Tomkins Revell. $3.95, 172 pp., T. S. Denison and Company, Inc., Minneapolis, 1964.*

This book differs from other manuals on diets for diabetics. The title might lead one to believe that it deals with diets for the diabetic who has not developed any complications. However, the author has written a book for use by diabetics who have developed vascular complications. She may also have their prevention in mind and in order to aid the physician has gathered together a variety of recipes which use special margarine and a high percentage of polyunsaturated fatty acids. By following the instructions in this book, it is believed that the fatty materials in the blood will be controlled as well as the sugar in the blood.

The Meal Plan Exchange Method developed by the American Dietetic Association and the American Diabetes Association is used. Certain changes in this exchange list have been made to "meet the dietary allowances in the serum cholesterol lowering regime for the diabetic patient." For example, butter and whole milk are not listed in the exchanges. Special margarine and skim milk are substituted. The author refers to the list as a Modified Exchange List.

Seventy-five recipes provide a great variety of interesting dishes. There is no index to the recipes. They are grouped under the exchange for which they are intended. The ingredients are given in household measures as well as in grams. The carbohydrate, protein, and fat values are given in grams. The calories for each ingredient are also included. The total value of the recipe is evaluated and the composition of one serving is given with its exchange value. Directions for preparing the recipe are clear. There is no uniformity in the number of servings resulting from the preparation of each recipe. It is apparently assumed that the final product will be served to all members of the family as well as to the diabetic. Two to three pages of blank recipe forms follow each group of recipes, making it possible to insert other recipes. A table of Common Food Equivalents follows the section on recipes. A list of fruits commonly used is listed in pound units followed by the yield in cups after cooking.

In the appendix one finds a table of composition of foods in common household measuring units. The foods listed are arranged alphabetically and much detailed information is found in these tables. Other foods which cannot be placed in measuring units are described by size measured in inches. The total grams of carbohydrate, protein, and fat for each food are given as well as the food energy expressed in calories.

The author of the book is a member of the American Dietetic Association. Therapeutic dietitians should find the book useful for teaching diets prescribed by physicians who wish to alter the type of fat and include greater amounts of unsaturated fats. The patient placed on the diet would also benefit by owning the book.

FAT AS A TISSUE. *Edited by Kaare Rodahl, M.D., and Bela Issekutz, Jr., M.D. $18.50, 428 pp., McGraw-Hill Book Company, New York, 1964.*

The proceedings of a conference held at the Lankenau Hospital in 1962 have been put together in book form. The subject has been divided into 1) structure, 2) metabolic aspects, 3) mobilization and utilization, and 4) pathophysiology. The book is notable in the quality of its contributors.

Thus, in the first section Isselbacher deals with absorption and transport of fat across the intestinal mucosa, and electron microscopists, Wassermann and Sheldon, discuss fat tissue as an "organ," together with the fine structure of the fat cell, with beautiful illustrations. In the second section transport, removal, synthesis and breakdown are discussed by Felts, Rodball, Steinberg, Vagelos, and Cahill, while the third section is concerned with hormonal effects (Vaughan), the utilization of free fatty acids by muscle (Spitzer), the effect of exercise (Issekutz), the possibility of neurogenic factors (Hausberger), together with a discussion of fat as an energy source (Dole). The last section is primarily concerned with obesity both in man and animals, and mentions possible genetic factors influencing fat (as a specific organ) and its distribution, gross body composition and changes occurring during weight loss (Behnke). Recent studies of metabolism in human biopsy specimens are interesting (Hirsch and Goldrick), as is the discussion of adipose tissue in diabetes (Winegrad, Goto, and Lukens). A discussion of metabolic aberrances in hereditary and induced obesity in mice by Mayer gives valuable knowledge to the field. Page's remarks about the relationship of fat to atherogenesis and circulation conclude the book.

Each section is followed by a panel discussion, which should help stimulate further investigations. The volume stands out in the breadth of its scope, and is well worth reading by scientist and practitioner alike. The passage of time has not detracted from the contents of the book.