HYPOGLYCEMIA IN CONGESTIVE HEART FAILURE

Episodes of disordered behavior, coma or convulsions are not infrequent during the course of severe, chronic, congestive heart failure. When observed, they are usually attributed to some process such as anoxemia, a cerebral vascular disturbance, drug intoxication, electrolyte imbalance, or some other alteration directly or indirectly related to the underlying cardiac disorder. The importance of the early recognition of the remediable causes of such occurrences is obvious, and hence the considerable therapeutic significance of the observation that they may occasionally be due to periods of hypoglycemia, readily reversed by the simple act of administering adequate glucose.1, 2

Such episodes of hypoglycemia have been observed in a group of patients with chronic congestive heart failure due to a wide variety of causes including rheumatic fever, syphilis, coronary sclerosis and myxoma of the left atrium. The common feature of all of these patients has been congestive failure of very considerable degree and of prolonged duration.

It is not at all difficult to overlook hypoglycemia as the cause of such manifestations as sweating, palpitations, peculiar behavior, lack of responsiveness and convulsions in a patient who is seriously affected by congestive heart failure. The symptoms and signs of hypoglycemia are nonspecific and may be produced by a number of other conditions which are commonly part and parcel of advanced cardiac failure. It is not surprising, therefore, that hypoglycemia has often been overlooked as a cause of these manifestations and frequently recognized ultimately only by virtue of a chance laboratory determination. It is only through constant awareness that hypoglycemia may complicate the course of congestive heart failure and produce these varied alterations that one can apply the dramatic therapeutic as well as diagnostic maneuver of giving glucose to the patient which may be life saving. Before administering glucose it is, of course, helpful to obtain a blood speci-

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PENTOSE METABOLISM IN MAN

Within the past few years great interest has been demonstrated in the metabolism of five carbon sugars, both in plant and animal tissues. This interest stems from the realization that D-ribose and D-xylulose as phosphorylated esters are important intermediates in the
pentose phosphate pathway of glucose metabolism. In addition, curiosity about pentoses has been stimulated by the observation that D-xylose and L-arabinose infused into eviscerate animals respond to insulin by increasing their volume of distribution in body fluids. The latter observation has lent support to the theory that insulin increases the permeability of cells to sugars of a specified chemical structure.

In normal man small amounts of pentoses are excreted daily in urine. Attention has been focused on those states where pentose excretion is excessive, namely congenital pentosuria, pentosuria associated with muscular dystrophy and neurologic diseases, and the alimentary pentosuria seen after ingestion of pentosans. Studies by Touster, Hutcheson and Reynolds have pointed to the defect in congenital pentosuria resulting in the excessive excretion in the urine of L-xylulose. Until recently, little information has been available concerning the metabolism of the pentoses. In 1930 McCance and Madders studied the rates of intestinal absorption of pentoses by human subjects. Experiments have recently been reported describing the dissimilation of infused pentoses in man. D-xylose, D-arabinose, L-arabinose and D-lyxose, when infused intravenously into a normal subject, were observed to disappear slowly from blood. In contrast, D-ribose is cleared from blood at an extremely rapid rate. The clearance of the pentoses (except D-ribose) from blood appears to be independent of the dose. In small doses D-ribose disappears more rapidly than any other sugar. When infused into diabetic subjects deprived of insulin, D-xylose and D-ribose left the blood at normal rates indicating that the mechanism for removal of these sugars is not insulin dependent. Radioactive CO₂ appears in expired air after the intravenous administration of pentose labeled with C¹⁴ in the first carbon atom except in the case of L-arabinose. Approximately 15 per cent of the administered C¹⁴ is so recovered in six hours. D-ribose, however, differs from the other pentoses by being rapidly metabolized. Fifty per cent of the injected C¹⁴ was recovered as C¹⁴O₂ in six hours.

About 50 per cent of infused D-xylose, D-arabinose, L-arabinose, and D-lyxose was excreted in the urine. Much less of infused D-ribose was found in the urine. The results of radioactive tracer studies also indicated the presence of metabolites of the pentoses in urine.

Little or no effect of pentose infusion on blood pyruvate and lactate has been observed. Decreases of serum inorganic phosphate values have been noted but the significance of this is open to question. The pentoses, however, do produce an alteration in blood glucose levels. D-xylose and L-arabinose produce slight increases while D-ribose may cause marked decreases of blood glucose values.

The significant lowering of blood glucose after D-ribose infusion has stimulated intensive study. Results of in vitro experiments have suggested that ribose 5-phosphate, a known product of ribose metabolism in mammalian tissue, inhibits phosphoglucomutase, the enzyme which catalyzes the conversion of glucose-1-phosphate to glucose-6-phosphate along the pathway of glycogenolysis. The ribose induced hypoglycemia appears to be due, at least in part, from an inhibition of glucose output from the liver and an interruption of the hepatic homeostatic mechanism for maintenance of blood glucose levels. That ribose causes insulin secretion from the pancreas may also be a factor in explanation of this observation. Hiatt has observed that this response to ribose is not seen in the pancreatectomized dog. The ribose effect on blood glucose seen in man appears to have species specificity since this pentose does not cause hypoglycemia in the rabbit or mouse.

Though a decline in blood glucose occurs after ribose infusion, experiments with isotopic D-ribose indicate that the ribose is rapidly incorporated into the body glucose pool. Glucose isolated from the urine of a diabetic given C¹⁴ D-ribose has been found to contain the C¹⁴ with a pattern of labeling which appears to be consistent with operation of the pentose phosphate pathway in man.

Goldstein et al demonstrated in the dog that insulin increased the volume of distribution of the pentoses D-xylose and L-arabinose. In similar studies in man, insulin was found to enhance the disappearance from blood of D-xylose and L-arabinose quite markedly, but little effect was found in the case of D-lyxose, D-arabinose and D-ribose. Calculations indicate that insulin increased the volume of distribution of D-xylose from 20 per cent to 32 per cent of the body weight. These studies show that the most insulin responsive pentoses in man are those which, as Goldstein et al pointed out, have a configuration of carbon atoms 1-3 similar to that of D-glucose.

The insulin responsiveness of D-xylose and L-arabinose in man has been used to compare the actions of insulin and the hypoglycemic agent—tolbutamide. Experiments recently published indicate that although intravenous sodium tobutamide causes a hypoglycemic response, it produces little or no effect on the blood levels of infused pentoses. The insulin effect on pentoses is presumably due to a peripheral action of insulin. The lack of pentose response to tobutamide is, therefore, inter-
presumed to mean that tolbutamide differs from insulin by neither affecting the transport of sugars across cell membranes, nor stimulating the secretion of insulin.

In human metabolism, these pentoses are negligible from a caloric standpoint. These sugars, however, do play a significant role in intermediary metabolism. Experiments have indicated effects not observed in other animal species. Still others indicate that pentoses are metabolized in man by as yet unknown pathways. Much biochemical ground has been traversed since the pentoses were regarded as mere structural components of plant and animal tissues. At the present time the true position of pentoses in intermediary metabolism may still be underestimated.

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BLOOD PYRUVATE AND ALPHA-KETOGLUTARATE IN DIABETES

Attempts to classify diabetic patients into groups have utilized various clinical, physiological and chemical criteria. All students have recognized the differences between the older, obese patients with mild diabetes and the young, thin patients with severe disease, easily subject to acidosis. The older French clinicians used the words "Diabète Gras" in contrast to "Diabète Maigre" to differentiate these two types of patients. In more recent years, differences in carbohydrate tolerance and insulin requirements have been common bases for differentiating these two groups of patients. With the introduction of methods for measuring the insulin content of the blood as well as of the pancreas, Lawrence postulated two major groups of diabetics: one obese and middle-aged in whom considerable, though not normal, amounts of insulin could be demonstrated in the blood, and the other thin and young in whom practically no insulin could be demonstrated in the blood. Current studies of the oral hypoglycemic agents also show a different response in these two groups of patients, the obese, mild diabetic proving responsive and the thin, severe diabetic refractive to sulfonylurea compounds. Recently, Smith and Taylor have studied blood concentrations of pyruvate and alpha-keto glutarate in normal and diabetic subjects and have found differences in the mild, obese group as contrasted with the more severe, thin patients of the Lawrence grouping.

Past studies of the blood concentrations of pyruvate and alpha-keto acids in patients with diabetes have resulted in conflicting reports. Increased blood levels of pyruvic acid and alpha-keto glutarate have been reported by some workers, whereas others have found normal values for these carbohydrate intermediates in ambulant diabetic patients. A number of workers have reported that little change in blood pyruvate occurs in diabetic patients following the administration of glu-