preted 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 with pentoses in other animal species may be duplicated in man in some but not all cases. Some 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[1] 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[2] have studied blood concentrations of pyruvate and alpha-ketoglutarate 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-ketoglutarate 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-

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cose,* but in the patients studied by Root, Stotz, and Carpenter,[3] a difference was observed between mild diabetics requiring little or no insulin and patients with more severe diabetes. In milder forms of the disease, a definite rise in blood pyruvate and lactic acid was observed after glucose administration, while this rise was delayed or absent in patients with severe diabetes. The recent studies of Smith and Taylor have confirmed these observations. Their studies were carried out in twelve normal subjects and sixteen diabetic patients. Of the sixteen diabetics six were classified as "obese" and seven as "thin" according to Lawrence's classification. Twenty-four hours after the withdrawal of insulin, and following an overnight fast, the subjects were given a 25 per cent solution of glucose (equivalent to 1.75 gm. of glucose per kg. body weight) by mouth, and blood specimens were collected at intervals of one, two and three hours. A definite and significant increase in blood pyruvate following the ingestion of the glucose was observed in the obese group of patients but did not occur in the group of thin subjects with more severe diabetes. The blood alpha-ketoglutarate increased steadily during the three hours in the thin diabetics; whereas in both the normal and obese diabetics there was a slight increase in alpha-ketoglutarate concentration, followed by a decrease at three hours. These results are of interest, because they document further differences in the carbohydrate metabolism of the obese, mild diabetic and the thin, severe diabetic.

The most probable explanation of the rise in blood pyruvate in the obese patients is that the administered glucose was actively metabolized. In these patients, one might postulate that the obesity was due to their ability to metabolize glucose without added insulin. The absence of an increase in blood pyruvate in the thin patients is evidence of their comparative inability to utilize glucose. This explanation is compatible with the demonstration by Lawrence of the presence of insulin in the blood of the obese diabetics and its absence in the thin diabetics. The authors offer another possible explanation, namely, that a greater glucose diuresis in the thin diabetic group might have caused an increased renal excretion of pyruvate with a subsequent lowering of blood pyruvate levels. However, this does not appear to be a very likely or sufficient rationale. The increase in the level of the blood alpha-ketoglutarate in the thin diabetics, in the absence of any evidence for the metabolism of glucose, as evidenced by pyruvate, is most interesting, and the following two hypotheses may bear on these results.

Alpha-ketoglutarate is not only an intermediate of carbohydrate metabolism in the citric acid cycle, but is also formed in the liver by the de-amination of glutamic acid. Normally, the equilibrium of the alpha-keto-glutaric-glutamic system favors the formation of glutamic acid which may then enter into protein formation. However, in the thin, severe diabetic, fasted and without insulin, protein synthesis is at a minimum; protein catabolism predominates. In this situation, it would be possible to conceive of a reversal of the normal equilibrium, and an accumulation of alpha-ketoglutarate in the blood. Against this hypothesis are the normal (in fact, slightly subnormal) initial levels of alpha-ketoglutarate in these patients. One would have to postulate an increased stimulus to protein catabolism by the administration of glucose.

Secondly, it is of interest to note that both pyruvate and alpha-ketoglutarate, in order to enter the tricarboxylic acid cycle, require as a first step the presence of co-enzyme A to produce acetyl-co-enzyme A or succinyl co-enzyme A respectively. A competition for a common co-enzyme might explain the disparate levels of pyruvate and alpha-ketoglutarate found in these patients.

When hypoglycemia is produced by the administration of insulin, the changes in levels of blood pyruvate and alpha-ketoglutarate may be compared with the changes observed when similar degrees of hypoglycemia are produced by Orinase. In seven normal subjects studied by Hennes, Wajchenberg, Fajans and Conn,[4] the intravenous administration of insulin produced an early rise in the level of blood pyruvate, whereas the intravenous administration of sodium Orinase produced a decline in the concentration of pyruvate. Following the oral administration of 6 gm. of Orinase, the blood levels of these two substances decreased at one hour and increased at two hours. Later changes in blood levels appeared to be associated and to result from hyperadrenalinemia. Their results did not show a constant pattern of change in blood levels of alpha-ketoglutarate in association with hypoglycemia although significant decreases did occur in four experiments in association with Orinase-induced hypoglycemia. The difference in blood pyruvate response suggests that rapid release of endogenous insulin is not the mechanism by which the sulfonylureas produce decline in blood sugar levels in normal subjects.

Other reports at the Conference of the New York Academy of Sciences, Feb. 14, 1957, emphasized differences in levels of these intermediary metabolites in the blood of normal and diabetic humans. Thus Miller, Craig, Mackenzie, Drucker, and Cammarn[5] gave tolbutamide (Orinase) and insulin to each of four normal and

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nine diabetic subjects intravenously. On separate occasions, insulin was given in amounts designed to produce a depression of blood sugar similar to that obtained after tolbutamide in the same individual. Under these conditions no definite difference in the pyruvate response followed either agent. The lactate changes were related to hypoglycemia. They concluded that differences in blood levels of pyruvate and lactate reflected differences in the rate of blood sugar depression rather than mechanism of action. However, using a method of hepatic vein catheterization they studied the splanchnic assimilations of fructose, glucose, pyruvate and lactate. Their results suggested that tolbutamide depressed splanchnic glucose production or release during fructose administration. Studies on the site of action of sulfonylureas in man by Renold, Martin, Boshell and Thorn[6] were carried out in an attempt to characterize the hypoglycemia produced by the sulfonylureas as the result of either increased glucose utilization or decreased hepatic glucose release. The decreased conversion rate of fructose to glucose concurrent with sulfonylurea-induced hypoglycemia suggested a decreased rate of hepatic glucose release or synthesis. In addition, these authors, in common with many others, failed to find convincing metabolic evidence of increased glucose utilization as a result of sulfonylurea action, and could not demonstrate increased levels of circulating plasma insulin under these conditions. They regarded these results as providing clear-cut evidence for an effect of the sulfonylureas on hepatic glucose release *in man*, although the possibility of an additional acute effect upon pancreatic insulin secretion was not considered as excluded. Such an effect on insulin secretion *in animals* appears well established.

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Albrecht von Graefe

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The man most deserving of the title, "Founder of Ophthalmology," Albrecht von Graefe, was born in Berlin on May 22, 1828. His father, one of the founders of German surgery, Director of the Surgical Clinic of the University of Berlin and author of many surgical works, was held in high esteem by the royal family. His renown might have been greater, except that he had an untimely death in 1840, and the great Dieffenbach became his successor.

Albrecht received his instruction at home from private tutors, then entered the French Gymnasium, where he attained proficiency in the French language. He was intensely interested in his studies, and at age of fifteen years entered the University of Berlin in the autumn of 1843. He studied logic and philosophy under Carl Ludwig Michelet and demonstrated zeal and intense interest in the natural sciences. The medical faculty at that time consisted of Johannes Muller, Schonlein, Dieffenbach and Juengken, as well as Emil Duboise Reymond, Ludwig Traube, Robert Remak, Rudolph Virchow and Ernst von Brücke. He learned anatomy not only from Muller but also from Schlemm. Among the younger teachers, Graefe was captivated by Virchow.

He had a very happy home and lived in prosperous circumstances. It was his privilege to gain friends quickly and to turn them into enduring friendships. Although his student days were spent in Berlin, he was afforded by his family's wealth and station the opportunity to travel abroad for further studies.

He studied in Prague with von Jaksch, Ditterich and

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