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## The control of acidosis and its relation to impaired sugar metabolism in human diabetes.

By FRANK P. UNDERHILL.

[*From the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven.*]

Acidosis exerts a distinct influence upon carbohydrate metabolism. This assertion is supported by the observation of Elias,[1] who demonstrated that the introduction of acid into dogs and rabbits leads to hyperglycemia and glycosuria. Moreover, the same author[2] has concluded that the so-called "hunger diabetes" of young dogs[3] is in part, at least, a condition due to acidosis, as determined by the carbon dioxide content of the blood and analysis of the alveolar air. Observations upon human diabetes teach that acidosis obtains in this condition also.

A state of alkalosis is likewise potent in exerting an action upon carbohydrate metabolism but this influence is contrary to that of acidosis. Pavy and Godden[4] showed that the glycosuria provoked by ether and chloroform disappears after the intravenous injection of sodium carbonate. Given by mouth or intravenously sodium carbonate will abolish the hyperglycemia of "hunger diabetes" and glycosuria will either entirely disappear or be greatly diminished, according to Elias.[5] After removal of the pancreas sodium carbonate introduced into the blood stream causes diminution in the excretion of sugar.[6] Later work by Murlin (reported at the December meeting of the Society for Biological Chemists) has shown that under the influence of sodium carbonate the respiratory quotient is increased in depancreatized dogs. At the December meeting of the Society of Biological Chemists Underhill reported that in the hyperglycemia produced by epinephrine the

[1] *Biochem. Zeit.*, 1913, 48, p. 120.

[2] Elias, *Biochem. Zeit.*, 1913, 52, p. 331.

[3] Hofmeister, *Arch. f. Exper. Pathol. u. Pharm.*, 1890, 26, p. 355.

[4] *J. Physiol.*, 1911–12, 43, Proc., p. vii.

[5] *Biochem. Zeit.*, 1913, 52, p. 331.

[6] Murlin and Kramer, *J. Biol. Chem.*, 1913, 15, p. 365.

intravenous administration of sodium carbonate will significantly lower the excretion of sugar in the urine, the hyperglycemia being correspondingly decreased in height and duration. It was also stated that the intravenous injection of sodium carbonate into normal animals will sometimes although not invariably cause a distinct fall in the blood sugar content.

From these illustrative observations it may be concluded that a condition of acidosis tends toward the elimination of carbohydrate from the body whereas alkalosis shows a tendency to conserve the carbohydrate. Otherwise expressed it seems tenable that carbohydrate metabolism of the organism is maintained in equilibrium by a balance between the acids and bases of the body.

Applying these ideas to human diabetes one gains the following conception of its chemical pathology: without reference to what may initiate the abnormal condition, a state of acidosis unquestionably develops and must tend to become aggravated, if anything, by the characteristic acid-producing foods that characterize the conventional diabetic dietary. From what has already been pointed out, however, it seens reasonable to conclude that anything which will counteract or neutralize the continuous stream of acid entering the body should benefit the individual. One is led to ask, what influence would this have upon the excretion of sugar if the organism were once saturated, so to speak, with alkali and enough alkali continually supplied to neutralize the exogeneous and the endogenous acid? These considerations have been put to the test in a young diabetic, 26 years of age, with a very severe type of diabetes. When first seen by me fifteen months ago there was a sugar excretion of 151 grams per day. On a restricted diet the output of sugar was reduced to 25–50 grams, acetone and diacetic acid always being present in relatively large quantities. After a year's interval in spite of very stringent dietary restrictions the sugar excretion suddenly increased to 70–80 grams daily. Gradually increasing doses of sodium bicarbonate to a maximum of 120 grams per day resulted in a gradual diminution of sugar output until the urine became sugar-free. The dosage of sodium bicarbonate was thereupon decreased at the rate of 7 grams per day until the intake amounted to 42 grams which has been maintained to the present time. Under the alkali treatment the urine

has remained free from sugar for a period of seventeen days during which the food ingested has been augmented little by little to the point where about 10 grams of carbohydrate in addition to that present in the previous strict diet are being ingested daily. Throughout the entire course of his treatment the patient has continued at his duties as an instructor in the university.

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## Possible inter-relations between acidosis and creatine elimination.

By FRANK P. UNDERHILL.

[*From the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven.*]

Current views associate the elimination of creatine with some perversion of carbohydrate metabolism. The probability of a close relationship of this sort is indicated by the well known fact that a deficiency of carbohydrate in the body leads to creatine elimination which may be checked promptly by ingestion of carbohydrate. There are experimental facts which the familiar hypothesis fails to explain. McCollum and Steenbock[1] found that in the pig a diet of corn products led to the appearance of relatively large quantities of creatine in the urine. Similar experiments of Folin (reported at the December meeting of the American Society of Biological Chemists) with oat feeding yielded comparable results. The dietaries employed can scarcely be regarded as lacking in carbohydrate.

Deficiency of carbohydrate usually means an accompanying acidosis, not necessarily caused by ketogenic substances, which presumably involve the tissues associated with creatine-creatinine metabolism. At any rate nearly every instance in which there is creatine in the urine is accompanied by an acidosis—generally a ketonuria also. These facts suggest the hypothesis that a condition of acidosis in the tissues is responsible for the appearance of creatine in the urine. To test it the following questions demand an answer.

[1] *J. Biol. Chem.*, 1912–13, 13, p. 209.