SPECIAL ARTICLES

THE PRODUCTION OF PERMANENT HYPERGLYCEMIA AND GLYCOSURIA BY THE PROLONGED ADMINISTRATION OF INSULIN

IT is apparent from the studies of Haist, Campbell and Best[1] and of Lukens and Dohan[2] that insulin, fasting or fat-feeding rests the islands of Langerhans, and that the procedures which permit the islets to rest also prevent or hinder the development of the diabetic state which results from the administration of anterior pituitary extracts to dogs. Accordingly, Haist, Campbell and Best recommended that the procedures established as beneficial for animals should be tried in man as a prophylactic measure for the prevention of diabetes, especially in the case of children with a diabetic family history.

However, since the administration of exogenous insulin can reduce the insulin content of the normal pancreas, it is possible also that it may depress completely the production of insulin and thereby induce a permanent diabetes in a patient with a relative deficiency. In order to put this possibility to test, from 30 to 75 per cent. of the pancreas was removed from dogs. Since such animals can become diabetic only if hyperglycemia is induced by the administration either of large amounts of carbohydrate or of anterior pituitary extracts, they may be regarded as being very susceptible to diabetes, but not as having diabetes. Such a situation may exist in the patient who eventually becomes diabetic.

After the immediate post-operative effects were over, the animals were treated with protamine zinc insulin to the limits of their capacity and were permitted to eat freely. The blood sugar level was studied carefully to maintain a constant hypoglycemia. In three animals that were studied for over one year, it was noted that hyperglycemia and glycosuria appeared in from 20 to 40 weeks after the beginning of the protamine zinc insulin treatment. Furthermore, these animals apparently developed a permanent diabetes since the hyperglycemia and glycosuria persisted for as long as 30 weeks thereafter.

Fig. 1 illustrates the history of a dog from which a maximum of 66 per cent. of the pancreas was removed and which, after several days, was started on daily injections of protamine zinc insulin, the dosage being increased to the limits of the animal's capacity to withstand hypoglycemia. The animal was permitted to eat freely and what remained was measured. It was noted that the blood sugar did not reach hyperglycemic values even when, in the 18th week, insulin was stopped for several days. Up until the 22nd week the animal's weight rose gradually and then a precipitous fall occurred. Thereafter, the animal exhibited all signs and symptoms of pancreatic diabetes with hyperglycemia, glycosuria and ketosis, the latter being apparent after insulin deprivation. With the administration of adequate amounts of insulin for the remaining 30 weeks of the study, the animal could be rendered aglycosuric. The degree of glycosuria was definitely related to the amount of carbohydrate ingested. Insulin was removed on the 54th week and the animal died in a cachectic state 11 days later.

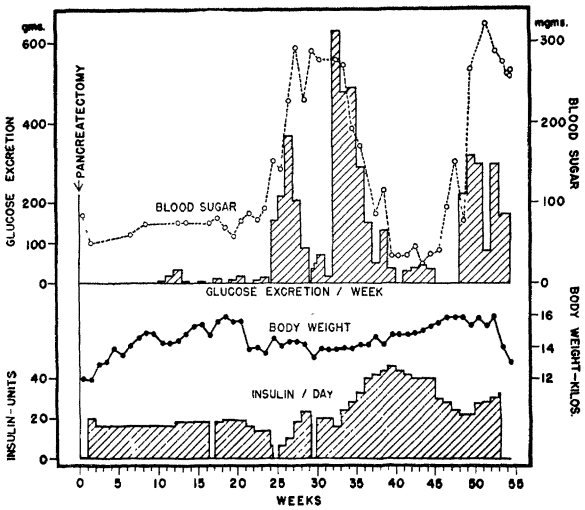

FIG. 1. Illustrating the influence of the prolonged administration of protamine zinc insulin to a partially depancreatized dog. The blood sugar values are the highest obtained during the week.

Autopsy revealed 4 grams of pancreas which did not appear abnormal on gross examination. Repeated sections made from numerous blocks of this tissue revealed no normal islet tissue. Only a rare area was found suggesting an islet of Langerhans that apparently was undergoing involution. These few islets were small, inconspicuous and showed changes suggestive of fibrosis.

In order to illustrate further the fact that the diabetes which was produced in consequence of the prolonged administration of protamine zinc insulin was essentially indistinguishable from that which results from total pancreatectomy, various periods during which insulin was stopped in the dog are depicted in Fig. 2. During the first and 18th weeks after operation, the removal of exogenous insulin did not result in glycosuria or hyperglycemia. However, during the 25th week glycosuria became apparent after exogenous insulin deprivation, and hyperglycemia more so thereafter.

These studies are in accord with the observations

[1] R. E. Haist, J. Campbell and C. H. Best, *New England Jour. Med.*, 223: 607, 1940.

[2] F. D. W. Lukens and F. C. Dohan, *Endocrinology*, 30: 175, 1942.

that insulin administration results in a decrease in the production of insulin by the islet tissue.[1,2] However, it is apparent that the prolonged use of protamine zinc insulin accentuates this phenomenon to such a degree that a "disuse atrophy" of the pancreas ensues.

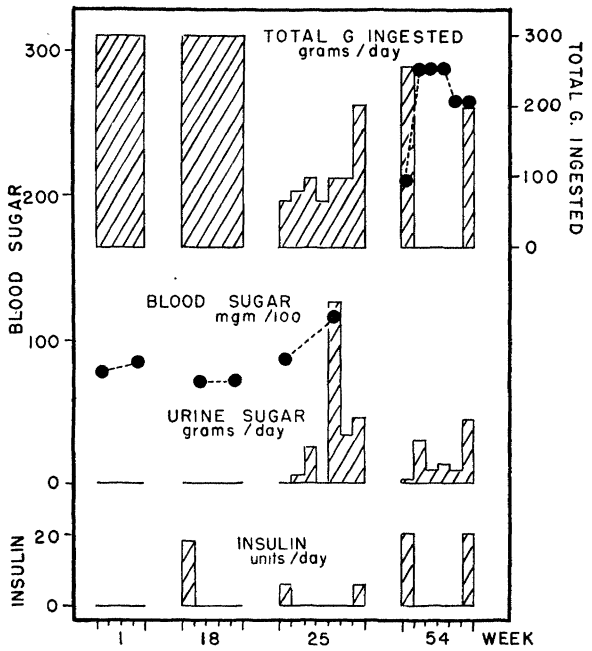

FIG. 2. Illustrating the influence of insulin deprivation at various intervals after the administration of protamine zinc insulin to a partially depancreatized dog.

This compensatory decrease in insulin secretion and its morphological counterpart is made more evident in these experiments, where the amount of pancreas present in the animal is relatively small, though adequate for normal maintenance. It is suggested, therefore, that it might be an extremely dangerous practice to utilize protamine zinc insulin as a prophylactic measure in man, in contrast to its beneficial influence in diabetes mellitus.

I. ARTHUR MIRSKY
NORTON NELSON
SAMUEL ELGART[3]
ISABELLE GRAYMAN

THE MAY INSTITUTE FOR MEDICAL RESEARCH,
THE JEWISH HOSPITAL AND THE
DEPARTMENT OF BIOLOGICAL CHEMISTRY,
UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO

ON CATARACT AND CERTAIN OTHER MANIFESTATIONS OF TRYPTOPHANE DEFICIENCY IN RATS[1]

IT is recognized that tryptophane deficiency leads to lesions in the eyes. Curtis, Hauge and Kraybill[2] in 1932 and Totter and Day[3] in 1941 reported the occurrence of cataract in tryptophane deficient rats, and the latter observers also noted vascularization of the cornea in this condition. We can amply confirm and extend these observations, and we have furthermore noted lesions characteristic of tryptophane deficiency in other organs.

TRYPTOPHANE CATARACTS

In our experiments a tryptophane deficient diet[4] similar to that employed by Totter and Day[3] (No. 5000) was employed. Young rats of about 100 grams in weight, when placed on this diet, developed cataracts with great regularity in from seven to eleven weeks, in contrast to paired feeding control animals on analogous diets containing tryptophane. Two different types of cataract have been observed in the tryptophane deficient animals—an *acute* and a *chronic* type.

The *acute type* starts in the posterior cortex of the lens, spreading within a few days to the perinuclear, nuclear and anterior cortical zones and maturing within two to three weeks. Within a week after the maturation of the cataract the animals die. The acute form of cataract can be arrested in its early stages by supplementing the diet with tryptophane, but some opacities still develop for a time after the supplement is instituted.

The *chronic type* of cataract is confined to the anterior and posterior cortex of the lens and does not mature within the life-time of the animals, which varies from four to nine weeks after the onset of the cataract. In one animal we have observed a combination of the morphological features of both types of cataract. We do not know what factors determine the type of cataract which develops, but our results suggest that the strain of rats studied may be important.

We have observed cataracts *only in growing animals*

---

[3] Leo Lehman fellow.

[1] This study was supported in part by grants for the study of amino acids in nutrition made by the Rockefeller Foundation, Merck and Company, Eli Lilly and Company and E. R. Squibb and Sons. This material was presented in part at a demonstration at the meeting of the Federation of American Societies for Experimental Biology in Boston, March, 1942. W. Buschke, A. A. Albanese and R. H. Follis, Jr., *Fed. Proc.*, 1: 175, 1942.

[2] P. B. Curtis, S. M. Hauge and H. R. Kraybill, *Jour. Nutr.*, 5: 502, 1932.

[3] J. R. Totter and P. L. Day, *Jour. Biol. Chem.*, 140: cxxxiv, 1941.

[4] The exact composition of the diet was as follows: Protein (acid hydrolyzed casein concentrate), 147 g; l-cystine, 1.5 g; sucrose, 150 g; starch, 420 g; agar, 20 g; salt mixture (see below), 20 g; Crisco, 190 g; Mead Johnson's cod liver oil substitute, 50 g; water to make to proper consistency. The salt mixture used had the following composition: NaCl, 18.9 g; $CaHPO_4$ anhydrous, 25.0 g; $MgSO_4$ anhydrous, 6.86 g; $KHCO_3$, 44.4 g; KCl, 2.88 g; Fe citrate U.S.P., 2.21 g; $CuSO_4$ anhydrous, 0.24 g; $MnSO_4$ anhydrous, 0.15 g; KI, 0.015 g; NaF, 0.03 g.