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THE PITUITARY AND DIABETES

Ten years ago it was supposed that diabetes was due simply to a deficient secretion of insulin. In 1930 Houssay[1] and his collaborators observed that the symptoms of diabetes in depancreatized dogs were relieved by hypophysectomy, and subsequently that injection of crude extracts of anterior pituitary material into such "Houssay dogs" (hypophysectomized-depancreatized animals) caused diabetic symptoms to develop. Since that time the influence of the anterior pituitary on carbohydrate metabolism has been the subject of intensive study. Much of this work has been undertaken in this country by F. G. Young, who has recently reviewed the present state of knowledge.[2 3] Before Houssay's classical observations it was known that the glycogen stores of the liver were derived not only from carbohydrate but also from protein and fat, and that the mobilization of this glycogen to supply a constant blood-sugar level was controlled by a number of factors of which adrenaline was one of the most important. Adrenaline was also responsible for helping to convert tissue glycogen to lactic acid. The hypoglycaemic action of insulin was due to its powers of preventing the formation of glycogen in the liver, to its antagonistic effect on the mobilizing function of adrenaline, and to its facilitating the conversion of blood sugar to tissue glycogen. If the supplies of carbohydrate were adequate the conversion of fat to glycogen was prevented by insulin. In the process of this conversion there was a tendency to liberation of ketone bodies, so that insulin in the presence of glucose diminished the tendency to ketosis.

F. G. Young[4] has shown that administration of crude anterior pituitary extracts to normal dogs gives rise to hyperglycaemia, glycosuria, and ketonuria. With small constant doses this diabetogenic effect tends to disappear, but can be made to reappear if the daily dose is increased, and if large doses are given the dogs are rendered permanently diabetic.[5] These animals, however, can survive indefinitely without insulin treatment and can readily manufacture sugar from protein,[6] so that, provided they are supplied with a high protein diet, their body weight is maintained or even increased. It appears that this diabetogenic effect is due not to inhibition of secretion of insulin but to the raising of the threshold of sensitivity to it.[7] Young[8] found that extracts of the lactogenic hormone of the anterior pituitary, prolactin, possess this diabetogenic activity, though he[9] subsequently demonstrated that the "glycotropic factor" is a contaminant of, but not identical with, prolactin. Although crude extracts of the anterior pituitary are "diabetogenic" neither prolactin nor the glycotropic factor will raise the blood-sugar level in intact animals, though they will provoke glycosuria in "Houssay dogs."[10] Furthermore, neither prolactin nor the glycotropic factor will induce ketonuria either in the intact[11] or in the "Houssay" animal.[10] So at least three different factors would appear to be required to produce the "diabetogenic" effect in the intact animal: the glycotropic factor, the ketogenic factor, and a factor responsible for inducing glycosuria in the intact animal. Further information as to the mode of action of the glycotropic factor is provided by the observations of Himsworth and Scott[12] that this substance is equally active in adrenalectomized animals, and that its effect therefore is not brought about by increasing the glycogenolytic power of adrenaline. In a histological study of the pancreatic islets in diabetic animals Richardson and Young[13] observed that, whereas in dogs rendered permanently diabetic there is evidence of degeneration of the Langerhans tissue, in rats receiving crude extracts of anterior pituitary there is an increase in the amount of islet tissue, and in dogs receiving small daily doses active mitosis of the cells is found. This is of significance in view of the observation that such animals tend to become resistant to the diabetogenic effect of small doses, and supports the evidence for the existence of a "pancreatropic" factor of the anterior lobe. Yet another aspect of this pituitary activity is the self-limiting mechanism which appears to be a function of all anterior pituitary factors. Young[14] has shown that by continuous treatment of monkeys with glycotropic substance it is possible to develop an "anti-prolactin" in the serum, though this antigenic substance does not appear to be consistently anti-glycotropic.

The story is by no means complete, but enough has been told to show that the normal animal, and presumably the normal human being, like the "Houssay dog" lives "precariously balanced between hypoglycaemia and diabetes," and that this balance depends on the efficient interaction of the anterior pituitary and the pancreas. It is still too early to apply these discoveries clinically, but we

[1] *Endocrinology*, 1931, **15**, 511.
[2] *Lancet*, 1936, **2**, 237, 297.
[3] *Proc. roy. Soc. Med.*, 1938, **31**, 1305.
[4] *Biochem. J.*, 1938, **32**, 513.
[5] Young, F. G. *J. Physiol.*, 1938, **92**, 15P.
[6] Marks, H. P., and Young, F. G. Ibid., 1938, **93**, 61.
[7] Cope, O., and Marks, H. P. *J. Physiol.*, 1934, **83**, 157.
[8] Ibid., 1936, **87**, 13P.
[9] *Chem. Ind.*, 1937, **55**, 237.
[10] Long, C. N. H. *Medicine*, 1937, **16**, 215.
[11] Young, F. G. *Biochem. J.*, 1938, **32**, 524.
[12] *J. Physiol.*, 1938, **91**, 447.
[13] Ibid., 1937, **91**, 352; and *Lancet*, 1938, **1**, 1098.
[14] *Biochem. J.*, 1938, **32**, 656.

may look forward confidently to a third milestone in the history of the treatment of diabetes which may prove to be not less important than the discovery of insulin by Banting and Best or the introduction by Hagedorn and Scott of the protamine-zinc-insulin compound.

RAW AND PASTEURIZED MILK

Two reports have already been issued describing work carried out under the supervision of the Milk Nutrition Committee on the comparative nutritive value of raw and commercially pasteurized milk. The first dealt with observations on rats, the second on school children. A third report[1] is now published dealing with experiments on calves carried out at the National Institute for Research in Dairying, Reading, and at the Rowett Research Institute, Aberdeen. At Reading sixteen pairs of bull calves from tubercle-free herds were compared. One animal in each pair was fed on raw and the other on pasteurized milk from the same source. The milk was given in proportion to the weight of the animals. A hay supplement was included after eight weeks and a meal supplement after seventeen weeks. The experiment terminated after twenty-six weeks. In assessing the results five pairs of calves were omitted on the ground that three calves on raw milk died of pneumonia, one calf on raw milk was ill, and one calf on pasteurized milk had intestinal obstruction. The average weight of the remaining eleven pairs was 453.9 lb. in the raw group and 454.36 lb. in the pasteurized. Body measurements showed a slight but insignificant advantage in favour of the animals on raw milk; but, since the difficulties of obtaining uniform measurements in calves are said to be great, little weight can be attached to this difference. Examination of the raw milk showed that 30 per cent. of samples contained tubercle bacilli, in spite of the fact that it came mainly from accredited herds. None of the pasteurized samples was found to be infected. Tuberculin tests made towards the end of the experiment showed that eight out of the eleven calves on raw milk and one out of the eleven on pasteurized milk reacted positively.

At Aberdeen two experiments were carried out on the same general lines as at Reading. In the first experiment six heifer and ten bull calves were included in each group. Milk was fed according to appetite up to four months and then limited to 20 lb. per head per day. Hay was not given, but oat straw was fed freely throughout. Meal was added after four months. In the second experiment ten pairs of bull calves were observed, milk being limited to 15 lb. daily, and meal added as soon as the calves would eat it. The milk supplied was the same in both experiments. Of the raw milk 74 per cent. of samples contained tubercle bacilli and 74 per cent. *Br. abortus*; of the pasteurized milk 7 per cent. of samples contained tubercle bacilli and 5 per cent. *Br. abortus*, though it is stated that the phosphatase test was uniformly negative. In the first experiment, omitting two calves that died in the raw milk group and one in the pasteurized, the average weight at 183 days of the animals fed on raw milk was 417.9 lb. and of the animals fed on pasteurized milk 402 lb. This difference cannot be regarded seriously, since throughout the experiment the growth curves of the two groups of animals were frequently crossing each other, and it so happened that at the time the experiment came to an end the animals on raw milk were in the ascendant. In the second experiment the average weight of the animals at the end of 187 days was 379.6 lb. in the raw group and 352.2 lb. in the pasteurized. In neither experiment was the difference in weight statistically significant. In the first experiment four calves in the raw group and three in the pasteurized reacted to tuberculin; in the second experiment the numbers were four and one respectively.

There are several different ways of carrying out experiments of this sort, and the answer obtained necessarily depends on the type of procedure adopted. Wilson, Minett, and Carling at Peppard endeavoured to make a pure comparison of the nutritive value of raw and pasteurized milk. For this reason they used calves from a healthy herd and fed them with milk that was free from both the tubercle bacillus and *Br. abortus*. As a result none of their animals became infected, and the results were not vitiated in any way by disease. Wilkie, Edwards, Fowler, and Wright at the Hannah Dairy Research Institute wanted to compare the general effect of raw and commercially pasteurized milk. For this reason they used animals from tuberculosis-free herds, fed them on ordinary raw and pasteurized milk, and kept them under completely separate housing conditions. The result was that twenty-four out of the thirty-six animals on raw milk became infected with tuberculosis and not one of the animals on pasteurized milk. In both these experiments, it may be noted, the average gain in weight of the animals was either equal or slightly higher in the pasteurized than in the raw group. The Reading and Aberdeen workers seem to have fallen between two stools. Some of their animals came from tuberculin-tested herds and others did not. Ordinary raw and pasteurized milk were given, but the animals were all housed together. It is not surprising, therefore,

[1] Milk and Nutrition. Part III. New experiments reported to the Milk Nutrition Committee. The effect of commercial pasteurization on the nutritive value of milk as determined by experiments on calves. Poynder and Son, Reading. 1938. Price 2s.