

Editorial

PANCREATIC EXTRACT AND DIABETES

THE treatment of diabetes consists in a reduction of the amount of carbohydrates and, if necessary, of protein in the diet to such a degree that the percentage of sugar in the blood returns to the normal level. When this is accomplished the functions of the body which control the metabolism of carbohydrates are relieved of the overstrain under which they have become progressively more and more weakened as the disease progresses. The rest afforded these functions by reduction of the diet allows them to recuperate, so that after some time it is not infrequently the case that some carbohydrates can again be tolerated without producing any of the symptoms of the disease. It is usually considered that some structure in the pancreas (the Isles of Langerhans) forms the organ which controls these functions, and that it accomplishes its work by means of an internal secretion. Final proof of this hypothesis has, however, been lacking, for although experimental diabetes of an extremely acute type inevitably follows complete removal of the pancreas in laboratory animals, and diabetes mellitus in man is frequently found to be associated with pathological changes in this gland, it has until recently been impossible to show that administration of an extract of pancreas has any constant and significant effect in reducing the disturbed sugar metabolism or in ameliorating any of the other symptoms of diabetes.

At intervals since 1887, when Minkowski discovered that excision of the pancreas in dogs causes diabetes, attempts have been made by numerous investigators to supply the evidence of an internal secretion. Some of these attempts have been crowned by a certain amount of success; notably, among recent in-

vestigators, those made by Knowlton and Starling, Kleiner, Murlin, E. L. Scott, and Paulesco; but so far as can be ascertained, the results have been considered, often by the authors themselves, to be insufficiently constant and significant to justify more intensive research with the object of securing preparations of greater potency that could be used for the treatment of diabetes in man.

In a paper appearing in the previous number of this Journal are given the results of a remarkable series of observations emanating from the physiological and pathochemical laboratories and the medical clinic of the University of Toronto, by F. C. Banting, C. H. Best, J. B. Collip, W. R. Campbell and A. A. Fletcher, in which it is shown that an extract of pancreas can be prepared capable of removing all the cardinal symptoms of diabetes both in animals and man. Thus, it caused the blood sugar to return to the normal level, the sugar of the urine to disappear, acetonuria to vanish and the respiratory quotient to rise towards its usual level. Not alone were the objective symptoms relieved, but the well-being of the patients definitely improved. The extract was administered subcutaneously. These clinical observations would not have been warranted had Banting and Best not previously shown by experiments on diabetic (depancreated) dogs conducted in the laboratory of the writer, that in one animal at least, by daily injections of extract, life could be prolonged far beyond the time during which untreated diabetic animals usually live.

Many other corroborative results of the remarkable potency of pancreatic extracts have been gathered, and great attention is being given to the best method

of their preparation in bulk. It has been thought advisable not to publish these methods in detail until they have been thoroughly worked out and the proper dosage determined; for it has been found not only that toxic symptoms may follow the administration of improperly prepared extracts, but that the antidiabetic effect is readily lost by apparently trivial deviations from the prescribed method. This large scale preparation of the extract is being done in the department of physiology by the aid of funds granted by the Connaught Laboratories of the University of Toronto.

As is frequently the case, on passing from small to large scale production great difficulties were encountered, so much so, indeed, that for over two months it was impossible to obtain extracts of anything like the potency of those used in the above referred to observations on diabetic patients. There is reason to believe, however, that these difficulties will soon be overcome and that details of the method of preparation of the extract can be published in detail. Meanwhile a sufficient amount of extract has been available to continue with the laboratory observations and many significant results have been obtained. These are important not only because of their scientific interest but also because they indicate the clinical possibilities of the extract.

The large amount of information collected has been the result of excellent team work by a group of workers including besides those already mentioned, J. Hepburn, H. K. Latchford, E. C. Noble and the writer. Briefly, the most significant of the results which have been obtained are as follows: Subcutaneous injection of the extract into normal rabbits causes the percentage of sugar in the blood to fall, and when this reaches a certain level (about 0.045 percent.), perfectly characteristic symptoms of a convulsive character appear and, if left alone, the animal passes into a comatose condition, which soon ends in death. If a solution of sugar be injected subcutaneously when the symptoms appear, the animal immediately recovers and

may remain perfectly normal or pass again into the convulsions which may be removed a second time by injections of sugar. Many observations have convinced us that these symptoms are definitely related to the lowering of blood sugar—they may indeed be called hypoglycæmic convulsions—and this is all the more interesting in light of the work of F. C. Mann who found similar symptoms to develop in dogs when the blood sugar was lowered to about 0.04 percent by isolation of the liver from the circulation. The discovery of this effect on normal rabbits has proved a most important one in connection with the isolation and purification of the extract, since it affords a readily available laboratory test object. It obviates the necessity of using depancreated dogs for testing the potency of the extract and therefore has greatly facilitated our work. As is to be expected an extract which acts only feebly on normal rabbits has a much more pronounced effect on the hyperglycæmia of diabetic dogs.

Not only is the blood sugar lowered in rabbits that are normal but also in those rendered diabetic by any of the experimental methods usually employed to bring this about. These are puncture of the floor of the fourth ventricle (Piquère), asphyxia, poisoning by carbon monoxide gas, ether, or adrenalin. None of these causes hyperglycæmia in rabbits after injecting them with sufficient amounts of pancreatic extract. There may occasionally be a slight increase in the percentage of blood sugar but never to anything like the extent usually observed without extract. The animals used for these experiments were always well-fed with carbohydrates and the glycogen content of the liver determined. The importance of this result is that it shows us that even the purely experimental forms of diabetes have much in common with the clinical forms.

Determination of the percentage of glycogen and of fatty acid in the liver, heart and blood of diabetic animals either injected or not injected with extract has revealed the fact that extract entirely alters the distribution and amount of

these substances. Thus, the liver of a pancreatic diabetic dog never contains more than a very small amount of glycogen even when the animal has been ingesting large amounts of carbohydrate; on the other hand this organ under these conditions is heavily loaded with fat. When extract is given, however, a very large amount of glycogen (over 12 per cent.) appears in the liver and the amount of fat coincidentally declines. At a certain stage in the treatment, of course, considerable amounts of both fat and glycogen may be present side by side. The blood of untreated diabetic dogs (depancreated) contains about two per cent. of fatty acid indicating a marked lipæmia, but if extract is given this disappears down to about 0.5 per cent. The heart of untreated diabetic animals contains the highest percentage of glycogen of any organ in the body but this becomes markedly lowered after treatment with extract.

The importance of these observations rests on the fact that they show that the function which is primarily regulated or controlled by the internal secretion of the pancreas is that concerned with the deposition of glycogen. They would seem to suggest that glycogen must be an essential preliminary stage in the utilization of sugar by the animal body and that when the pancreatic hormone is absent excess of sugar leads to the mobilization of large quantities of fat.

The various effects which are described above all indicate a profound influence of some constituent of the pancreas on the earlier stages of carbohydrate metabolism, namely, the glycogenic function and the blood sugar level, but it might well be that these could be affected with-

out there being any change in the ultimate utilization of sugar by the tissues. This latter process is after all the most important one and its partial or complete failure is the most striking symptom of diabetes. The extent of this combustion of sugar in the body is gauged by determining the respiratory quotient which is done by analysis of the expired air to find out how much carbon dioxide is being given out and how much oxygen is being absorbed by the body. This should always be done by reliable apparatus and by trained observers. In a normal person or laboratory animal fed on carbohydrates the quotient (R. Q.) rises nearly to 1.0 but in a diabetic patient or animal it fails to do so and may be as low as 0.65 its height varying with the severity of the disease. When pancreatic extract is administered along with carbohydrates in diabetes, on the other hand, the quotient rises as in a normal person clearly indicating that utilization of carbohydrate in the tissues has been restored.

In the light of these various types of evidence we feel justified in expressing the belief that it will be possible by administration of pancreatic extract, to treat diabetes in man much more satisfactorily than has hitherto been the case. Dietetic control must no doubt still remain an important feature of treatment, and will probably be all that is necessary in the earlier stages of the disease but in the later stages and in the various crises that are otherwise unmanageable it is hoped that administration of extract will prove of value. What other therapeutic uses the pancreatic extract may have remains as yet undetermined.

J. J. R. MACLEOD

TREATMENT OF DIABETES MELLITUS BY PANCREATIC EXTRACTS

WITH the recent communication from the Toronto School in the March number of this Journal, upon the treatment of diabetes mellitus, one naturally wonders whether a new era in medical history has been opened. We feel that

they are working along the correct and rational lines for the ultimate solution of the problem, but from published data such has not been reached as yet.

It would appear that a potent extract with low toxicity of the internal secre-