An abridgment from THE CANADIAN MEDICAL ASSOCIATION JOURNAL, MARCH, 1922

PANCREATIC EXTRACTS IN THE TREATMENT OF DIABETES MELLITUS

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Since the year 1889, when von Mering and Minkowski produced severe and fatal diabetes by total removal of the pancreas in dogs, many investigators have endeavoured to obtain some beneficial effect in diabetes mellitus, either by feeding pancreas, or by administration of pancreatic extracts.

. . . The whole question has been reviewed recently by Allen: by him, and, indeed, by the majority of recent writers, it is usually stated that pancreatic extracts have no clinical value whatsoever. During the past ten months, two of us (F.G.B. and C.H.B.), working in the Department of Physiology of the University of Toronto, have reinvestigated the problem. Certain of the results obtained have already been published, others are now in press. These may be briefly reviewed here.

Believing that extracts of the pancreas, as usually prepared, did not satisfactorily demonstrate the presence of an internal secretion acting on carbohydrate metabolism, because the active principle was destroyed by the digestive enzymes also present in such extracts, attempts were made to eliminate these enzymes. In the first experiments, this was done by taking advantage of the fact that the acinous tissue (from which the digestive enzymes are derived) but not the insular tissue of the pancreas degenerates in seven to ten weeks after ligation of the pancreatic ducts. Extracts were therefore made with ice-cold Ringer's solution, of degenerated pancreatic tissue removed ten weeks after the ligation of the ducts. The extract obtained by this procedure, when injected intravenously or subcutaneously into diabetic dogs, invariably caused a marked reduction in blood sugar and in the amount of sugar excreted in the urine. It also enabled a diabetic dog to retain a much higher percentage of injected sugar than it otherwise would. Extracts of liver or spleen, prepared in the same manner as the extracts of degenerated pancreas, were found to have neither of these effects. The active principle of the extract of degenerated pancreas was destroyed by boiling in neutral or acid solution or by incubating for two hours at body temperature with pancreatic juice.

In later experiments, it was found that the pancreas of foetal calves of under five months development did not contain proteolytic enzymes, thus confirming the observations of Ibrahim. By extracting such foetal pancreatic tissue, a highly potent and readily procurable preparation was obtained. . . . A method was finally evolved by which an active extract, which would retain its potency for at least one month, could be obtained from normal adult ox pancreas. Daily injections of pancreatic extract (foetal calf or adult beef pancreas) prolonged life of a completely diabetic dog to seventy days, at the end of which time the animal was chloroformed. Allen states that in his experience completely diabetic dogs do not live more than fourteen days. The first results of a study of the respiratory exchange in completely diabetic dogs, before and after administration of extract, showed that the extract confers on the diabetic animal the power to burn carbohydrates. Thus, in a diabetic dog, on starvation or lean meat diet, the respiratory quotient was found to be in the neighborhood of 0.7. The ingestion of carbohydrate caused no

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rise in the CO_2/O_2 ratio, but when preceded by an injection of extract gave a value which approached I.O., indicating that carbohydrate was being burned. Besides the above, it should be recorded that the administration of extract very quickly caused striking improvement in the various symptoms known to be characteristic of complete pancreatectomy.

As the results obtained by Banting and Best led us to expect that potent extracts, suitable for administration to the human diabetic subject, could be prepared, one of us (J.B.C.) took up the problem of the isolation of the active principle of the gland. As a result of this latter investigation, an extract has been prepared from the whole gland, which is sterile and highly potent, and which can be administered subcutaneously to the human subject. The preparation of such an extract made possible at once the study of its effects upon the human diabetic, the preliminary results of which study are herein reported.

. . . Up to the present time, February 22nd, 1922, the effects of these preparations have been observed in seven cases of diabetes mellitus and it is now evident that certain definite results can be obtained by their administration. The effects observed in depancreatized animals have been paralleled in man. The fall in blood sugar occurs and in two cases, repeatedly examined, a rise in the respiratory quotient, indicating carbohydrate utilization, occurs more or less coincidently with the attainment of a normal blood sugar level. Patients report a complete relief from the subjective symptoms of the disease. The sugar excretion shows marked decrease or, if dosage be adequate, disappears. Ketonuria is abolished, thus confirming a similar observation by Collip in diabetic animals, (results as yet unpublished). These results taken together have been such as to leave no doubt that in these extracts we have a therapeutic measure of unquestionable value in the treatment of certain phases of the disease in man. In agreement with observations of other investigators on laboratory animals, it has been found that without careful control severe toxic reactions may be encountered and this will undoubtedly be a factor in the evaluation of the ultimate therapeutic utility of the method.

The following case report illustrates these observations:

Name.—L. T. (Boy), *Aged*—14.

Admitted to the Medical Wards, Toronto General Hospital, December 2nd, 1921.

Present Illness.—About December 1919, he was taken to his family physician because he had been wetting the bed at nights, and also because his ankles became swollen occasionally. One month later, sugar was found in the urine. He states that at this time he was in good health, his appetite was somewhat excessive, but no increased thirst was complained of. Careful dietetic regulation was prescribed and he states that he adhered to this diet fairly well. This his family physician will not confirm. Fasting was also tried apparently without success. The glycosuria persisted, he began to lose weight, frequency of micturition, both day and night, increased up to the time when his physician recommended admission to hospital.

Past Illness.—Always healthy up until two and one half years ago, with the exception of an attack of chicken-pox at the age of ten and, of discharging ear for two years as a baby.

Personal History.—Born in Canada, went regularly to school, able to work well up to time of onset of present illness. Has always been fond of sweet food and previous to the onset of this condition ate freely of candy.

Family History.—Mother and father, one brother and two sisters, all in good health. No diabetes or other familial diseases known.

Examination.—On admission he was poorly nourished, pale, weight 65 pounds, hair falling out, odour of acetone on the breath, tonsils and teeth in good condition, abdomen large and tympanitic. Blood pressure 100-70. He appeared dull, talked rather slowly, quite willing to lie about all day. Hands show marked xanthochromia. No findings of note in examination of cardio-vascular, respiratory, abdominal systems or of the blood. The urine at the time of admission was strongly acid, specific gravity 10.30 to 10.40. The test for sugar strongly positive. Rothera and ferric chloride tests for ketones strongly positive. 24 hours amount of urine, 3-5 litres. Blood sugar 5.8 mg. per c.c.

Treatment.—He was put to bed and was quite content to remain there most of the time. However, when he wished to do so, he was allowed to get up and wander about the ward, which he did very little during the first month. His diet was as follows:—

Dec. 2nd.—5, 10 and 15% vegetables as much as desired.

Dec. 11th.—60 grams lean meat daily added to diet.

Dec. 15th.—4 bran cakes daily added to diet.

Jan. 4th.—Daily ration to consist of 50 grams lean meat, 5 and 10% vegetables, and fruits and bran cakes to make up exactly 100 grams of carbohydrates per day. Clear broth, cocoa, tea and coffee in moderation. Total intake about 450 calories.

No further change in diet was made.

This case was one of severe juvenile diabetes with ketosis. Previous to admission, he had been starved without evident benefit. During the first month of his stay in hospital, careful dietetic regulation failed to influence the course of the disease and by January 11th his clinical condition made it evident that he was becoming definitely worse.

The extracts given on January 11th were not as concentrated as those used at a later date, and, other than a slightly lowered sugar excretion and a 25% fall in the blood sugar level, no clinical benefit was evidenced.

Daily injections of the extract were made from January 23rd to February 4th (excepting January 25th and 26th). This resulted in immediate improvement. The excretion of sugar became much less. On days of treatment, this varied from 7.5 gms. to 45.1 gms. compared with a previous amount well over 100 gms. daily. The acetone bodies disappeared from the urine. The boy became brighter, more active, looked better and said he felt stronger. No extract was given from February 5th to February 15th. During this time sugar again appeared in the urine in large amounts along with traces of acetone. Administration of extract in smaller doses after February 16th again resulted in lowered sugar excretion and disappearance of acetone from the urine. . . .

. . . Although the other six patients treated by these extracts were all favourably influenced by its administration, particular reference might be made to one—a severe case who had been excreting 20 gms. of glucose on a diet containing 10 gms. carbohydrate and 24 hundred calories per day. Following injection of the extract his urine became sugar free, and he obtained complete relief from severe depression and extreme lassitude. Respiratory quotients in this same case showed a definite rise after injection of the extract, confirming the increased utilization of carbohydrate. All patients were improved clinically. . . .

SUMMARY

Following the production of what appears to be a concentrated internal secretion of the pancreas and the demonstration of its physiological activity in animals, and, under careful control, its relatively low toxicity, we are presenting a preliminary report on the pharmacological activity of this extract in human diabetes mellitus. Clinical observations at this juncture would appear to justify the following conclusions:—

(1) Blood sugar can be markedly reduced even to the normal values.

(2) Glycosuria can be abolished.

(3) The acetone bodies can be made to disappear from the urine.

(4) The respiratory quotient shows evidence of increased utilization of carbohydrates.

(5) A definite improvement is observed in the general condition of these patients and in addition the patients themselves report a subjective sense of well being and increased vigor for a period following the administration of these preparations.

For their hearty co-operation and kindly assistance and advice, we have great pleasure in presenting our best thanks to Professor J. J. R. Macleod of the Department of Physiology, to Professor V. E. Henderson of the Department of Pharmacology, to Professor J. G. Fitzgerald of the Department of Hygiene, and to Professor Duncan Graham of the Department of Medicine of the University of Toronto.