

PANCREATIC EXTRACTS IN THE TREATMENT OF DIABETES MELLITUS

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SINCE the year 1889, when von Mering and Minkowski (1) 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.

Minkowski, Sandmeyer (2), Pfluger (3) and others found that feeding pancreas was followed by negative or even harmful results. More recently, Murlin (4), Kleiner (5) and Paulesco (6) have tried the effects of aqueous extracts of the pancreas intravenously, on depancreatized animals and have found transitory reduction in the percentage of blood sugar and in the sugar excreted in the urine.

In 1907, Rennie and Fraser (7), recognizing the possibility that pancreatic enzymes might have harmful effects on the internal secretions, secured islet tissue from teleostean fishes, where it exists separately from the rest of the pancreas, and fed it to human diabetics. Their studies demonstrated no beneficial influence on the condition of the patient. E. L. Scott (8) in 1912 sought to eliminate the influence of proteolytic enzymes by using alcoholic extracts of the pancreas. He did not find, however, that such extracts caused as marked a reduction in the urinary sugar or in the G-N. ratio as when extracts were made with acidulated water. The whole question has been reviewed recently by Allen: (9), 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, (10) 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 (11). By extracting such foetal pancreatic tissue, a highly potent and readily procurable preparation was obtained. Besides affording a much more practicable method for securing larger quantities of extracts, this result demonstrated that the active principle is essentially the same from whatever animal it is prepared. 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 rise in the $\frac{CO_2}{O_2}$ 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. The extract containing the active principle is being further purified and concentrated. A detailed report of the method of extraction, purification and concentration will be published at an early date.

For the investigation of the clinical application of these extracts in the treatment of human diabetes, Professor Graham has placed at the disposal of two of us (W. R. C. and A. A. F.) the cases of diabetes mellitus in the wards of the Medical Service of the Toronto General Hospital.

Patients were placed on a constant diet, varying with the severity of each individual case, and their reaction to such treatment studied for

a period of a week, after which various samples of extract were administered and the effects observed. The ordinary routine clinical examinations were carried through. Blood sugar was estimated at intervals by the revised Folin-Wu method, urinary sugar by Benedict's methods, the acetone bodies by Van Slyke's methods, and the respiratory quotient by the Tissot-Haldane and Douglas-Haldane methods.

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 coincidentally 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, fre-

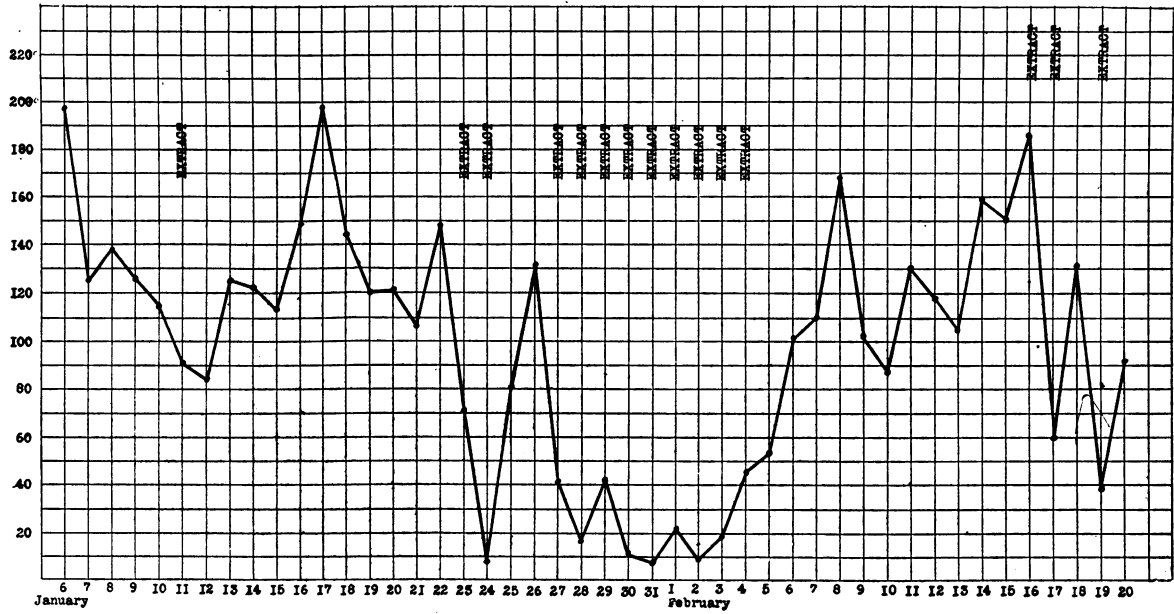


CHART I.—Effect of extract on glycosuria

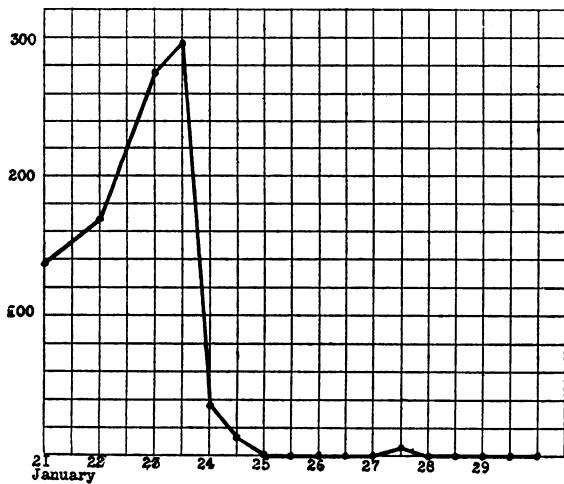


CHART II.—Showing the cessation of ketonuria following administration of extract

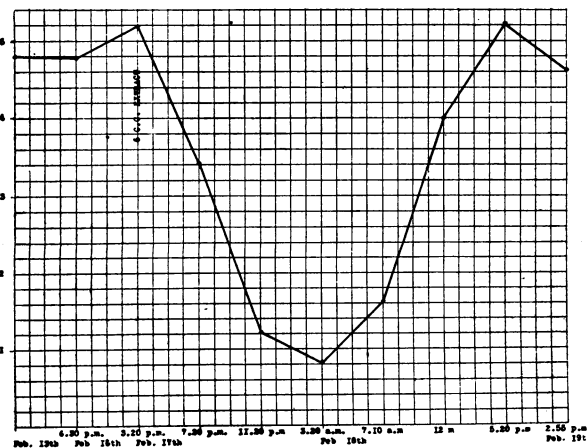


CHART III.—Effect of one injection of extract on Blood Sugar (mgs. per c.c.e=tenth per cent)

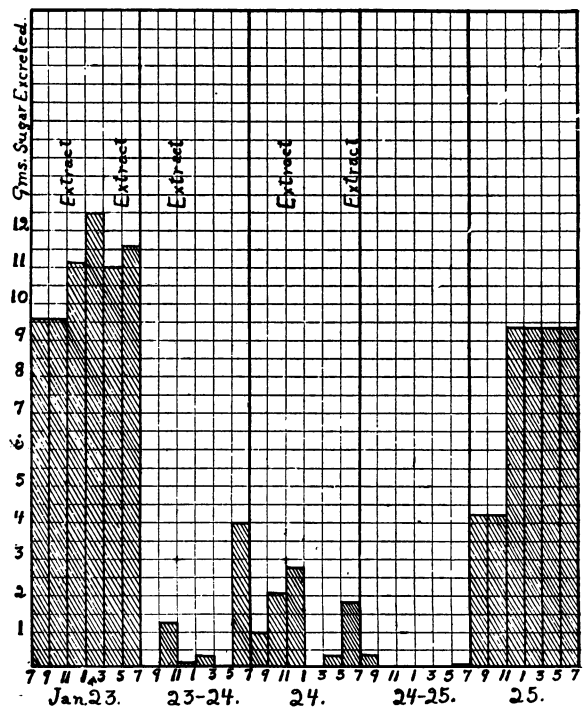


CHART IV.—Curve of glucose excretion during extract administration. Large dots indicate blood sugar

quency 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 condi-

tion 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 as shown in Chart I 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. Chart II shows the fall in the total acetone bodies of the urine during the periods of treatment after January 23rd. Chart III gives a four hour record of the blood sugar following the administration of a single dose of 6 c.c. extract on February 17th. Chart IV shows the influence of extract on the amount of glucose excreted in each two hourly period when extract was being used. Table I records the volume of urine and amount of sugar excreted each day and blood sugar determinations. The qualitative test for the daily excretion of acetone bodies in the urine and the amount of extract given is also tabulated.

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. It is difficult to put in words what is meant by clinical improvement. Those who have been treating diabetes will have recognized as early signs of

improvement a certain change in the skin, the appearance of the eyes, the behaviour of the patient, his mental and psychic activity, and the physical evidences, as well as his testimony, of increased vigor and desire to use his muscles. Under present day treatment, such improvement occurs in diabetics free from acetone but is un-

doubtedly more striking in patients recovering from a ketosis. This is the nature of the improvement seen clinically as a result of the administration of these extracts, and, while it is of a temporary nature, we believe that it justifies the hope of more permanent results following more adequate and carefully regulated dosage.

TABLE I.

Date	24 hr. amount of urine in c.c.	24 hr. excretion of glucose in gms.	Blood Sugar in mg. per c.c.	Rothera Test		Total acetone bodies in mgs. per litre	Subcutaneous injection of pancreatic extract in c.c.	
							A.M.	P.M.
Dec. 12th.....	5.8	plus	plus
20th.....	4.5	plus	plus
29th.....	5.2	plus	plus
Jan. 3rd.....	5.2	plus	plus
6th.....	4500	187.8	plus	plus
7th.....	4020	126.2	plus	plus
8th.....	3650	137.2	plus	plus	72
9th.....	3690	126.7	6.2	plus	plus	540
10th.....	6870	114.0	plus	plus
11th.....	3625	91.5	3.2-4.4	plus	plus	188	15 c.c.
12th.....	4060	84	4.9	plus	plus	69
13th.....	3950	125.5	plus
14th.....	3780	123.5	plus	plus
15th.....	3900	114.7	plus	plus
16th.....	3910	148.0	plus	plus
17th.....	3960	197.3	6.7	plus	plus
18th.....	4300	144.6	plus	plus
19th.....	3770	120.6	plus	plus
20th.....	3840	121.9	plus	plus
21st.....	4580	107.3	plus	plus	137
22nd.....	4540	148.5	plus	plus	167
23rd.....	4210	71.1	5.2	plus	plus	282	5 c.c.	20 c.c.
24th.....	4120	8.7	1.2-3.0	plus	30	10 c.c.	10 c.c.
25th.....	3880	80.5	0	0	0
26th.....	5070	130.3	0	0	0
27th.....	3040	42.2	plus	4	4 c.c.	4 c.c.
28th.....	5125	16.7	trace	0	2 c.c.	4 c.c.
29th.....	3275	42.5	0	0	0	4 c.c.
30th.....	2715	11.5	trace	0	4 c.c.	4 c.c.
31st.....	4415	7.5	0	0	0	4 c.c.	4 c.c.
Feb. 1st.....	3145	21.8	0	0	0	4½ c.c.	4 c.c.
2nd.....	2700	9.1	0	0	0	5 c.c.	4 c.c.
3rd.....	4150	18.2	0	0	0	5 c.c.	4 c.c.
4th.....	3740	45.1	0	0	0	5 c.c.	4 c.c.
5th.....	3475	53.3	0	0	0
6th.....	3900	101.5	0	0	0
7th.....	3700	110.1	0	0	0
8th.....	4910	167.1	trace	0
9th.....	4940	101.7	0	0	0
10th.....	4710	86.9	trace	0
11th.....	4510	129.9	trace	0
12th.....	3170	117.7	4.87	trace	0
13th.....	2595	106.7	4.9	trace	0
14th.....	4670	158.5	trace	0
15th.....	3275	151.4	trace	0
16th.....	4611	185.0	4.73	neg.	0	5 c.c.
17th.....	3930	60.4	0.85-5.2	neg.	0	6 c.c.
18th.....	4790	132.3	2.0-4.5	neg.	0
19th.....	3105	39.6	neg.	0	4 c.c.
20th.....	3985	92.0	neg.	0

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.

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New Opium Laws in Great Britain.—In compliance with the agreement at the Hague International Opium Convention in 1912, Great Britain in 1920 adopted a law for the regulation of traffic in narcotic drugs. This bill would doubtless have been adopted long before, had it not been for the war. The regulations under the act went into effect September 1. "As originally drafted by the Home Office," says the *British Medical Journal* editorially, "they were open to much legitimate criticism; but after emendations by a departmental committee, in accordance with the recommendations of the British Medical Association, these are now in a form better calculated to achieve the end desired without impeding the legitimate use of the drugs in question." In addition to the international agreement under the Hague Convention, the Versailles treaty creating a league of nations, contained a paragraph pledging all of the powers that were signatories to the treaty to enact effective laws for the regulation of dangerous drugs within twelve months from the time that these treaties went into effect. The advisory committee appointed by the Council of the League of Nations will present a report at the assembly of the league in Geneva this month, summarizing the action taken by the various nations. The advisory committee, on the initiative of Dr. Wellington Koo, Chinese minister to

Great Britain, proposes to undertake investigations to ascertain approximately what amount of opium, morphin and cocain is required for legitimate medical purposes, with a view to inaugurating international methods for restricting the manufacture of these drugs to the amount necessary for medical and scientific requirements. It has been generally recognized by those interested in the regulation of narcotic drugs that this problem could never be satisfactorily solved except through general international agreement and co-operation. Restriction of the growth and manufacture of these drugs to the amount necessary for legitimate needs, and international co-operation for the prevention of smuggling across boundary lines, are the most essential features in any plan for the control of this traffic. The problem is world-wide, and the co-operation of all civilized nations is essential for its solution.—*Jour. A. M. A.*, Sept. 24, 1921.

WE understand that a bust of Dr. W. T. G. Morton, the discoverer of anæsthesia, will be placed in the Hall of Fame. At the annual dinner of the American Anæsthetists Dr. S. A. Knopf proposed that the price should be contributed in great part by the anæsthetists of America, and urges those who are interested to make a contribution.