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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 teleosteal 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

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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 $\frac{C02}{02}$ 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 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, fre-

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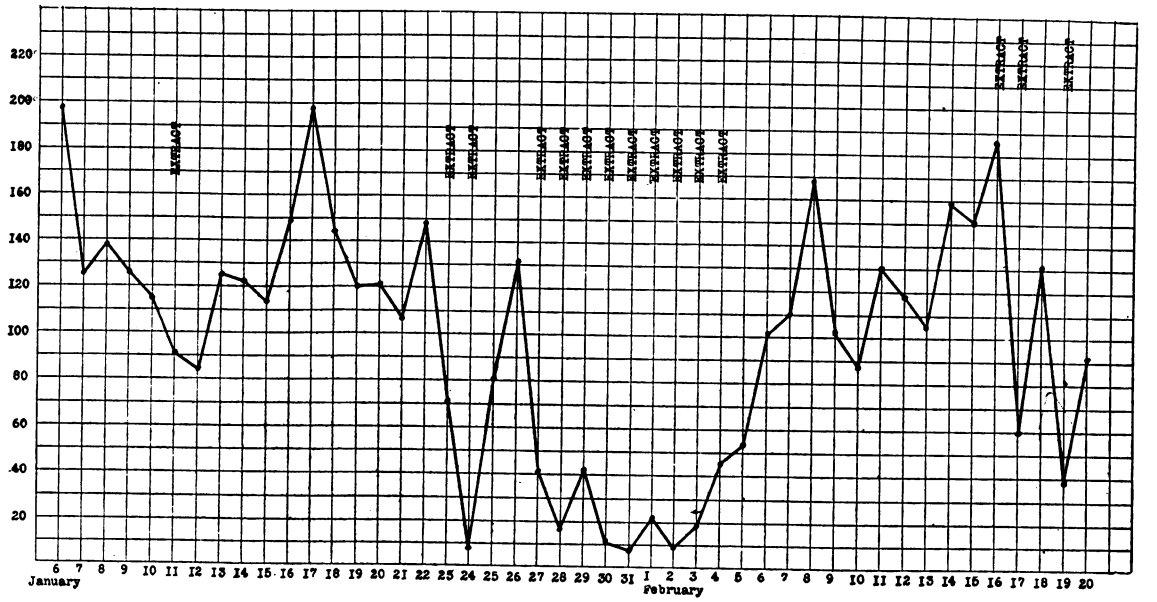

CHART I.—*Effect of extract on glycosuria*

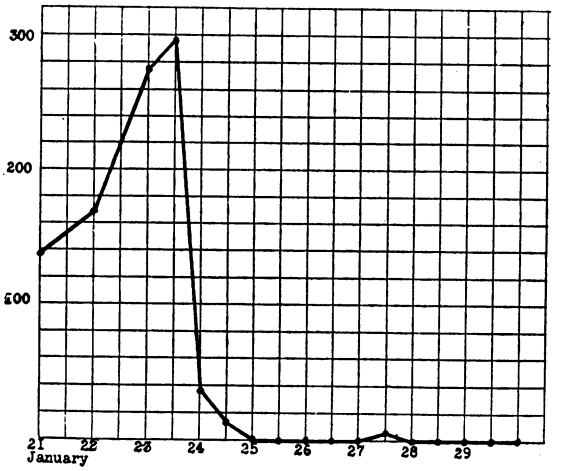

CHART II.—*Showing the cessation of ketonuria following administration of extract*

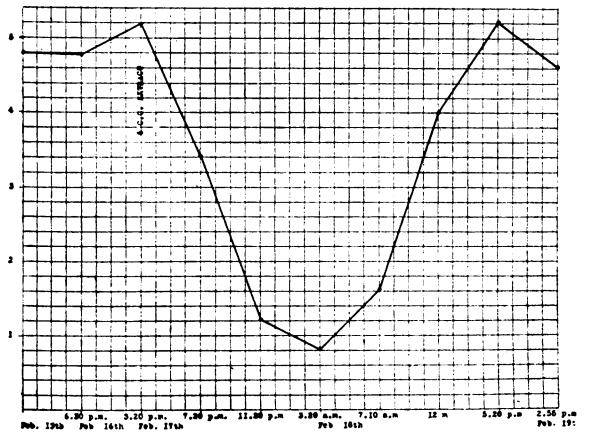

CHART III.—*Effect of one injection of extract on Blood Sugar (mgs. per c.c.e=tenth per cent)*

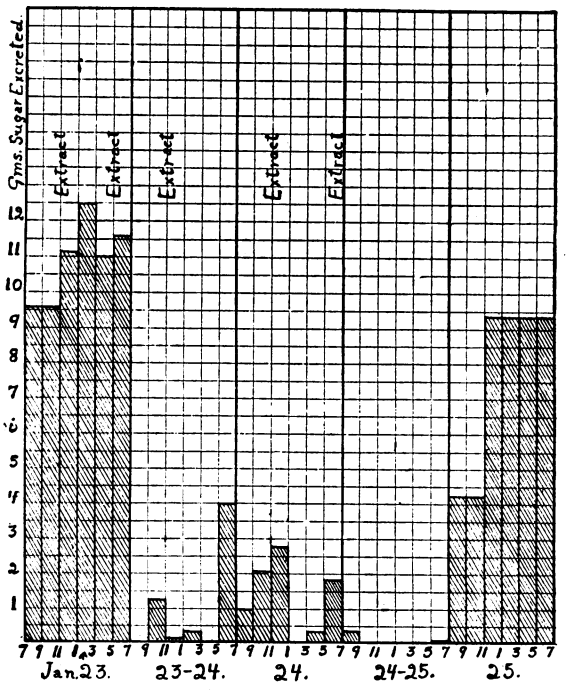

CHART IV.—*Curve of glucose excretion during extract administration. Large dots indicate blood sugar*

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 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 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. Repiratory 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

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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 undoubtedly 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	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	....	
26th	5070	130.3	....	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	4 c.c.	
30th	2715	11.5	....	trace	0	4 c.c.	4 c.c.
31st	4415	7.5	....	0	0	4 c.c.	4 c.c.
Feb. 1st	3145	21.8	....	0	0	4½ c.c.	4 c.c.
2nd	2700	9.1	....	0	0	5 c.c.	4 c.c.
3rd	4150	18.2	....	0	0	5 c.c.	4 c.c.
4th	3740	45.1	....	0	0	5 c.c.	4 c.c.
5th	3475	53.3	....	0	0	....	
6th	3900	101.5	....	0	0	....	
7th	3700	110.1	....	0	0	....	
8th	4910	167.1	....	trace	0	....	
9th	4940	101.7	....	0	0	....	
10th	4710	86.9	....	trace	0	....	
11th	4510	129.9	....	trace	0	....	
12th	3170	117.7	4.87	trace	0	....	
13th	2595	105.7	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:—

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(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.

REFERENCES

(1) VON MERING AND MINKOWSKI—*Arch. f. exp. Path. u. Pharmakol*, 1889, XXVI, 371.

(2) SANDMEYER, W.—*Ztschr. f. Biol.*, 31, 1895, 12-85.

(3) PFLUGER—*Pflugers Arch.*, 118, 1907, 265-321.

(4) MURLIN—*Jour. Biol. Chem.*, 1913, XV, 365.

(5) KLEINER—*Jour. Biol. Chem.*, 1919, XL, 153.

(6) PAULESCO—*Comp. rend. de Soc. de biol.*, July 1921

(7) RENNIE AND FRASER—*Biochem. Jour.*, Vol. I, 1907, 7.

(8) SCOTT, E. L.—*Am. Jour. Phy.*, Vol. XXIX, Jan. 1912, 3.

(9) ALLEN, F. M.—Glycosuria and Diabetes, Cambridge, 1913.

(9) ALLEN, F. M.—*Glycosuria and Diabetes*, Cambridge, 1913. ALLEN, F. M., STILLMAN, E., AND FITZ, R.—*Monograph No. II*, Rockefeller Institute for Medical Research, New York, 1919.

(10) BANTING AND BEST—*Jour. Lab. and Clin. Med.*, February 1922.

(11) IBRAHIM—*Biochem Zeitsch*, 1909, XXII, pp. 24-35

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

DIABETES MELLITUS

One of the most widely heralded methods of treatment of diabetes is the so-called oatmeal diet therapy. . . Apparently its chief benefit is its nauseating tendency, which prevents the gratifying of the craving appetite ever present in the diabetic. . .

Not many months ago Sewall reported that he had found some diabetics, past middle life, improve greatly when given an infusion of lean meat acidulated with hydrochloric acid. . .

Inulin is said by Strauss to be of value in the treatment of diabetes. He recommends that the patient be given vegetables such as dandelions, artichokes, etc., which are rich in inulin.

Blum is of the opinion that the vegetable albumins are more useful to the diabetic than are the meat albumins.

Remarkable results are reported by Cowles in a case in which he fed the patient from one to six uncooked pancreases every day. Such heroic and unusual treatment was made possible by the fondness of the patient for raw or underdone meat. Marked improvement is said to have followed as long as the raw pancreases were eaten, but the symptoms returned after his diet was abandoned, and the disease finally killed the patient.

Dr. E. I. Spriggs is entirely correct when he insists that the success of the dietetic treatment of this disease is largely dependent on the way the allowable food-stuffs are presented to the patient. The importance of good cooking and of variety in presentation of food is great enough, in all conscience, to the well man, but to the diabetic these points are vital, and equal to, in importance, the very quality of the food itself.

While the real cause of diabetes is, in the majority of cases, doubtless, due to gross errors in eating, resulting in a long-continued toxaemia, or auto-intoxication, it is probably true that the immediate cause lies in the failure of the pancreas to manufacture its internal secretion. Assuming such to be the case, it has been thought that, by giving the diabetic pancreatic extract, the lacking secretion would be supplied. In practice, however, the use of pancreatic extract has not produced the results that have been hoped. This is probably due to the fact that while the normal pancreas is pouring its secretion all the time, it is impossible to administer enough of the extract to supply more than the smallest fraction of the amount required by the organism. Personally I have never seen any beneficial effects from large doses of the various pancreas extracts on the market. Possibly if we could use the uncooked pancreases, as used by Cowles, we might gain satisfactory results.

Nor has the attempt to isolate a hormone that would act as a stimulator of sugar-oxidation been more successful. Torschbach, who has done splendid work in this direction, admits that the only results of giving this hormone is to produce toxic symptoms in the patient. It is true that the excretion of sugar is temporarily reduced in such cases, but not more than might be explained by the febrile temperature which the administration of the hormone produced.

Leschke also has experimented exhaustively with extract of pancreas, but with no better results. In fact, it may be conservatively said that in the present state of our knowledge we are not justified in attempting to treat diabetes by means of pancreatic extracts.

The experiments of Hedon should be mentioned. This investigator had long held that the question of the pancreas producing an internal secretion was not proved. By experimenting, however, with normal and diabetic dogs, Hedon was able to adduce additional testimony in favour of the "internal secretion" hypothesis. He also demonstrated that we may have to modify our views of the cause of this disease. That is, we may be forced to conclude that diabetes, instead of being immediately due to a diminished power of the pancreas to oxidize sugar, is really caused by an actual over-production of sugar in the liver caused by the over-ingestion of the various sugars and starches, or more than the liver is able to properly take care of.—A. J. Hodgson: *Canad. Med. Ass. J.*, 2: 877, 1912.