ON THE TREATMENT OF DIABETES MELLITUS BY ACID EXTRACT OF DUODENAL MUCOUS MEMBRANE

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The carrying out in the Bio-Chemical Laboratory of the experiments on the secretion of organic acids in diabetes described in the previous paper supplied an opportunity for testing the hypothesis that the *internal* secretion of the pancreas might be stimulated and initiated (similarly to the external secretion) by a substance of the nature of a hormone or secretin yielded by the duodenal mucous membrane ; and that in certain cases of diabetes the appearance of sugar in the urine might be due to functional disturbance occasioned by the absence of such an intestinal excitant of the internal secretion.

The fact that an internal secretion of the pancreas is necessary for the regulation of carbohydrate metabolism, and that in the absence of this secretion oxidation of dextrose cannot be carried out, with the result that death occurs from acute diabetes, has been clearly proven by the experiments of Minkowski and v. Mering,[1] and others on complete and partial pancreas removal, and the history of the subject is too well-known to require detailed description here.

It was suggested by Schäfer that the formation of the internal pancreatic secretion might possibly be due to peculiar nests of cells of different form and staining properties to the other secreting cells of the gland.

These cells from their isolated appearance, and after the name of the observer who first described them, are called the 'islets of Langerhans.'

1. *Archiv. of Exper. Path. u. Pharm.*, 1890, Vol. XXVI, p. 371; Minkowski, *Arch. of Exper. Path. u. Pharm.*, 1893, Vol. XXXI, p. 85.

More recently, however, it has become doubtful whether these peculiar cells have in reality any special connection with the internal secretion of the gland, for it has been shown by Dale[1] that after prolonged excitation of the external secretion of the gland by means of secretin, there is a great increase in the number of the islets of Langerhans, from which it would appear most probable that the islet condition is only a phase into which the normal secreting pancreatic cells pass as a result of activity.

It will be shown later in this paper that the solution containing secretin at the same time that it stimulates the external secretion also probably stimulates the internal secretion, so that the hypothesis is not quite ruled out that the prolonged chemical stimulation of the cells of Langerhans may have been responsible for the changes observed in the islets.

The more probable hypothesis is, however, that the pancreas contains but one type of secreting cell which yields both the internal and external secretion, and that the cells of the islets of Langerhans are ordinary pancreatic cells in a phase of exhaustion.

If this be the case the likelihood is increased that anything which stimulates the external secretion will also stimulate the internal secretion which passes either directly or indirectly by the lymphatics to the blood stream.

It has been clearly shown by Bayliss and Starling,[2] that the activity of the pancreas as far as its external secretion is concerned is normally called forth by chemical agency by means of a substance termed by these authors *secretin*, which is formed by the cells of the duodenal mucous membrane and carried to the pancreatic cells in the blood stream.

Bayliss and Starling were also able to prepare by treatment of the scraped off mucous membrane by dilute hydrochloric acid, a solution containing the active substance, secretin, which called forth most powerfully an external secretion from the gland on being injected into a peripheral vein.

1. *Proc. Roy. Soc.*, 1904, Vol. LXXIII, p. 84.

2. *Proc. Roy. Soc.*, 1902, Vol. LXIX, p. 352; *Jour. of Physiology*, 1902, Vol. XXVIII, p. 325; *Ibid*, 1903, Vol. XXIX, p. 174.

The active material was also shown to be capable of withstanding boiling so that it is not a coagulable proteid, and other properties of the active substance were worked out by W. A. Osborne.

Now if the view be taken that the cells of the pancreas are all of one type it is very probable that in the process of excitation of the external secretion by secretin, the internal secretion is also involved, and even if the functions of internal and external secretion by the gland be regarded as distinct and separate processes, it becomes highly desirable to test whether the duodenum does not also supply a chemical excitant for the internal secretion of the pancreas.

This line of argument appears to have occurred to the discoverers of secretin themselves, for Starling mentions a case of diabetes which was tested by Spriggs by injections of secretin solutions but with negative results.

It would, however, be illogical to rule out the hypothesis outlined above upon the evidence of one negative case, or even a number of negative cases of treatment of diabetes with secretin. For the position is one which can be proven by a certain percentage of positive results even if negative results occur alongside.

If, for the purpose of argument, we take it that the duodenum does yield a chemical excitant for the internal secretion of the pancreas, and that in the absence of the internal secretion glycosuria results, then there are three places in the chain at which weakness due to functional or other disarrangement may occur and lead to a breakdown and the appearance of diabetic conditions. First, the breakdown may occur at the duodenum, on account of the non-secretion of the excitant ; secondly, the breakdown may take place at the pancreas, so that although the excitant is formed at the duodenum and carried to the pancreas, yet these cells are not capable of excitation, either from complete morbid change or from some functional alteration in their metabolism ; and thirdly, there is the possibility, that even when the duodenum is normal and supplying its excitant, and although the pancreas is also normal and yielding, as a result of the action of the excitant, its internal secretion, yet there are changes in the oxidizing tissues such as the liver or muscles which prevent the oxidizing function of these from coming into operation.

It is clear that it is only in the first class of case that benefit might be expected to follow in a diabetic from administration of extracts of duodenum, even granting that the experimental difficulties of administration had been so overcome that the active material entered the circulation and reached the pancreas as if it had naturally been formed in the patient's duodenum.

Accordingly, it is scarcely to be expected that in all cases administration of extracts of duodenal mucous membrane will cure, or even benefit, diabetics, and to prove the existence of a specific chemical excitant for the internal secretion of the pancreas formed in the duodenum, it is only necessary to show in a fair percentage of cases that abolition of glycosuria follows administration of the extract of duodenal mucous membrane.

The three cases recorded in this paper form a commencement in this direction, and, although the number of cases is small, the results are promising, and we publish them in order to attract attention to the subject, and have the matter tested by other observers in a larger number of cases, premising that positive results cannot, for the reasons given above, be expected in all cases.

Before passing to the description of the cases, it may be pointed out that the view that diabetes may, in a certain percentage of the cases, arise primarily at the duodenum and not at the pancreas, may, if substantiated, cast light upon some of the *post-mortem* findings in diabetes.

Although in a certain number of cases gross lesions are found in the pancreas (put down by some authorities at about 30 per cent. of the cases), yet, in the majority of cases, no such lesions are discoverable, and the gland, both macroscopically and microscopically, is to all appearances normal. Nor has any causal connection with diabetes been found in the condition of the islets of Langerhans, which are, in the majority of cases, found with their normal appearance. A percentage of such cases, at least, of normal pancreas associated with diabetes, may find their explanation in the fact that the mischief lay in the duodenum.

Method used for preparing the extract. The upper three or four feet (about one metre) of the small intestine of the pig, obtained fresh from the abattoir, is taken, and laid open from end to end. The mucous surface is then rapidly and as thoroughly as possible washed free from adherent matter with normal saline or water, but the washing must not be too long continued. As the extract is afterwards sterilized by boiling there is no fear of infection from any slight trace of adherent material. The strip of intestine is then laid with the mucous surface upward upon a plate of clean glass, and the mucous membrane scraped off with a broad blunt knife, the blade being held perpendicularly to the surface, and five or six inches being cleared at a time. The scrapings are next passed through a fine sausage machine or disintegrator, from which they come out as a homogeneous, soft, semi-fluid mass. This mass is thoroughly mixed up for about five minutes in a mortar, with an equal volume of a dilute solution of hydrochloric acid, containing about 0·4 per cent. of hydrochloric acid, made by adding 10 c.c. of pure, strong hydrochloric acid to a litre of water. The mixture is then placed in a beaker, and, while being stirred, is raised to the boiling point. Finally, sodic hydrate is added until the mixture just remains acid to litmus paper. The resulting preparation is given by the mouth, either as it is, or after removal of the coarse, precipitated proteid. The solution if kept in a bottle roughly sterilized by boiling water will, if left slightly acid, keep well for three or four days. It should not be used later than this because it slowly loses activity, which takes place more rapidly in alkaline solution, for which reason, also, it is best to keep in acid solution.

Description of Cases

Case I. A man of 25 years, by occupation a street car conductor, or driver, was admitted to the Royal Infirmary, Liverpool, under the care of one of us (J. H. A.), on Sept. 14, 1904, suffering from polyuria, loss of weight, weakness, and excessive thirst.

The urine on admission measured 3400 to 3700 c.c. (110 to 120 ozs.), and contained on an average 195 grams (or 3000 grains)

of sugar. Placing the patient on a diabetic diet did not materially reduce the output of sugar. On Sept. 24 the patient was put upon 1 drachm (3·6 grams) of sodium bicarbonate daily, and this was maintained until Nov. 18. On Oct. 11 the patient was placed upon codeia, ½ grain (0·03 gram), three times daily, which was maintained until 24th Nov. No decrease of sugar followed the administration of the codeia, the amount being maintained unaltered till 23rd Nov., when the patient was put on phenazonum, 5 grs. (0·3 gm.), three times daily.

After the commencement of the phenazonum the amount of sugar slowly decreased in a fluctuating fashion until at the middle of January, 1905, it lay between 40 grams (600 grains), and 65 grams (1000 grains) daily, and was constant at this level.

Without taking off the phenazonum, the patient was given by the mouth extract of duodenal mucous membrane prepared as above described; half an ounce (15 c.c.) three times daily, and on Feb. 8, 1905, the amount given was doubled.

The amount of sugar during the first three weeks after the treatment began showed no alteration, but on the 28th Feb., 1905, there occurred a sudden drop to 32 grams (490 grains). On March 2 the amount of sugar was 25 grams (390 grains), and for some time after this the amount fluctuated between 21 grams (300 grains) and 30 grams (450 grains) daily. The amount of sugar continued to drop, and about the end of May the urine became entirely free from sugar, the patient increased in weight, and the polyuria disappeared. The patient returned to his work, and shortly afterwards stopped coming for the extract. The patient remained well, and continued at his work, as an electric street car driver, until the 14th Aug., 1905. About this time he contracted a cold as the result of a chill obtained at his work, and from this date he grew weaker and lost in weight. On Oct. 13 the patient returned to hospital, he had about 4 to 5 per cent. of sugar on a daily quantity of 2500 to 3000 c.c. (80 to 100 ozs.) of urine. In spite of treatment with the extract there was no material reduction in the sugar, and it was soon discovered that the patient

was suffering from phthisis, which progressed rapidly, and on Dec. 17, 1905, the patient died.

The *post-mortem* examination showed that the pancreas was to all appearance normal, the duodenum had undergone too much alteration for histological examination, and the immediate cause of death was caseous pneumonia of the lungs due to tuberculosis.

Although this first case terminated fatally it is to be observed that for a considerable period after treatment with the extract, the urine was entirely free from sugar. It was this positive result, apparently following the administration of the extract, which led us to continue the treatment in the other two cases which we have to record.

Case II. The case was that of a boy *aged 7 years*, seen by one of us (J. H. A.) in consultation with Drs. Macfie Campbell and Graham Martin.

The patient was never robust in constitution, but had had no very serious illness. He was fairly well during the early part of the year 1905; his mother, who had been absent from home in June, noticed on her return that he had lost flesh, was much paler, languid, always thirsty, and had a huge appetite.

On July 3rd, the patient was seen by Dr. Martin, who found that the urine had a sp. gr. of 1040, and contained 8·3 per cent. of sugar on a daily quantity of 2170 c.c. (70 oz.), that is 179 grams of sugar daily in a child aged 7 years.

The patient was immediately put on a strict diabetic diet, except a small amount of torrified toast, which was also stopped on 13th July, and gluten bread substituted.

He was given phenazonum in 5 grain doses three times daily, and also acid extract of duodenum, prepared as above described in, at first, 2 drachm doses (about 8 grams) thrice daily, and in a week this was doubled in quantity. From the 14th July till the 18th of August, the patient, on account of constipation, was also given *sodii sulphas effervescens.*

The progress of the case is shown in the following table :—

Date 1905	Daily amount of urine in c.c.	Percentage of sugar	Total daily amount of sugar in grams	Weight of patient in kilograms
July 3	2170	8·3	179	18·659
„ 5	The patient was dieted and also given acid extract of duodenal mucous membrane			
„ 7	1980	4·3	85	18·955
„ 9	1890	5·1	96	18·909
„ 12	1860	4·0	74	18·773
„ 14	1610	3·2	52	19·114
„ 17	2170	2·6	56	19·409
„ 19	2170	3·9	85	19·432
„ 21	2360	3·2	76	19·750
„ 23	2360	2·3	54	19·773
„ 24	1460	2·4	35	—
„ 26	2360	0·625	14·7	19·795
„ 28	2570	0·812	20·9	19·682
„ 30	2170	1·083	23·5	20·090
„ 31	2050	1·063	21·8	20·090
Aug. 2	1920	0·771	14·8	20·205
„ 4	1920	0·521	10·0	20·455
„ 6	1800	0·583	10·5	20·455
„ 10	2040	0·417	8·5	20·500
„ 15	1950	0·250	4·9	20·545
„ 18	2420	0·125	3·0	20·295
„ 20	1420	Trace	—	19·864
„ 24	1300	„	—	19·886
„ 30	1180	Absent	—	19·773
Sep. 5	1270	„	—	20·090
„ 13	1460	„	—	20·568
„ 19	1610	„	—	20·590
„ 25	1270	„	—	20·590
Oct. 1	1490	„	—	20·590
„ 11	1360	„	—	20·545
Nov. 20	—	„	—	20·654
Dec. 26	—	„	—	20·932

NOTES.—The initial drop down to 74 grams on July 12, may probably be ascribed to the dieting. On July 13, the small amount of dried toast was discontinued which caused a further small decrease.

A marked drop occurs on July 24, and is continued on the following days. By August 18, the percentage of sugar has fallen to the limit of error of the method used (Gerrard's modification of Fehling's method). Shortly after this the urine showed no trace of reduction on qualitative testing by ordinary Fehling's solution. The phenazonum treatment was reduced to one dose daily on October 27, and stopped entirely on November 14. The duodenal extract was reduced to one dose daily on November 20th, and discontinued completely on December 2nd. Up to the time of writing the urine remains entirely free from sugar.

Case III. A girl, *aged* 9 *years*, a patient of Dr. Matthews, of Blundellsands.

It is difficult to judge how long the child had suffered from glycosuria, before it was discovered (November 12, 1905). For three months or so it was noticed that she was getting thin, but as she was growing taller, and was active and strong, no special attention was paid to the thinness. It is known, however, that she weighed 68 pounds (30·91 kilograms) a year ago.

The first sample of urine examined, was passed on November 12, 1905, at 1 p.m., the sp. gr. was 1040, and the sugar estimated volumetrically by Fehling's method was 10 per cent.

The child was at once put on a stricter diet, but carbohydrate was never completely excluded throughout the entire case, potato being allowed at dinner time, and a small quantity of milk. Manhu bread, which contains some starch, was given up to Nov. 19, after which diabetic bread (Callard and Co.) was employed. Phenazonum and alkaline carbonates were administered during the first ten days, but later were entirely discontinued, and the case was treated, from the commencement of the employment of the acid extract of duodenum, on that alone.

Throughout the case the urine was only collected from 8 a.m. to 8 p.m., so that for purposes of comparison for twenty-four hours the figures ought to be doubled, but otherwise they are strictly comparable throughout.

The following table shows the progress of the case :—

Date 1905	Amount of urine in c.c. from 8 p.m. till 8 a.m. daily	Percentage of sugar	Total sugar in this period in grams	Weight of patient in kilograms
Nov. 13	740	8·0	59·2	29·090
„ 15	740	6·0	44·4	—
„ 17	740	6·5	48·1	29·090
„ 19	740	5·5	40·7	29·140
„ 21	740	3·0	22·2	—
„ 23	560	3·0	16·8	29·090
„ 25	775	3·0	23·2	—
Acid extract of duodenal mucous membrane given after this time.				
„ 27	530	2·75	14·5	29·540
„ 29	620	2·25	13·9	—
Dec. 1	530	1·5	7·9	—
„ 3	340	1·0	3·4	—
„ 5	590	1·5	8·8	30·000
„ 7	510	1·0	5·1	—
„ 9	370	0·5	1·8	—
„ 11	590	0·75	8·8	—
„ 13	370	0·75	2·7	—
„ 15	500	0·50	2·5	—
„ 17	460	0.30	1.4	—
„ 19	460	0·20	0·9	—
„ 21	Diarrhoea	—	—	—
„ 23	220	Absent	—	29·540
„ 25	470	„	—	—

NOTES.—The initial drop between November 12 and 15 probably arose from the stricter dieting, also that between November 19 and 21 arose from stoppage of the Manhu bread, and substitution of starch-free bread. The amount then remained stationary for a week until the acid extract of duodenal mucous membrane was given, when, without further change in the diet, and without complete stoppage of carbohydrate diet, the sugar fell ultimately to zero. A decrease is also seen in the amount of urine secreted.

During the treatment of the first case, two other patients in Dr. Abram's wards were also treated, the results were negative, but the periods of observation were short, and the dose administered was not adequate in amount, so that no conclusion can be drawn from these cases.

Conclusions

No sweeping conclusions can be drawn from such a small number of cases, and they are here given as preliminary, aud in order to excite further work upon the subject.

Still, the prognosis in diabetes occurring in young patients is regarded as so unfavourable, that it is very remarkable that in two cases, such as Nos. II and III, where the amount of sugar was so high, complete absence of sugar should be attained so rapidly following the use of the extract.

As to the cause of the glycosuria and the recovery from it in these cases, if a causal connection exists, it is most probable that the cause of the glycosuria is a failure of the chemical excitant from the duodenum, and that this in the end would lead to permanent abolition of the internal secretion of the pancreas. The supply in the extract of the stimulant to the pancreas restarts the internal secretion, and since the glycosuria does not reappear on stoppage of the extract, the administration appears to stimulate the functional activity of the duodenum. The cases, however, still require further watching, and the number of cases requires to be increased before definite conclusions can be drawn.