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

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In a preliminary paper published in this Journal,[1] we described three cases of diabetes mellitus in which improvement appeared to follow administration of an acid extract of duodenal mucous membrane by the mouth, the sugar diminishing gradually and finally disappearing from the urine.

In that paper we were careful to point out, in the first place, that no sweeping conclusions could be drawn from such a small number of cases and that they were given as preliminary in order to excite further work upon the subject; and secondly, that even granting the hypothesis upon which the treatment was based, it was not likely that more than a certain percentage of cases would be benefited by the extract.

The following is a quotation from our previous paper showing the line of argument employed :—

> '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

1. Vol. I, p. 28.

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.'

Since the publication of the preliminary paper we have tested the effects of duodenal extract in a considerable number of cases, and have had the benefit of reports from other observers employing the treatment.

In the majority of these cases our results have been the same as those recorded by Bainbridge and Beddard in the preceding paper; that is to say, there has been no appreciable fall in the output of sugar in the urine following the administration of the duodenal extract. In some of these negative cases there has been noticed, however, an improvement in the digestion, and in certain cases the patient's weight has increased.

In a smaller number of cases, we have found a decided drop in the output of sugar after the commencement of the administration of the duodenal extract, which we believe was not to be attributed to change in diet, since the patients were kept upon a constant diet for some considerable time before the treatment was started, and during its continuation.

In some cases there appears to be an escape after a time from the influence of the secretin, as if the pancreas had been temporarily stimulated to greater activity and then had become fatigued or exhausted.

We have not been able, in any case observed since the appearance of our previous paper, to reduce the output of sugar to zero.

With regard to the criticism of Bainbridge and Beddard, that the fall in amount of sugar was due to dieting and not to the action of the duodenal extract, we should like to make the following observations.

The patient in Case I had been in hospital upon a diabetic diet for a period of four months before the administration of the extract was commenced, so that the effect of diet ought by that time to have been completely eliminated, and the dieting was not at all varied until after the sugar had fallen considerably. The patient then left hospital, and the final drop to zero occurred when he was under out-patient treatment and probably not under nearly as strict a diet as while under observation in the hospital.

In Case II, the patient was too ill to defer treatment until the effects of dieting had been established, but the first great fall due to dieting occurred within the first four days, and then a second sudden sharp drop in about three weeks occurred which presented none of the features of a dietetic fall.

Case III was never throughout the treatment put upon a carbohydrate free diet, potatoes (about 3 ounces) being allowed daily, and a small quantity of milk. Also, the patient had been put upon the diet, fully restricted as far as was done throughout, for over a week before the treatment was begun, and the output of sugar had been steady at 3 per cent. for a week before treatment was attempted. Further, the patient reacted rapidly to change in diet which was accomplished in two stages, each accompanied immediately by a fall in the sugar. Although there was during the treatment no change in diet, yet the output of sugar rapidly fell and finally reached zero. Finally, the case proved to be one which was only temporarily stimulated by the secretin, for after the urine had been free of sugar for about a week, it reappeared, although no change had been made in the diet, and was apparently no longer influenced by the secretin, gradually increasing in amount until it reached its former level of about 3 per cent.

The urine in Case No. II of our former paper still remains free from sugar as long as the patient is kept on a carbohydrate-free diet; over 3 ounces of carbohydrate foods lead to an appearance of sugar, which promptly disappears when the carbohydrate is cut off. No treatment by secretin has been since employed.

In further evidence that the positive effect sometimes obtained with the extract does not stand in relationship to diet, we reproduce a chart showing a fall in amount of sugar in a patient who had been kept in hospital upon a constant diet for several weeks before the commencement of the secretin treatment, and in whom a decrease in output promptly followed administration of freshly prepared acid extract of duodenum, in which the acid was applied as soon as the duodenum could be taken out of the animals (pigs).

The positive evidence in the smaller number of cases appears to us to outweigh the negative evidence in the larger number for the reason above given, that it is only in that class of patients in which the duodenal secretion is at fault that benefit can be expected, and since such cases cannot be diagnosed, it is only by routine employment of the treatment in a considerable number of cases that a final opinion

can be arrived at as to whether cases occur which can be permanently benefited by the treatment.

At present no specific treatment for diabetes is known and only palliative treatment by dieting, and in a lesser degree by drugs, can be attempted.

There exists clear physiological evidence of a connection between the functional activity of the pancreas and diabetes, and also as to the pancreatic activity being influenced by the secretion of the duodenum.

To this there may now be added from the work of Bainbridge and Beddard, that *secretin*, the pancreatic hormone, is absent in many cases of diabetes. Under such conditions, the indication appears to us to be clear that some attempt should be made in cases of diabetes, to supply from without this stimulus usually lacking in the diabetic's duodenum.

If this stimulus could be applied in an efficient fashion at an early stage, before the pancreas began to grow functionless from disuse, and the pancreas were normal otherwise, so that the stimulus did not form a mere whipping up of a feeble gland, then advantage might be expected to follow such stimulation.

In those cases where the pancreas is the seat of organic disease, or is in a condition of atrophy, no such stimulation by the duodenal secretion would, obviously, be of any service.

The observation by Bainbridge and Beddard that in a de-pancreatized dog, which was therefore suffering from severe diabetes, there was still active secretin present in the animal's duodenal mucous membrane, does not seem to touch the question at issue, but rather to illustrate one of those conditions leading to diabetes which would not be affected by secretin treatment. In such an animal, the duodenal stimulant is present, but there is no pancreas to stimulate to the formation of its internal secretion, and the animal becomes diabetic.

The secretin does not directly act upon the diabetic condition, but only by stimulating the pancreas, if the pancreas is absent or diseased, the secretion of the intestine is still formed, but is valueless in the presence of the altered condition of the pancreas.

It is in the reversed condition where the secretin from the patient's own duodenum is lacking or deficient in quantity and the pancreas is normal, that the treatment by secretin becomes desirable.

The observations of Bainbridge and Beddard indicate that in the majority of diabetics, *prosecretin* is absent from the duodenum, and if this is the primary condition in some of these cases, then if secretin could be supplied in similar fashion to that in which it normally enters the circulation at the duodenum, an effect should be obtainable.

We believe that our observations show that in certain cases such an effect has actually been obtained ; that such an effect should always be obtained we have never claimed, in fact in our earlier paper we mentioned that two cases had given us negative results.

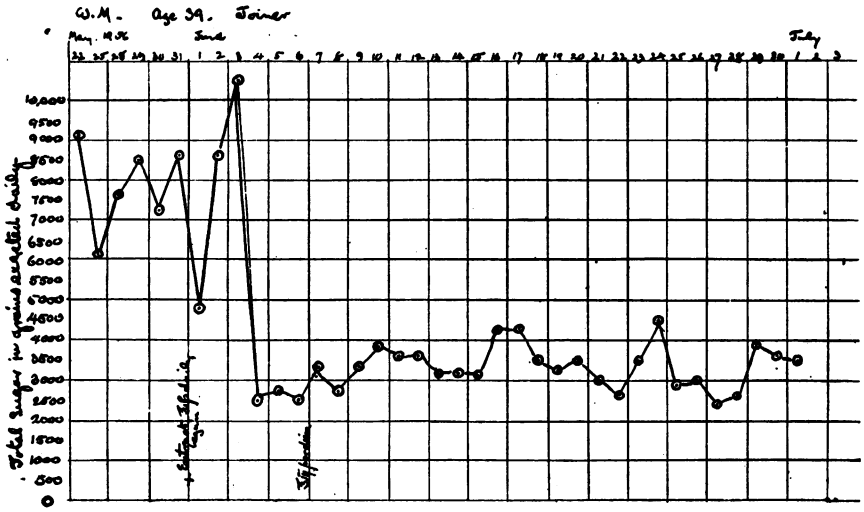

FIG 1.

The chart given above shows the daily output of sugar before and after treatment with an acid extract of duodenal mucous membrane, prepared at once from the duodenum of the pig, taken as soon as possible from the animal after slaughtering and at once placed in acid, otherwise the mode of preparation was identical with that previously described.

The case was one under the care of Dr. Bradshaw in the Royal Infirmary, Liverpool, and we are indebted to him for his kindness in permitting us to publish it, as also to Mr. J. L. Cox, who made the sugar estimations daily by Gerrard's method.

The patient, W. M., a joiner by trade, aged 39, was admitted March 22nd, 1906, complaining of intense thirst, and weakness in the legs, he was much emaciated and stated he had lost two stones in weight during the past month. The urine on admission was 110 ozs. in 24 hours, containing 5·3 per cent. of sugar (23·3 grains per oz.) and acetone and di-acetic acid were present. A sample of blood taken for estimation of the alkalinity of the serum showed lipaemia.

The patient was put on diabetic diet on March 31st and given 1 drachm of sodii bicarb. every four hours, as he was drowsy and had refused food.

No fall whatever in the amount of sugar followed the dieting, but the amount continued to rise slowly.

On April 5th he was put on an extract of duodenum, prepared by the action of acid but the acid was not applied immediately on removal of the duodenum, and the extract was not manufactured in the laboratory. No effect followed this treatment, the sugar continuing to rise and now (April 10th and 11th) standing at 5,500 grains (= 356 grams) daily, instead of at 3,000 grains (= 195 grams) as on admission.

On May 15th the treatment with this acid extract was stopped and the patient was put on codëia, ½ gr. t.i.d., this drug produced no effect, the sugar continuing to increase and averaging 7,500 grains (= 487 grams) between May 22nd and 30th.

On May 31st he was put on acid extract of duodenum, prepared freshly in the laboratory, the duodenum being placed in acid as soon as possible after removal from the animals (pigs). No change was made in the diet. The movement in total daily amount of sugar is shown on the accompanying chart. On June 31st, the total amount was down to less than 5,000 grains, as against 8,500 on the previous day, the following day it rose to 8,500, and on the next to 10,500, the highest output recorded throughout the case. The following day it dropped suddenly to 2,500, and remained stationary at about that level for three days, and then slowly rose to between 3,000 and 4,000, where it remained until the patient left hospital.

Here we have a patient presenting a severe type of diabetes, who is dieted for nine weeks without effect, and treated with codëia without change in the output of sugar, and upon placing on a properly prepared acid extract of duodenum, there is at once a change in the amount of sugar excreted, the end result being that the total output falls to nearly one-third of the former quantity.

The result may, of course, have been a coincidence, but it is difficult to explain otherwise than in connection with the administration of the extract.

Another case gave a similar effect only less marked, there being here also a preliminary rise followed by a fall from 5,500 grains daily before treatment to 2,800 after treatment.

In another case under the care of one of us and Dr. Calvert of Oswestry, a man, aged 45, under restricted diet, which was not varied during the treatment, gave the results shown in the accompanying chart (Fig. 2). The patient had been under observation for six months

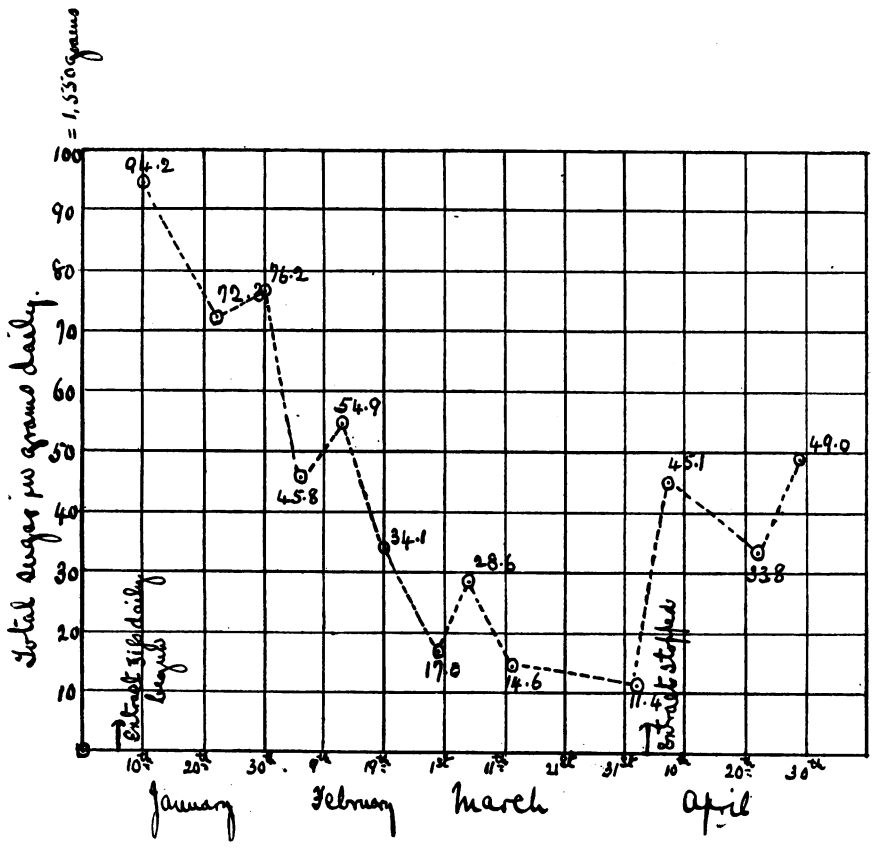

FIG. 2.

before treatment by acid extract was begun and the sugar was not reducible by dieting. Almost at once the dyspepsia from which he was suffering was relieved, and his general nutrition improved to such an extent that he regained over 18 lbs. in weight, which he had previously lost, this improvement was accompanied by a complete recovery of his mental and physical energies.