4. The reading is no indication of the amount of dyspnoea in disorderly action of the heart or functional disease.

5. It is of little value in the early diagnosis of cardiac conditions, owing to the variability of normal standards.

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ORAL ADMINISTRATION OF PANCREATIC AND OTHER PREPARATIONS IN THE TREATMENT OF DIABETES.

BY

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THE discovery of insulin entirely changed the former more or less hopeless outlook in cases of diabetes mellitus. It has enabled diabetic patients, who under previous conditions would have been dead before now, to lead active and useful lives in comparative good health. Such emergencies as operations and coma arising in the diabetic patient are no longer regarded with the same dread as formerly, for, in the majority of cases, both can now be dealt with successfully.

The mode of action of insulin is still a matter of conjecture, but it apparently helps to store carbohydrate in the liver and other tissues; at the same time it plays a part in the combustion of sugar. In the normal individual there is found an almost constant difference between the arterial and venous blood sugar content, the latter being less by approximately 0.04 per cent. In cases of diabetes this difference is reduced or disappears, showing an inability on the part of the tissues to deal adequately with supplies of glucose. Similarly in diabetes the lengthening of the normal blood sugar curve after the ingestion of carbohydrate shows that the liver is unable to store glycogen from the portal circulation as in the normal individual. After adequate treatment with insulin and suitable diet both these abnormalities show a return towards the normal.

It has been proved definitely that insulin is destroyed both by the gastric and the intestinal juice; whether given in acid or alkaline media, or in alcohol or glycerin, it exerts no appreciable effect on the blood sugar or carbohydrate metabolism. Oral administration on a full or empty stomach appears to make no difference; no absorption of active substance takes place. It was hoped at first that some way could be found of giving insulin by the mouth to obviate the unpleasantness of frequent hypodermic injections, but so far these attempts have not been attended with success.

In this respect insulin seems to bear a close resemblance to the extract of the posterior lobe of the pituitary gland, which on hypodermic injection has a definite effect in raising blood pressure and causing all unstriated muscle in the body to contract, whereas after oral administration it has no demonstrable effect.

Thyroid extract, when its value was first discovered in the treatment of myxoedema, was given by injection, but later it was found that it could equally well be given orally, as it was absorbed and exerted its effect in the same manner. For this reason after the discovery of insulin a fresh impetus was given to the use of various

pancreatic and other extracts for oral administration in the cases of diabetes mellitus.

The continued hypodermic injections in the case of patients on insulin treatment soon become irksome and may give rise to considerable trouble through sepsis if the patient be not careful with his cleansing of skin and syringe. In the case of the hospital class of patient the expense of the insulin very often gives rise to difficulty, though now, since the considerable decrease in price, this is not of so much importance as formerly.

These points have made it seem worth while to investigate some of the many oral preparations which are at present on the market for use in the treatment of diabetes mellitus. The claims made for these preparations are many and varied. In some cases the pamphlets even go so far as to claim cures on an ordinary mixed diet. For example, the synthetic insulin tablets A and B were said to produce a cure in a fortnight whilst the patient was on an ordinary diet. A similar claim was made for the diatana mixture.

Parke Davis's pancreatic extract (Mackenzie Wallis) is claimed to be of value in some cases of diabetes; in from two to three weeks on a suitable diet the extract is said to cause a reduction in blood and urine sugar and an improvement in the patient's clinical condition. Messrs. Parke Davis state that if no improvement is found in from two to three weeks the treatment should be discontinued. The improvement alleged in some cases might quite well be due to the strict dieting, and not to the pancreatic extract at all. They state that they do not aim at reducing the blood sugar to the region of 0.1 per cent., but they endeavour to reduce the blood sugar to the region of 0.15 to 0.20 per cent., and to decrease the sugar in the urine. No reference is made to the effect on the ketone bodies, which are in many respects of more importance in estimating the patient's condition than the amount of glycosuria.

Messrs. Carnrick, in their literature relating to the pancreatic extract put on the market by them, give a graph showing the blood sugar and urine sugar in a case treated on their preparation. In this case the sugar disappeared from the urine and the blood sugar fell to normal in a few days. They state, however, that the patient was placed on a restricted diet, presumably at the same time as he started taking the pancreatic extract, so that the fall in blood and urine sugar may have been due to the restricted diet. Indeed, in the light of my observations (recorded later) there is little doubt that the diet was the only effective factor.

Another point which must be considered is the fact that diabetes is well known to vary from time to time, and that temporary improvement may occur apparently spontaneously.

Various claims as to the exact method of action of pancreatic preparations for oral administration are made by the vendors. In most cases these claims are rather vague, and generally state or infer that the active component is insulin. These assertions must obviously be wrong, as insulin is destroyed rapidly in the stomach and intestine. It is, however, possible that there may be some other substance, not insulin, present in these preparations which, when administered orally, may be absorbed and stimulate some mechanism which controls carbohydrate metabolism in the body.

It has been found experimentally in dogs that if the pancreas be completely removed, injections of insulin will only keep the dog alive for a short period. If, however, a very small portion of the pancreas be left, insulin injections will keep the dog alive for an indefinite period. This rather points to the fact that the pancreas may secrete some other internal hormone besides insulin, and it is conceivable that this substance, whatever it may be, might be present in the oral preparations and might be absorbed from the alimentary tract when administered by the mouth. If this were so it might benefit cases of diabetes to be treated with these preparations, even though, of course, they were not absorbing any of the insulin contained in the preparations. All kinds of theories could be formed as to the type and mode of action of this pancreatic secretion, but as its presence is a pure hypothesis, conjectures as to its

mode and site of action seem rather far-fetched. As several cases which have been under my care seem to show that this substance, if present, is not at any rate absorbed in sufficient quantity to be observable clinically, the question becomes even less worthy of consideration.

Insulin seems to be rendered inert very rapidly by gastric and intestinal juices, but alcoholic extract of insulin has been found to produce a slight effect on the blood sugar when given by the mouth, and this is presumed to be due to the rapid absorption of part of the insulin with the alcohol before the gastric secretion has had time to destroy it. From the practical point of view this method is of little value, as the percentage absorbed is too small to make it a satisfactory proposition from the economic standpoint.

It is claimed for most of the pancreatic extracts that they increase the percentage of the food absorbed during digestion. If this be so it seems to be a disadvantage rather than an advantage, because the fault in diabetes lies not in the absorption, but in the utilization of the food after absorption. If we increase the absorption we increase the amount of materials with which the body has to deal, thereby throwing a greater strain on the carbohydrate metabolism. It is well known that it is exceedingly difficult to get diabetic patients to adhere for any length of time to a very rigid diet, and this would increase the difficulty; at the same time, any action of this kind would tend to diminish the bulk of the faecal matter, which is a disadvantage.

It is possible that these pancreatic extracts given by the mouth may stimulate some internal secretion other than insulin which aids in the utilization of carbohydrate within the body, and if this is the case the effect would be reflected in the blood sugar estimations and in the general condition of the patient. On these grounds it was determined to give these preparations a trial under standard conditions to see if they did produce any alteration in the patient's condition.

Some difficulty was found in finding suitable patients on whom to test these preparations, as an endeavour was made to get some mild and some moderately severe cases. Unfortunately some of the latter, whilst they were being standardized on a comparatively low diet, showed symptoms of the onset of diabetic coma, and had to be placed on insulin to prevent their condition getting worse. This has somewhat reduced the number of cases treated on these preparations, but the evidence of those cases in which the treatment was carried through is extremely constant.

In carrying out the investigations each patient was placed on a moderately low diet—say, 980 or 1,050 calories in most cases. The twenty-four-hourly collection of urine was examined daily, the total sugar and acetone being estimated; after the excretion of sugar had been constant in amount for several days the oral preparations were administered for periods of a week to a fortnight, controlled by daily estimations. In some cases preparations containing pulvis cretae or pulvis cinnamomi were made similar to the real preparations, and these were administered without the patient knowing of the substitution. This was done after the real preparations had been administered over a period of several days in order to rule out any psychical factor which might be influencing the results. In other cases sugar tolerance curves were done on the blood, first of all without and then following a large dose of one of the preparations. The sugar estimations on the urines were done by Bertrand's method, and the acetone estimations by acid distillation method, whilst the blood sugars were estimated by MacLean's method.

The following case is typical of a number in which the various preparations were employed. Details of these cases are unavoidably omitted owing to lack of space. The results were similar in all the cases.

A single man, aged 38, was admitted to hospital on October 25th, 1923. All his family had been healthy. The patient had had mumps, diphtheria, measles, and whooping-cough as a child. He was rejected for the army owing to his eyesight and varicose veins. Five years ago, when working in Canada, he noticed that he always felt tired, was thirsty, and had a nasty taste in his mouth. His doctor told him he had diabetes, and gave him a diet, to which he kept more or less for three years, since when he had not dieted. In August, 1923, he had a return of his original symptoms. In addition he lost 2st. in

weight, and had numbness and pains in the legs and marked hunger. On admission no definite physical signs were found. The urine was acid, specific gravity 1030, sugar and acetone present.

He was first placed on a diet equivalent to 1,050 calories, and then starved, and worked up gradually to a diet consisting of 51 grams of carbohydrate, 61 grams of protein, and 33 grams of fat, with a total calorific value of 980. On November 22nd, 1923, he started to take 5 capsules of Carnrick's internal secretion of pancreas C three times a day before meals. On December 4th he started taking 10 capsules three times a day, and two days later 20 capsules three times a day. On December 11th the patient commenced to take 5 imitation capsules, containing pulvis cretae, three times a day, and on December 14th he was given 10 units of insulin twice daily, his diet being altered to carbohydrates 40 grams, protein 56 grams, fat 184 grams.

The patient felt weak when on the low diet, but said he felt much stronger when he started on the capsules. When taking the larger number of capsules daily he did not feel so well, and complained a lot of flatulence, but he said that he felt very well indeed while taking the capsules of pulvis cretae. His weight fell during starvation, but just before starting the insulin his weight was 8 st. 5 lb., the same as on admission.

The patient was discharged from hospital on January 5th, 1924.

Table showing Preparation given, Blood Sugar Concentration, and Amount of Sugar Excreted.

Date.	Preparation Given.	Blood Sugar per cent.	Sugar Excreted per Day in Grams.
1923.			
Nov. 20			11.2
" 21		0.235	8.0
" 22	5 Carnrick's capsules t.d.s.	0.245	36.0
" 23	" " "	0.255	48.8
" 24	" " "	0.262	40.0
" 25	" " "	0.262	47.5
" 26	" " "	0.262	55.0
" 27	" " "	0.260	35.5
" 28	" " "	0.260	56.8
" 29	" " "	0.258	34.5
" 30	" " "	0.256	32.0
Dec. 1	" " "	0.253	41.0
" 2	" " "	0.250	42.0
" 3	" " "	0.245	43.0
" 4	10 Carnrick's capsules t.d.s.	0.210	44.0
" 5	" " "	0.165	52.0
" 6	20 Carnrick's capsules t.d.s.	0.287	31.0
" 7	" " "	0.295	63.0
" 8	" " "	0.212	50.0
" 9	" " "	0.216	41.8
" 10	" " "	0.227	39.5
" 11	5 capsules chalk powder t.d.s.	0.236	44.8
" 12	" " "	0.256	26.0
" 13	" " "	0.228	62.5
" 14	" " "	0.125	72.0
" 15	Insulin given	0.157	17.0
" 16	" " "	0.162	7.5

Hourly Blood Sugar Estimations.

Time.	Nov. 21st 1923. Diet Only.	Dec. 3rd, 1923. 15 Carnrick's Capsules per Day.	Dec. 9th, 1923. 60 Carnrick's Capsules per Day.
9 a.m. ...	0.222	0.241	0.271
10 " ...	0.207	0.302	0.218
11 " ...	0.221	0.266	0.244
12 " ...	0.236	0.216	0.227
1 p.m. ...	0.252	0.229	0.246
2 " ...	0.284	0.241	0.222

CONSIDERATION OF RESULTS.

From the clinical point of view none of the cases showed or felt any improvement in their general condition whilst having the various pancreatic extracts; in fact, two patients complained of feeling weaker while on the extracts. One of these patients had to be rather hurriedly put back on insulin injections, as he developed a rapid pulse, went off his food, complained of abdominal discomfort, and became drowsy, with breath smelling of acetone. In fact, he exhibited the premonitory symptoms of coma.

Three patients were treated with Parke, Davis and Co.'s pancreatic extract (Mackenzie Wallis). One of these, a married woman, aged 35, showed little alteration in her blood sugar levels whilst taking the tablets; the glycosuria, on the other hand, possibly showed a fall at the start, but for the last few days before ceasing to take the tablets had returned practically to the original level. The acetone-uria, on the other hand, tended to rise rather than fall during the exhibition of the tablets. As far as can be seen this patient was not influenced by the administration of

the tablets, and her blood sugar remained between 0.25 and 0.30 per cent. After being put on insulin injections and an increased diet she improved very rapidly, and has since done extremely well. This patient's blood sugar estimations, done at hourly intervals, showed a greater variation when she was taking the tablets. As far as can be seen from this case, one of moderately severe diabetes, the patient was not in the least benefited by the administration of the pancreatic extract.

Another of these patients, a married woman, aged 53, said she felt better whilst taking the tablets, but she also said so whilst she was having the imitation capsules containing pulvis cinnamomi compositus. Her acetonuria and blood sugar curves showed little alteration. The urinary sugar also was little affected whilst taking the tablets. After being placed on injections of insulin and a much increased diet, consisting of carbohydrates 56 grams, protein 63 grams, and fat 182 grams, her acetonuria and glycosuria disappeared in about a week and her resting blood sugar fell to between 0.100 and 0.150 per cent. She has since kept very well. While this patient was taking the imitation capsules the blood sugar finished at a higher level than at other times, but at one period fell to a lower level. From the other data, too, this patient was not materially affected by the exhibition of the pancreatic extract.

In the third patient the curve after the pancreatic extract rose to a higher level than it did when no extract was being given, but the final reading two and a half hours after the glucose was slightly lower than in the curve when no capsules were taken. These variations were of no significance.

With regard to the patient whose case is recorded in the text, during the period while he was taking the capsules the glycosuria reached its maximum when he was taking the largest number of capsules—that is, sixty a day—and the blood sugar was also highest at this point. Whilst taking the capsules the blood sugar and glycosuria levels did not appear to be appreciably altered, and the blood sugar remained above 0.200 per cent., even on the low diet he was then having. Immediately after being placed on insulin the blood sugar fell to the region of 0.150 per cent., in spite of an increased diet. The first blood sugar curve, taken while the patient was on diet alone, showed a lower resting blood sugar level, but a higher level at 2 p.m. than either of the other two curves. The second curve, taken while the patient was having five capsules three times a day, showed a very marked rise after breakfast to over 0.300 per cent. There followed a marked fall, and at 2 p.m. the sugar concentration was about 0.240 per cent. The last curve, taken while the patient was having fifteen capsules three times a day, showed a high resting blood sugar, 0.270 per cent., but the readings then kept lower, ranging between 0.220 and 0.250 per cent. Possibly this last curve shows a lower average level than the other two, but it must be remembered that the blood sugar curves vary in the same person from day to day, and there is no real improvement in the average level in spite of the fact that the patient was taking the enormous number of forty-five tablets a day, a number which it would be difficult to get a patient to continue taking over a long period of time.

A fifth case, that of a labourer, aged 26, was a severe and long-standing one, with considerable emaciation and marked asthenia. He was on diurnal injections of insulin and a diet of 40 grams of carbohydrate, 56 grams of protein, and 186 grams of fat for six weeks before the exhibition of the capsules, and improved considerably in his general condition. He was receiving 25 units of insulin night and morning, but this was stopped for a period and the patient then given five capsules of Carnrick's internal secretion of pancreas three times a day before meals. On examining the blood sugar, glycosuria, and acetonuria estimations it was found that on ceasing the insulin injections there was a very marked rise in glycosuria, acetonuria, and to a less extent in the blood sugar levels. At one period while he was taking the tablets the patient was excreting as much as 5 grams of acetone bodies daily in the urine. Immediately after recommencing the injections

of insulin the glycosuria and acetonuria fell rapidly, and the blood sugar dropped to nearly normal limits.

Another patient, a girl, aged 15, was given some synthetic "insulin" tablets. The tablets were divided into two kinds, A and B, and these were supposed to be taken alternately every two hours, six in all being taken during the day. While the patient was taking the tablets there was no improvement in either the glycosuria, acetonuria, or blood sugar levels, but before discharge on 5 units of insulin twice daily her urine was free from sugar and acetone, and her blood sugar had fallen to the region of 0.100 per cent.; she had put on weight and felt very well in herself.

The last patient was a man, aged 49, with a history of diabetes for seventeen years and a ten days' history of a patch of superficial gangrene on the right big toe. He was placed on a liquid preparation called "diatana," which was credited with curing diabetes on any diet in a fortnight. Later on he did well on insulin.

In considering the various cases together from the point of view of results, the value of the different varieties of treatment must be looked at from several aspects.

In the first place, are they a cure? In no instance has there been any evidence of cure, but in the case of most of the preparations no claim that the treatment would produce a cure was made.

In the second place, is there any evidence that the treatment was beneficial to the patient? In no case is there definite evidence of any improvement whatever whilst under treatment. The patients either remained stationary or tended to go downhill, in spite of the fact that most of them were on low diets, which would have been quite insufficient for them to live and work on outside. The labourer whose case is referred to, who was on a sufficient diet to get on with outside, after being on capsules for five days had to be hurriedly put back on insulin injections owing to the fact that he was in the early stages of diabetic coma.

In June, 1923, a married woman with diabetes, who was being treated on a strict diet and Parke Davis's pancreatic extract (Mackenzie Wallis), was admitted to hospital in coma. With injections of insulin and other appropriate treatment she was able to leave hospital later comparatively well.

Besides the above, many patients have been treated at St. Thomas's Hospital with pancreatic mouth preparations during the last two years. In no case was the slightest benefit produced.

CONCLUSIONS.

From the consideration of the data given it is clear that the administration of oral preparations of pancreas in severe cases of diabetes is a waste of time, and likely to be harmful to the patient by delaying the proper treatment with diet and insulin injections. Other mouth preparations, such as "insulin synthetic" and diatana, I have found to be useless.

As regards the milder cases, in none of the above patients could any definite improvement be traced, either in the clinical condition of the patient or in the blood sugar levels. In those patients on whom blood sugar curves were taken over several hours no definite difference in the mean blood sugar level could be detected as the result of treatment with oral preparations. In fact, all the above results point to the conclusion that the oral preparations tried are of no value in the treatment of diabetes, and that probably the improvement attributed to the oral preparations has in reality been due to the strict diet the patient has been put on at the same time. In other words, the patients would have done equally well if put on the diet alone. The only value the tablets seem to possess is that some patients, if placed on a strict diet alone, feel that they are not receiving proper treatment, and the giving of the oral preparations obviates this difficulty.

I am indebted to Professor H. MacLean for his kindness in allowing me to carry out these investigations in his wards, and to Dr. C. H. Budge for his help with the laboratory work.