

THE POST-GRADUATE MEDICAL JOURNAL

VOL. I.

MARCH, 1926.

No. 6.

SOME OBSERVATIONS ON DIABETES AND INSULIN IN GENERAL PRACTICE.*

BY

HUGH MACLEAN, M.D. ABERD., D.Sc.,

M.R.C.P. LOND.,

PROFESSOR OF MEDICINE, UNIVERSITY OF LONDON,
ST. THOMAS'S HOSPITAL.

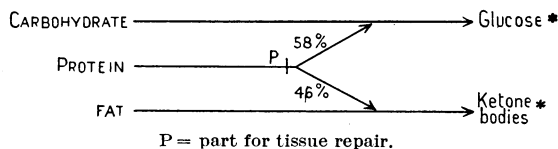
THERE is probably no disease which has been the subject of more experimental and clinical investigation than diabetes, but we are still ignorant of its fundamental nature. One of the most characteristic symptoms associated with diabetes is the presence of sugar in the urine, but it must be clearly understood that glycosuria may be present in an individual who shows no evidence whatever of diabetes. The successful and rational treatment of diabetes demands an elementary acquaintance with certain facts regarding food metabolism in the body. From the clinical point of view, it is important to remember that diabetes is not dependent on a defect of carbohydrate metabolism alone, but is a condition in which there is a definite and well-marked disturbance in the utilisation of protein and fat as well. In short, diabetes is a disease in which the body is more or less incapable of using food; consequently, there results an accumulation of various waste products in the body which ultimately, in the absence of suitable treatment, give rise to the toxic condition known as diabetic coma.

METABOLISM IN DIABETES.

Since food is not metabolised and burnt in the ordinary way, a large amount of the food taken in is excreted in the urine unchanged or partially oxidised. Thus, carbohydrate material such as starch and sugar is thrown out in the form of the sugar glucose, while fats are excreted in the form of partially degraded oxidation products—oxy-butyric acid, aceto-acetic acid, and acetone. These substances are known as the *ketone* bodies. Normally, the end-products of both fat and starch metabolism are carbon dioxide and water, but in diabetes this final stage of oxidation is not reached by all the food. Of course, even in the most severe cases, a certain amount of the ingested food is completely oxidised, but a large amount is wasted and lost to the body. Protein

differs from fats and starches in having nitrogen in the molecule; this nitrogen is essential for the repair of tissue waste, but protein is present in such large amounts in our diet that only a comparatively small part of it is required for tissue repair. The remainder, after being deprived of its nitrogen, is utilised either in the form of sugar or fat. Thus, protein can form both sugar and ketone bodies in the diabetic organism; according to various investigators it can give rise to about 58 per cent. of its weight of sugar and about 46 per cent. of its weight of ketone bodies.

In diabetes, therefore, the ultimate fate of our three chief classes of food-stuffs may be represented as shown in the diagram.



* Bodies formed in diabetes and thrown out in the urine.

From a consideration of these points it will be obvious that the mere substitution of one class of food-stuff for another is of little value in the dietetic treatment of diabetes, for a marked decrease in one class will, of necessity, require an increase in another; all food-stuffs are harmful when given in excess. This has been very effectively demonstrated by Allen, who showed that when dogs were deprived of the greater part of the pancreas, the ultimate fate of such dogs depended on the amount of food they consumed. When a low diet just sufficient to maintain the animal in fair condition was given the general result was that the dog went on enjoying good health for an indefinite period. When a large amount of food was given the dog soon got glycosuria, and before long died of diabetic coma. A most interesting point about these experiments was that it did not seem to matter what classes of food-stuffs were given. When the diet contained excessive amounts of protein or carbohydrate or fat the result was the same; glycosuria soon became established, ketone bodies appeared in the urine, the animal lost weight and died in coma. The secret of successful dieting in diabetes depends on giving the patient as little food as possible consistent with health and the maintenance of nitrogenous metabolism.

THE DIFFERENCE BETWEEN DIABETES AND GLYCOSURIA.

It is frequently stated that diabetes is a much more serious disease in the young than it is in the

* A Post-Graduate Lecture delivered at the Prince of Wales's General Hospital.

old. This, however, does not appear to be the case, for true diabetes is apparently equally severe at all ages. This statement may be apparently contrary to clinical experience, but it is nevertheless true. The real fact is that many of the conditions diagnosed as diabetes are not diabetes at all, but more or less intensive glycosurias. It is certain that this kind of glycosuria is common in elderly people and uncommon in the young. To appreciate the position fully, it is necessary to consider very shortly the various stages through which sugar passes in the animal body. The bulk of our carbohydrate is eaten in the form of starch. In the alimentary canal starch is very quickly hydrolysed and changed into glucose. The glucose is then absorbed and passes through the liver. Here a great deal of it is held up and stored in the form of glycogen; only a small portion at a time is allowed to go right through the liver barrier to the tissues and organs. In the tissues, glucose, as already mentioned, undergoes combustion.

Now, in true diabetes the essential defect, as far as sugar metabolism is concerned, is an inability on the part of the tissues to oxidise or burn sugar. Since sugar cannot be burnt in the normal way, it accumulates in the blood and body fluids to be ultimately excreted in the urine. The same is true of fat metabolism; fat is broken down to the stage of aceto-acetic acid, but this fails to get burnt in the body, and is thrown out in the urine. The liver constitutes a depôt for the storage of sugar, and from this storehouse the tissues draw sugar in small amounts as they require it at any particular time. When, for instance, sugar is wanted in the peripheral muscles, a message is sent to the liver to liberate some sugar into the blood. This released sugar travels to the muscles and supplies their wants. In diabetes the muscles and organs are, so to speak, hungry for sugar, since, owing to some metabolic defect, they cannot use sugar; they are, therefore, constantly calling out for more sugar with the result that the liver gives up practically all its glycogen and no longer acts as an efficient storehouse for sugar. It would seem that the condition stimulating the production of sugar from liver glycogen is associated with the inability of the tissues to oxidise sugar; the fact that there is nearly always an excess of sugar already present in the tissues does not seem to affect the demand for more sugar from the liver.

The result is that in severe diabetes little or no glycogen is found in the liver, while the liver soon loses its power to store sugar as glycogen. In diabetes, therefore, there are two important factors present which tend to cause an increase of sugar in the blood. The first factor is the inability on the part of the liver to store sugar as glycogen in the normal way; the second is the inability on the part of the tissues to burn sugar. Though the second of these factors is by far the more important one in diabetes, yet the liver change is very marked and can be detected at the very earliest stages of diabetes.

It is most important to remember that while defective combustion of sugar in the tissues always results in defective storage in the liver, yet defective storage in the liver may be present as a primary defect *without any evidence whatever of defective tissue oxidation*. It is quite common to see patients whose livers have largely lost the power to store sugar, and yet in these patients tissue oxidation of sugar seems to be quite up to the normal standard. This is the condition which so often occurs in elderly individuals; it results in an excess of blood-sugar and marked glycosuria, but though generally labelled as diabetes, this condition is not diabetes at all. It might be called hepatic glycosuria. There are, therefore, two different conditions which are usually included under the term diabetes: (a) True diabetes, in which storage and oxidation of sugar are defective. (b) Hepatic glycosuria, in which sugar storage is defective but oxidation is not interfered with.

Hepatic glycosuria may be distinguished from diabetes by the fact that true diabetic symptoms are not present; also the urine, though containing large amounts of sugar, shows little or no indication of the presence of ketone bodies. Hepatic glycosuria is extremely uncommon in the young, but is very common in the aged and middle aged. It may give rise to certain symptoms such as neuritis, pruritus, retinitis, trophic disturbances, and general weakness of the muscles, but is never associated with the wasting and acidosis which accompanies true diabetes. This glycosuria is usually not serious, and may go on for 20 years or more without causing any bad effects, while true diabetes, unless treated by insulin, usually proves fatal in from four to five years.

The so-called diabetes of the elderly individual who has done himself well is usually of this hepatic type. Examination of the urine for ketone bodies will usually determine to which category the patient belongs. The most useful practical examination of the urine is the test for acetone. This is done according to Rothera's method by taking about an inch of urine in a test-tube and adding a small pinch of powdered sodium nitro-prusside and an excess of ammonium sulphate. After shaking, an equal bulk of strong ammonia solution is added and the whole gently mixed. The presence of acetone is indicated by a definite permanganate colour appearing in the liquid. When this colour forms very quickly a large amount of acetone is present; when the appearance of the colour is markedly delayed only a small amount of ketone bodies is present. The addition of a small quantity of 10 per cent. ferric chloride solution to one inch of urine in a test-tube gives a port-wine or reddish colour in the presence of comparatively large amounts of ketone bodies. When the nitro-prusside test and the ferric chloride test are both present, it may be assumed that the patient is suffering from a considerable acidosis and that immediate treatment is indicated. In general, it may be said that when a marked reaction for ketone

bodies is obtained in the urine of a glycosuric patient, diabetes is present, unless a change in diet with marked restriction of carbohydrate has recently taken place. Hepatic glycosuria has no tendency to produce coma. Its most pathetic symptom is the dimness of vision and blindness which sometimes develop. These patients also not infrequently complain of very severe pains about the legs and shoulders; these pains are generally worse at night and may be exceedingly severe. Their true nature is often overlooked, and I have known them to be mistaken on more than one occasion for the lightning pains of locomotor ataxia. The frequent absence of the knee-jerk in glycosuric patients tends to suggest this diagnosis. When properly treated the pains generally disappear, but in order to obtain this beneficial result it is necessary to keep the blood-sugar well down towards the normal level. If this cannot be done by diet, insulin must be used.

BLOOD-SUGAR IN DIABETES.

In the healthy individual the normal blood-sugar concentration is about 0.1 per cent. After meals containing starch the blood-sugar rises to about 0.16 per cent. to 0.18 per cent., but very quickly falls again to the normal level. What happens is that during the earlier phase of absorption the liver allows some sugar in excess of the normal to pass through into the general circulation, thus raising the blood-sugar content. Soon, however, the liver mechanism for storing sugar comes into play, with the result that the sugar reaching the liver through the portal system is immediately caught up and stored for future use. The blood-sugar in the general circulation now falls, even though absorption from the intestine may be going on as rapidly as before. It is an extraordinary fact that in the average healthy person the blood-sugar cannot be raised much above 0.18 per cent., however much starch or sugar is ingested. There is an excellent reason for this. Whenever the blood-sugar rises above the region of 0.18 per cent. sugar is excreted in the urine, but below this concentration no sugar is allowed to pass through the kidney and the urine remains sugar-free. Though 0.18 per cent. blood-sugar represents the average "threshold" for sugar in the normal individual, yet a considerable number of people have a much lower threshold than this. Since it is quite physiological for the blood-sugar to rise to 0.18 per cent. or so after meals, these people will have their thresholds for sugar exceeded on two or three occasions each day and so their urines will contain sugar at these periods.

In some instances, indeed, the threshold value is so low that sugar may be always present in the urine. This leak of sugar through the kidneys gives rise to the condition known as "renal glycosuria." This glycosuria has nothing whatever to do with diabetes, and gives rise to no special symptoms, but it is very frequently mistaken for

diabetes. Renal glycosuria is a comparatively common condition—much more common than diabetes—and the possibility of a renal leak must be remembered in all difficult cases of glycosuria. While in several of these cases the glycosuria is restricted to the period after a meal, in others a certain amount of sugar may be present at all times. When in doubt it is well to give the patient 50 g. of glucose dissolved in a few ounces of water, and to estimate the blood-sugar at intervals of half an hour for two hours after the ingestion of the sugar. In renal glycosuria the blood-sugar curve will remain normal, but the urine will contain considerable amounts of sugar, while in diabetes the characteristic long drawn out curve with high blood-sugar content will be found. Renal glycosuria is of no importance as far as the health of the patient is concerned; it never does any harm and requires no treatment. There is, of course, a slight loss of sugar in the urine, but from the point of view of the total daily diet this loss is insignificant.

TREATMENT OF GLYCOSURIA AND DIABETES.

The nature of the treatment prescribed in diabetes must depend on various factors. There are only two methods by which we can hope to do any good to the diabetic patient: (*a*) by the use of suitable diet, and (*b*) by giving insulin. No drugs given by mouth have any influence whatever on the disease. The same may be said of the various pancreatic mouth preparations which are so extensively recommended by their vendors. I have carried out a thorough investigation of the effects of these various products on diabetic patients, but in no single instance was the slightest evidence obtained that they had any effect whatever. They do no harm in mild cases, but in patients suffering from severe symptoms it is much too dangerous to trust to these inert preparations.

In considering the best treatment for any case of "diabetes" the problem generally is whether we should use insulin or trust to diet.

DIETETIC OR INSULIN TREATMENT?

The first point to consider in the treatment of any case is whether the condition is true diabetes or only fairly intense glycosuria. If the patient is young and shows the usual symptoms of diabetes with sugar and large amounts of ketone bodies in the urine, then it may be said at once that in all probability insulin will be necessary. It is a safe rule to give insulin to all patients under 20 who are suffering from true diabetes. In young children insulin is always essential. Indeed, it is becoming more and more evident that insulin should be used in all cases of true progressive diabetes whatever the age of the patient. There is no objection to trying the effect of diet in all cases, but it is common experience that diet alone is seldom of much ultimate value in severe cases, especially in young people, though, to begin with, brilliant results are often

obtained. No doubt in many cases diet seems to work wonders for a time, but gradually it loses its effect with the result that the amount of food allowed has to be constantly diminished until a point is reached at which the amount of food the patient can take without danger is no longer sufficient to maintain life. During the last few years I have frequently attempted to treat diabetes in young persons by diet instead of putting them on to insulin at once, but without exception all these patients relapsed and insulin had to be used later on. If diet is tried in cases of severe diabetes it should be the rule to use insulin whenever it becomes evident that diet is not going to prevent the advance of the disease. It is most important to use insulin at a comparatively early stage in such cases, for unless this is done treatment with insulin may be much more difficult than it would otherwise have been. The great practical difficulty with insulin treatment is that the advanced diabetic is very liable to infections of various kinds which tend to be very severe in spite of the administration of insulin; indeed, these infections often inhibit very considerably the usual beneficial effect of insulin so that death may take place even when insulin is being used. On the other hand, these infections are neither so common nor so severe in early cases of diabetes. There is thus every reason why insulin should be given early in severe and progressive cases which do not respond to diet alone.

In the hepatic glycosuria of middle life or old age insulin is usually not necessary, but when the glycosuria is accompanied by definite symptoms such as eye changes, gangrene, and general ill-health, insulin may be essential. Everything depends on the condition of the particular patient, and no general rule can be laid down. When no definite symptoms are present, but only a feeling of slight weakness, dietetic treatment usually suffices. Gangrene of the toes and feet is much more common in long-continued cases of glycosuria than it is in true diabetes. With insulin much may be done even when gangrene is present, and by its use many limbs can be saved from the mutilations of the surgeon. It is no longer good practice to amputate the leg above the knee when gangrene occurs in a toe. With sufficient insulin to keep the blood-sugar within normal levels, and the use of dry dressings, it very frequently happens that only a very minor operation to separate the dead parts is necessary.

Generally speaking, unless some special symptoms demanding attention are present, it is unnecessary to give insulin unless the glycosuria is accompanied by a considerable amount of acetone in the urine.

DIETETIC TREATMENT.

In ordinary hepatic glycosuria all that is required in many cases is to cut down the *amount* of food normally consumed; the carbohydrate of the diet must be more or less specially restricted, and the patient should live largely on protein and fat.

These patients are usually too fat to begin with, and feel much better when their weight is considerably reduced. The change in diet frequently produces what appears to the patient to be an alarming decrease in weight, and he may become anxious about this. Many of these patients, however, can afford to lose 2 or 3 st. with great advantage to themselves, so that decrease in weight should be viewed with favour rather than with alarm. When the diet is changed such patients may not, at first, feel quite so well, but this phase soon passes over, and in the course of a few months many of them feel better than they have done for years.

When diet is tried in a true diabetic case the method adopted is to starve the patient until the urine is free from sugar, and then to give gradually increasing amounts of food until a diet is obtained which contains the necessary amount of nourishment for the patient without producing glycosuria or ketosis. It is quite impossible to give details of this dietetic treatment in a short address, but anyone interested will find the whole subject fully discussed in my monograph on diabetes where specimen diets are given.¹

Nowadays drastic dietetic treatment is bad practice. When a suitable diet cannot be evolved for the patient he should be given the benefit of insulin at once.

INSULIN TREATMENT.

The question whether insulin can be safely used by the general practitioner has been asked again and again. The answer admits of no doubt. Insulin can be used with safety in general practice and should be used by all medical men when necessary. There is no danger whatever in its use under the conditions of general practice, provided the medical man is guided by one essential principle and never deviates from it. This principle is *that insulin should always be given in small doses to begin with in all ordinary cases of diabetes, and the amount should be increased very slowly*. This is the fundamental point in the use of insulin. Of course, in severe cases where coma is threatening it is quite safe, and often necessary, to use large amounts immediately, but only in these exceptions should large doses be used at the beginning of treatment. When this advice is followed no medical man need have any fears of untoward accidents arising from the administration of insulin.

Frequently patients refuse insulin because they think that once they begin to have it insulin must be administered for the remainder of their lives. This is an entirely erroneous view, for there is nothing whatever in insulin treatment which necessitates its continuous use; indeed, it is frequently used for short periods in getting certain patients into the best possible condition for operation. It is quite true that in the majority of cases of severe diabetes insulin has to be continued for

¹ Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes. London: Constable and Co.

the rest of the patient's life, but this is only the case because of the disease being so severe that without insulin death would quickly ensue. Exactly the same statement might be made with regard to our food. Once we begin to take food it must be taken for the rest of our lives, otherwise we would perish. The important point is that as far as insulin itself is concerned there is no more need to continue with it permanently once it has been used than is the case with any other therapeutic agent.

In giving insulin it is well to begin with not more than five units twice daily; after a few days this is increased to six units and then to seven units, etc., until the urine becomes free from sugar. When this happens the patient is kept on the particular dose he was having when the glycosuria disappeared. The great importance of going slowly cannot be over-emphasised if safety is to be achieved in all cases.

What happens in the diabetic patient is that during the first few weeks of insulin treatment there is a certain amount of increased tolerance; probably certain of the pancreatic cells which were tired out now revive once again with the result that the patient himself secretes more insulin than he did at the onset of treatment. It may, therefore, happen that a dose of insulin which is too small for the patient at the beginning of treatment may be quite excessive after a few weeks. It is owing to neglect of the fundamental principle of going slowly that accidents happen with insulin. Again, the rather foolish kind of statement sometimes made that "the use of insulin is worse than the disease" is probably dependent on lack of experience of the best method for the administration of insulin. Insulin is by far the greatest boon that has ever been conferred on the suffering diabetic patient, for through its proper use he may, in almost every instance, regain a great measure of health and strength. Though insulin must be given as a hypodermic injection yet the inconvenience resulting from the needle puncture is trifling on the whole, and patients get quite accustomed to it and do not mind the injection. Of course, a preparation which could be taken by mouth would be preferable, but there is, unfortunately, no prospect that insulin can ever be administered in this way.

When insulin is used it is all-important that the diet and insulin dosage should be carefully correlated, but in every case a sufficient diet can be arranged. The above are the chief points to be observed in the treatment of diabetes with insulin in general practice. Space does not allow of the various details of treatment being discussed, but anybody interested in the subject will find full details in my monograph.¹ Finally, I should like to emphasise the statement that when given as here described insulin may be used with safety by any general practitioner without the necessity for a single blood-sugar determination.

CHRONIC LESIONS OF THE STOMACH.

A Special Clinical Demonstration for Members of the Fellowship of Medicine, at Westminster Hospital, on Jan. 27th, 1926,

BY

E. ROCK CARLING, F.R.C.S. ENG.,

SURGEON TO THE HOSPITAL.

THE first three cases here described I am using as the text of my remarks on the problem of chronic lesions of the stomach. All three patients complained of their stomachs in answer to the first interrogation by the clinical clerk.

The first, a man of 62, has suffered from abdominal pain after food and from vomiting, symptoms which have been present for five months. To be more precise, the pain is in the upper abdomen, occurs from three to three and a half hours after food, and is invariably relieved by vomiting. It is doubtful if hæmatemesis has ever occurred. There have been intervals of freedom from symptoms from time to time. At present he has a very poor appetite, and is taking only milky foods. Loss of weight has been considerable, and of recent date he has suffered from constipation. He is a thin, pallid, ill-looking man. The teeth are all artificial. There is a cicatrix of the abdomen; he says he had an operation for appendicitis three years ago, although the position of the scar hardly suggests this operation. Occasionally one sees peristaltic waves passing from left to right. On palpation the right rectus is found to be rigid, and in this situation there is tenderness preventing any attempt at stimulating peristalsis. It is, nevertheless, possible to distinguish a mass in the right side of the epigastrium. The test meal result is a total acidity of 0.24 per cent. with free hydrochloric acid 0.11. It will be convenient to postpone consideration of the barium meal until the other cases have been dealt with.

The second patient is 21. He also complains of pain after food. His past history is that, without any previous complaint referable to digestion, he underwent an operation for perforation of a pyloric ulcer ten months ago, since when he has never been comfortable. Pain occurs in the left upper abdomen and extends downwards to the hip; it has no relation to meals and it often occurs at night. There is no vomiting, but flatulence is a prominent symptom. The appetite is good. The patient looks healthy, his teeth are good, the tongue is clean but flabby. Beyond some tenderness in the left side of the abdomen nothing is palpable. In his case the test meal shows: total acidity, 0.27 per cent.; free HCl, 0.2 per cent.—i.e., distinctly high. Organic acids are only present as a trace. Again I postpone consideration of the radiograms.

The third patient, a man of 50, complains of pain after food and vomiting. In 1918, he was operated upon elsewhere for duodenal ulcer and gastro-enterostomy was said to have been performed. You will see later that we have some reason to doubt the nature of the operation, and, unfortunately, our inquiries for information have led to no response. The operation had been preceded by five years' symptoms, but after his operation he was well until last October, when he began to suffer from a recurrence of pain and vomiting, the pain coming on at variable periods from half to two hours after food. In his case also flatulence is very troublesome. He has occasional periods of freedom from symptoms. His appetite has lately been poor, but there is no suggestion of distinct distaste for food.