Medical.

A LECTURE ON DIABETES.¹

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THE subject which I have selected for this lecture is "Diabetes, its Causation and Treatment, with Special Reference to Toxic Causes."

First, let us consider what we mean by the term "diabetes." Jocelyn gave a definition which, I think, is a very good one. He said the presence of glucose in urine demonstrable by the common test is, *ipso facto*, a proof that the person suffers from diabetes, unless the contrary is proved. All cases of glycosuria are presumably diabetes unless the contrary is proved. The old-fashioned test was to give the person a meal containing 50 grm. of glucose, a cup of coffee and roll and butter, and then test the urine. If afterwards sugar was found the case was regarded as diabetes. That is rather a crude test, and we have advanced a deal on that. The modern way of testing is to test the urine for sugar and for acetone and diacetic acid, and take a sample of blood—a very small quantity suffices. It is put into a tube mixed with something which prevents clotting, a little oxalate of potash or citrate of soda. One can give the person 30 or 50 grm. of glucose and take the blood an hour afterwards. The blood-sugar should be under 0·18 per cent.; if it is over that the person is a diabetic. If you do not give the patient a test meal, you must always remember that in diabetes the time in relation to food taken at which the urine is passed and the time at which the blood is tested for sugar must be noted; otherwise the estimation is of no value. So if you take the blood before the person has a meal you expect a low figure; in the normal person it should not exceed 0·1 per cent. fasting, i.e., before food is taken in the morning.

A more refined way of ascertaining whether a person is suffering from diabetes is to do a glucose tolerance test. Test urine and blood before doing anything, then give 50 grm. of glucose, 25 grm. to a child. In some hospitals only 30 grm. are used for an adult. I think 50 grm. is a rather severe quantity and am content with 30 grm. for an adult, 15 grm. for a child. The blood is tested every half hour and the curve plotted out.

In a normal person the peak of the curve occurs in one hour and is under 0·18 per cent. The curve falls in two hours to below the initial level. If there is diabetes, the curve will start higher and will remain high. The peak of the curve is much higher than 0·18 and the curve will not fall to the normal level in two hours.

I will remind you now of what is called the threshold in diabetes. In the normal person when the blood-sugar rises about 0·18 per cent., sugar appears in the urine. Some people are abnormal in this respect, and they have a threshold which, instead of being 0·18 per cent. is, perhaps, 0·14 per cent. These people may have sugar in the urine at any odd times, irrespective of the diet they are having. If they go to have their lives

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insured they may be disqualified. And here comes in the value of the glucose-tolerance test.

The peak of the curve is under 0·18 per cent., and in two hours the blood-sugar has recovered or even fallen below the initial figure before the test. This proves that the person is the subject of renal glycosuria and not a case of diabetes.

Another type of person with sugar in the urine is one who has a "lag" curve. A meal containing glucose is given, and the blood-sugar goes up to just over 0·18 per cent. but comes down quickly to the normal level within two hours. People with the lag curve are accepted by intelligent Life Assurance Offices as first-class lives. I am a member of the Board of one of the "intelligent" Life Assurance Companies, the Medical Sickness and Accident Company. That Company goes very carefully into all these questions of glycosuria, and will pass the types I have just described as first-class lives.

While I am talking about thresholds I want to tell you something else. All my audience are practising doctors, and we do not put our patients on to insulin because they have sugar in the urine, and not even if the blood-sugar is high; we use our discretion.

I will give you an example :—

Old people who have "done themselves well," such as prosperous City people round about 60 years of age, have at times, in a considerable percentage of cases, sugar in the urine. If you diet these gentlemen too rigorously they do not do at all well, they feel faint and sometimes may have anginal attacks. What is the explanation of this? It is a very simple one. In elderly people often the renal threshold is higher than normal. I saw the other day a plethoric City gentleman with sugar in the urine, and his renal threshold was 0·25 per cent. He only got sugar in his urine when the blood-sugar was over 0·25 per cent. One gives these cases a dietary which will keep their blood-sugar lower than their own threshold. It is not advisable to bring their blood-sugar down to the normal threshold of young persons. If you reduced the blood-sugar to always below 0·18 per cent. symptoms of malaise and weakness may supervene.

As regards the ætiology of diabetes. The physiological explanation of the cause of diabetes is that it is due to a deficiency in the internal secretion of the pancreas. When post-mortem examinations are made on diabetics, often one cannot, by naked eye, find anything wrong, as these people are not subjects of gross lesions, such as cancer or calculi, or hæmorrhages. It is only when one microscopes the pancreas that one finds the islands of Langerhans absent or degenerated in diabetic cases. It is remarkable that these unimportant-looking cells should play such an important part. It is these cells which produce the amboceptor "insulin." When carbohydrate is eaten glucose is absorbed into the portal circulation. The combination with the amboceptor which the pancreas secretes is carried to the liver and stored as glycogen. The prime factor in the causation of diabetes is that there is something which stops the functioning of the cells in the islands of Langerhans. The cause is generally some toxic condition. Just as alcohol will cause cirrhosis of the liver or a hepatic deficiency of function, so toxins will poison these important cells in the pancreas and will cause diabetes.

Insulin is not produced only by the pancreas, though that organ is the main source of its production. Recent researches have shown that there is some insulin in the kidneys, in the spleen, in the muscles, and probably a little is produced in other organs as well; otherwise people with diabetes would not live as long as they do when their pancreas is badly damaged.

If you have a very bad diabetic case and you give him 1 grm. of sugar by the mouth sugar appears in the urine. You have cut off his carbohydrate and his tolerance of carbohydrate is *nil*. You can give that person 100 or even 200 grm. of glucose by the rectum and yet there will be no trace in the urine. If you put a fine tube into the rectum and draw off amounts of your solution at intervals, the glucose diminishes in percentages, it starts at 5 per cent. and goes to 1 per cent. It goes somewhere and you may say the bacteria in the bowel decompose it. But I made up glucose with boracic acid in it, this acting as an antiseptic, but still the glucose disappeared. Therefore glucose given by the rectum does not appear in the urine in the diabetic case. The explanation probably is that the tubular cells in the colon are highly filled with zymogen granules, and there is probably some insulin in the cells which fix the glucose and prevent it being excreted. Sir Arthur Keith gave a lecture on the colon a few years ago and called attention to the great function which these cells in the colon must carry out.

So much for the pancreas. The liver is an important organ concerning the ætiology of diabetes, because it is the storehouse of sugar in the form of glycogen, and if the liver is affected there may be glycosuria. In cases of catarrhal jaundice you often find sugar in the urine. Any temporary appearances of sugar in the urine from fright or shock may be due to the glycogen stored in the liver suddenly being converted into glucose. The liver may be likened to the swinging balls on what is called the governor of an engine, it regulates the smooth working. The thyroid, the pituitary, and the suprarenal glands also play a part in the causation of diabetes; excessive secretion of them causes glycosuria. Their excretions act on the liver and turn the glycogen into glucose, freeing it in the body. And if too much is set free you get sugar in the urine. It has been known for years that adrenalin injections cause glycosuria, so will a large dose of thyroid, so will an injection of pituitary. The kidney is only associated with diabetes indirectly, in that the condition of the kidney cell determines what the threshold is. Sometimes if the kidneys are damaged the threshold drops and glycosuria results. You have heard of phloridzin glycosuria; if phloridzin is injected into the body the patient gets glycosuria, because it damages the renal epithelium and lowers the threshold and sugar is excreted when it is present in the blood in the normal amount of 0.1 per cent.

Many of you have seen cases of mixed type; I have seen at least twenty in which persons passed albumin and sugar in the urine, a low specific gravity urine, 1005 to 1010 with sugar in it. Very little has been written about those cases recently. There is a group of cases in which diabetes and chronic nephritis are associated.

Heredity plays a part in diabetes too, but the real explanation is that it is the diathesis which is inherited. In the case of diabetes persons may inherit a susceptibility to having the pancreas involved in such a manner that diabetes results.

As to infection, commonly one sees diabetes in both husband and wife, and in other people who live together. The reason infection plays a part is that diabetes is in many cases a disease with deficient pancreatic function caused by some infection.

As to statistics, diabetes is still as common as formerly in spite of the discovery of insulin, which does prolong the life and health of patients.

With regard to race, Hebrews are liable to diabetes; Indians are, too. Indians eat very largely of carbohydrates. Nervous shock, nerve strain, emotion, and so on may lead to diabetes.

So much for the aetiology. Now let me say a little about the treatment of diabetes. Up to 1914 nothing was known about the treatment of diabetes. For a long time it has been known that diabetes existed: Shakespeare knew about it, because in one of his plays it is reported that a specimen of the urine of Falstaff was sent to the doctor, probably to be tested for sugar, since Falstaff had many of the characteristics of a glucosuric.

Up to 1914 we took diabetic cases into hospital, and they often died of coma while they were in hospital; in those days I never saw a case of diabetic coma recover. We used to give phosphate of soda, opium or codeine in pill, uranium acetate, and alkalies, but with no real benefit. And we used to cut off the carbohydrates and keep the patients on plenty of meat, but they never improved. Then an interesting thing happened in 1913. Dr. Guelpa, an Italian physician who lived in Paris, published the Guelpa method of treatment, which was called the "Disintoxication Treatment," and it was considered to be a cure for almost everything. The patient was given an ounce of Glauber or Epsom salts dissolved in water every morning, and only water allowed for three or four days, no food being given. Guelpa found he could cure glycosuria temporarily in any person, and he even claimed that he could cure aneurysm by that treatment. He said that he treated wounded soldiers by the disintoxication method, and that his patients did better than did the soldiers in other hospitals.

In 1914 Allen, an American doctor who had read Guelpa's papers, found it was not the salts which cured the glycosuria but the fasting. He did some brilliant experiments on animals and showed that fasting removed the glycosuria; this was a very great step. Jocelyn, who was a clinician in America and was working at the clinical side, and was closely in touch with Allen, elaborated a treatment which marked a brilliant advance. I remember what a change then came over the treatment of our hospital cases. It was possible to get rid of the glycosuria in a patient by dieting. The Allen method, which I still use for my cases at St. Mary's, is a very simple one. One can get rid of the glycosuria in a patient by fasting, but acidosis must be avoided. By the Allen treatment the patient, for two or three days, is put on an oatmeal diet, with an orange and green vegetables, and then the fast is commenced. If there is a lot of acetone in the urine the acidosis diet is prescribed, which contains a fair amount of carbohydrate, and is continued until the ketone bodies have disappeared from the urine. The diacetic acid in the body turns to acetone and causes acetone in the urine. It is the diacetic acid which is toxic, and that is converted into acetone.

Having got rid of the diacetic acid and acetone bodies, you let the patient fast for one or two days, i.e., until the sugar disappears from the urine. Then you give increasing amounts of carbohydrate, 10, 20, 40, 50 gm. a day, together with protein and fat in low amounts. If the sugar goes when the carbohydrate has reached 50 gm., the tolerance is determined and then an allowance of under 50 gm. with some protein and fat in the diet are permitted. That is the Allen treatment. One can always get rid of glycosuria with the Allen treatment; but to get good results a fast day must be given periodically so that pancreatic rest is ensured. The Allen treatment is based on pancreatic rest and recovery. The criticism of the method is that many persons have no carbohydrate tolerance, and therefore the diet which keeps them free from sugar in the urine does not provide them with sufficient energy for their work.

Then came a great advance. Attempts were made to produce an extract from the

pancreas and to cure diabetes with it. Zuelzar, in 1908, prepared an alcoholic extract of pancreas, and found he could cure the glycosuria in diabetic cases by injections. The preparation, however, was very toxic and septic, poisoning frequently resulted, so that it fell into disuse.

In 1922, the Canadian workers, Banting, Best and Macleod, had been at work for two or three years, and they produced a pure solution containing this pancreatic amboceptor insulin. By injecting insulin the diet of a diabetic can be increased, and with insulin one can cure the incipient coma. This constitutes a wonderful advance.

In treating a diabetic case the patient is first put on to the Allen diet and so got free from sugar. The next step is to see whether the patient has any toxic focus. We all know that carbuncle is often associated with sugar in the urine, and one knew before the Allen treatment was introduced that if the carbuncle was cured the glycosuria often vanished. If there is an abscess and glycosuria when the abscess is drained the sugar often goes. But latent infections, such as those of the teeth, tonsils, antra, bowel, chronic appendicitis, diverticulitis, colon and bladder infections, all produce toxins which are a very great factor in the causation of diabetes. Therefore in a case of diabetes as soon as the urine is free of sugar one should get to work and eliminate the toxic factor. Sometimes in very bad cases one may have to put the patients on to a little insulin, so as to give a *modus vivendi*, a means of dealing with the case. Then one attacks toxic foci if they are removable. Tonsils, antra, teeth, can be dealt with surgically. There is no real risk in operating on a diabetic case provided that care is taken. By dieting the glycosuria is got rid of and the blood-sugar reduced to normal limits. As an anæsthetic gas and oxygen or ether may be used but chloroform should be avoided. After removing the septic focus in a diabetic case, there occurs a spread of the toxins and this may cause a little glycosuria. Afterwards there is permanent improvement and an increased carbohydrate tolerance. If one has the case of diabetes early, namely, in the first three or four months, then by removing the causal factor one can often obtain wonderful benefit, and in many cases bring about a practical cure. If the diabetes has been present a long time, the cells of Langerhans are so damaged that such a dramatic improvement is not possible.

Having removed any focal infection the next step is to ascertain the carbohydrate tolerance, and then consider the question: should this patient have insulin? There are certain cases in which insulin is needed. It is by no means always required. When acidosis is threatening coma you must give very big doses, not 10 or 20 units, but 30 or 40 or more, repeating this every two or three hours, first testing the urine and the blood. A wonderful example of diabetic coma occurred at St. Mary's Hospital; the case of a boy, aged 15, who came in comatose and was given 300 units of insulin in twenty-four hours, which resulted in recovery. Septic tonsils were present and were afterwards removed. The boy left hospital with his urine entirely free from sugar, and on a generous diet.

He was admitted to hospital a year afterwards in diabetic coma again, and was given 30 to 40 units every two hours until the coma ceased. He recovered in twenty-four hours. At that date he had not had his bowels opened for a week or so; it was an *intestinal* case. He left hospital after two or three weeks, and is now living in good health on a fairly normal diet. When coma is threatening there is not much danger of overdosing with insulin. Recently a case at St. Mary's was admitted into my care

suffering from diabetic coma, continuous large doses, 30 units every two or three hours, of insulin being required. The urine was found to be full of pus, and cystitis was present and was causing the hyperglycæmia. After bladder lavage daily, together with urinary antiseptic, the cystitis cleared up and the glycosuria disappeared.

Cases of low carbohydrate tolerance need insulin. Cases of diabetes, if they get acute inflammation on top such as influenza or pneumonia, should be given insulin. Diabetes with complicating conditions, such as boils, skin diseases, eye trouble, are benefited by insulin, because it enables things to heal up by preventing hyperglycæmia. I showed in 1922, in a Presidential Address at the West London Society, that toxic absorption in a case of diabetes neutralizes insulin, and that large doses are needed in toxic cases. It is obvious that if a person with diabetes has a toxic factor this should be removed, because the insulin will then act more beneficially and will not be neutralized by the circulatory toxine so that smaller doses are required.

Insulin is a dangerous poison, and must be used with care, because people vary in the degree of their susceptibility to it. Two hours after giving a dose of insulin the blood-sugar will fall, and will keep down eight to twelve hours; therefore the effect of insulin is much more prolonged than the effect of sugar, for if you take an ounce of sugar you have got rid of it in two hours. You should not give big doses of insulin in the evening. One may give a large dose at breakfast time, another dose after lunch, and the last at 3 or 4 o'clock in the afternoon. If one gives a large dose in the evening, the person may develop hyperglycæmia, become comatose, and die at about 1 or 2 in the morning. And it does not follow that because a person has high blood-sugar and much sugar in the urine that one can give a big dose. An old man in St. Mary's Hospital had had 6 per cent. of sugar in the urine, and his blood-sugar was over 0.3. He was given 10 units of insulin, and became comatose from hypoglycæmia after six hours. It was necessary to give glucose subcutaneously to revive him. You should so regulate your insulin that the blood-sugar is kept well below 0.18.

As to hypoglycæmia, it begins in a strange way. Persons feel a little faint and restless, mentally disturbed; they have hot and cold flushes, and often get excited; men use bad language, women are likely to weep, and then they suddenly become drowsy and go into coma, and death may occur very quickly. Hypoglycæmia is much more rapid than diabetic coma; the latter takes twenty-four hours, or more, to develop, and lasts some time. Insulin may cause coma within six hours or so, and death two or three hours later. Rabbits get convulsions, human beings do not, usually. In hypoglycæmia one must give glucose at once by the mouth, in orange juice or other suitable manner; or, if the patient cannot swallow, give 10 per cent. sterile glucose solution intravenously or subcutaneously.

In hyperglycæmia one can give pituitrin or adrenalin.

Insulin is sold in two strengths; in one of them a minim is equal to a unit, and in the other two units equal a minim.

There is no substitute for insulin. All sorts of pancreatic substances are put on the market, but they are useless. A substance was put on the market about 1927, synthalin, which was thought to be a substitute for insulin; it is one of the liver poisons and may cause toxic jaundice. It has been found to be of no value in diabetic cases and is sometimes harmful.

May I remind you of diabetic gangrene, which surgeons are very interested in.

Diabetic gangrene is not a complication of diabetes alone. In those cases with diabetic gangrene one finds very marked arteriosclerotic changes, and it is the cardiovascular changes which are responsible for the gangrene. Diabetes plays a part in the causation because the tissues of the diabetic patient are not so healthy as are those of the normal person. Often in cases of diabetic gangrene after amputation at the knee and removal of the septic condition the glycosuria clears up. Diabetic gangrene usually occurs in a person with arteriosclerosis, who probably has a raised renal threshold to sugar and gets sugar in his urine from time to time. One does not see gangrene in young people with acute diabetes.

FOR NOTES.