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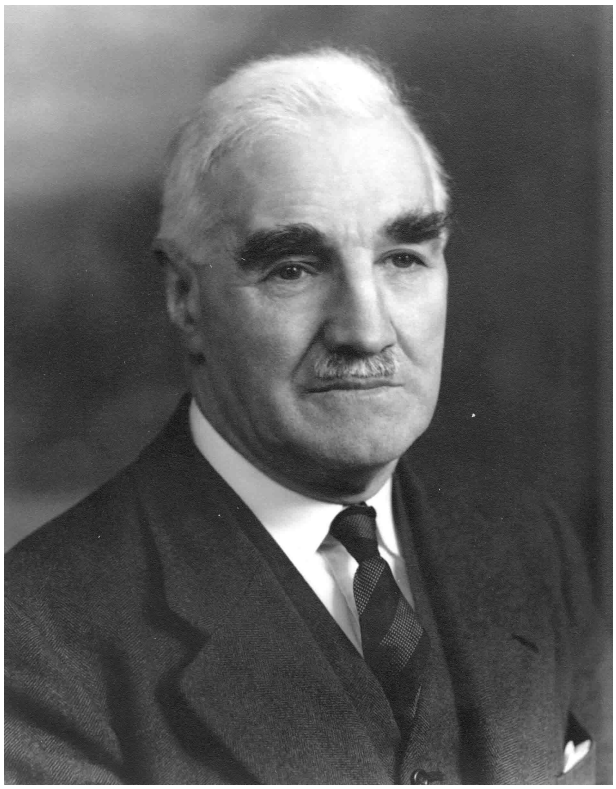
DIABETES: PAST, PRESENT AND FUTURE

I make no apology for speaking to you tonight in my presidential address on diabetes. During more than thirty years I have done much work at this disease, having seen more than ten thousand cases of it in all, and having been concerned in its investigation and treatment both in the pre-insulin and insulin eras. At the beginning of my medical life very little in the way of practical useful treatment was available to sufferers from the disease, and I doubt whether half a dozen blood sugar estimations had been carried out in the North of Ireland. The life of the diabetic was then indeed a miserable existence, in which he went on in a state of semi-starvation and invalidism, trying to postpone for as long as possible the evil day when he would die in coma, or of some intercurrent infection. Today, with proper care and a not unduly exacting co-operation, he can be perfectly fit and well, and carry on successfully with almost any work he cares to undertake. I often hear the remark, "Your diabetics look so fit and well." Last year, in the Royal Victoria Hospital alone, twenty thousand blood sugar determinations were carried out.

I would briefly like to review the medical history – not the history of diabetes itself, for that is probably longer than that of the human species. It is now known to occur in some of the lower animals.

The disease was mentioned in the Ebers papyrus, which dates from approximately 1500 B.C., almost one thousand years before the birth of Hippocrates. It was recognised as a clinical condition in very early Indian writings and was then probably, as now, prevalent among Hindus. The early Greek physicians seem to have been ignorant of it, but it was mentioned by those of a later date. Knowledge of the pancreas was set forth by Galen in the second century A.D., but he, of course, did not appreciate its connection with diabetes, of which condition he only recognised two cases. About the same period the disease was named "diabetes" by Aretaeus the Cappadocian, who described it as "a wonderful affection, melting down the flesh and limbs into



urine." Not much further knowledge of the malady was acquired until the advent of Thomas Willis, who lived from 1621 to 1675. He might be regarded as the first clinical pathologist, and while carrying on the largest fashionable practice in London, found time to make many researches in natural and experimental philosophy, anatomy, and chemistry. His account of the disease was not published until 1679, four years after his death. It is the first important medical treatise on the subject in the English language. In it he reports the case of "a certain noble Earl who became much inclined to excessive urination and when, for several months he had been used every now and then to make great quantities of water, he at last (it seemed) fell into a diabetes, which was obstinate and strong and almost desperate. For beside that, in a space of twenty-four hours, he voided almost a gallon and a half of limpid, clear and wonderful sweet water that tasted as if it had been mixed with honey, he was likewise troubled with an extraordinary thirst – and, as it were, an hectic fever, with a mighty languishing of his spirits, weakness in his limbs and consumption of his whole body."

He then goes on to describe the remedies prescribed consisting of whites of egg, tops of cypress, gum arabick, rhubarb, syrup of poppies, etc. His diet was to be only of milk, with some barley and white bread taken several times a day. "By the use of these things he grew daily better and better and seemed within a month to be almost quite well. When he began to be pretty hearty his urine, which was insipid, did not much exceed the quantity of that liquid matter which he took in. But yet the disposition to this distemper did not so totally leave him but that afterwards oftentimes, through his diet, and, perhaps, irregularities in the seasons of the year, being inclined to a relapse, he made water at first in great quantities and then clear and sweet, with thirstiness, feverishness and languishment of his spirits."

Evidently even in those days a little was understood of the importance of diet, and patients sometimes broke it. A century after Willis's death another Englishman, Dr. Dobson, in the Liverpool Infirmary, by the investigation of "a white cake about 2 os. 4 drachms and 2 scruples in weight" obtained by evaporating down diabetic urine, determined that the sweetening substance was glucose. The presence of acetone was discovered by Peters in 1875 and Kulz and Minkowski identified oxybutyric and diacetic acids in 1884, completing the knowledge of the existence of the ordinary pathological urinary constituents. At this point – seventy years ago – the ordinary clinical knowledge of diabetes was pretty much as it is today, but the knowledge was only skin deep. Nothing was known of the underlying causes.

CAUSATION.

In 1878 Claude Bernard, by puncturing the medulla in the floor of the fourth ventricle, brought about a marked glycosuria, but it was soon realised that the condition so produced had little in common with the disease of diabetes.

The epoch-making advance was when, following an argument about the possible effect, von Mering and Minkowski, working under Naunyn in 1889, by removing *in toto* the pancreas of a dog, produced to their surprise a condition substantially similar to that seen in acute and severe diabetes mellitus, and when later Minowski showed that, if previously some of the pancreas had been grafted under the skin, removal of the main pancreas caused no ill effects.

In Berlin, in 1869, Paul Langerhans, in a thesis for his M.D. degree, described the islets in the pancreas which since bear his name. Between 1900 and 1902 Opie, in the Johns Hopkins and Ssobolew in Berlin described the hyaline degeneration and destruction of the islets which they had observed in cases of diabetes. It was noted, too, that by blocking the pancreatic duct in dogs, degeneration of the pancreas followed but that diabetes did not immediately supervene. They found that, although the acinar tissue of the gland had degenerated, the islet tissue still at first remained intact but that later, after about four months' interval, when the islet cells also had degenerated, diabetes then supervened. The significance of these facts was not lost on the observers and Ssobolew suggested that a method was thus available for studying the secretion of these islands. In 1912 an attempt was made to prepare an extract from a pancreas so degenerated to the first stage, and in 1916 Schafer, in Edinburgh, believing that the islets contained an internal secretion, a deficiency of which caused diabetes, named it "Insulin." Ten years later Dr. Frederick Banting, in the Toronto Medical School, and Charles H. Best, one of his second-year medical students in Professor MacLeod's laboratory, made its separation an accomplished fact.

In 1943 it was discovered that animals given alloxan intravenously rapidly developed a complete destruction of the islets of Langerhans, followed by a diabetes very closely resembling that seen clinically in man.

With all this evidence it would seem that the proof that diabetes is caused by failure of cells in the islets of Langerhans was complete. There were one or two disconcerting facts, however. Firstly, by the methods of examination then known, cases of diabetes might show no demonstrable abnormalities of the islet tissue, and, secondly, persons in whom a complete surgical pancreatectomy had been carried out were found to require only thirty to fifty units of insulin daily for control. Many cases of ordinary diabetes required very much larger amounts, sometimes, indeed, running into thousands of units.

Recently, more specialised methods of tissue staining have been developed which shew up much lesser degrees of damage of the islet cells than could previously be demonstrated, and counts of the islets themselves have sometimes shown notable diminution of their numbers, or of the number of beta cells (which are now believed to secrete the insulin) relative to alpha cells where no actual deterioration of the individual cells was manifest. These findings go some way to answer the first objection but the second is not so easily met, and there are probably other factors of which we are only partly cognisant. If thirty to fifty units of insulin are adequate to metabolise an ordinary day's food, it would follow that in those cases where a larger amount is required

there must be present another substance which in some way neutralises the additional amount.

About 1932 several workers both in the British Isles and in America had produced a hormone from the anterior pituitary gland which they designated the growth hormone. When given to young puppies daily for many months it produced an increased physical development, but when continued after full growth had taken place it was found that many of the puppies became ill and wasted, and were found to have developed diabetes. In the early stages, when growth was taking place, it was noted that the islet cells showed increased activity, but that in the diabetic phase degenerative changes were present. It was as if the islets had been called on for an increased insulin secretion because of partial neutralisation of circulating insulin, and that under the excessive strain had failed. An interesting finding about the growth hormone is that it stimulates milk production in many lactating animals and, although it produces diabetes when administered to ordinary adult animals, it will not do so in a mother suckling a litter. Evidently the increased lactation gives the necessary outlet to the anabolic action of. the hormone and stimulation of the islet cells does not occur. These findings probably supply the explanation of the classical experiment of Paul Best in France in 1884, when he carried out mastectomy on pregnant goats, and produced at parturition a transient diabetes thereby. It would appear that there is a physiological increase of secretion of growth hormone in the later stages of pregnancy and during lactation. How often does one get an account from an obesity patient of its onset after her first pregnancy with a steady step-like increase after each succeeding birth.

The growth hormone may evidently do one of three things– (1) accelerate growth; (2) increase lactation; (3) if neither of these two courses is possible, diabetes may result.

Another observation which suggests that many diabetics may first suffer from increased growth hormone is the now well-known tendency of certain women to have over-large babies and then develop diabetes at a later date.

In 1936 Houssay, in the Argentine, found that experimental diabetes could be greatly alleviated by removal of either the whole of the pituitary gland or of its anterior lobe.

For a few years the dominant role of the anterior pituitary in the development of diabetes held the field in the minds of many investigators, but a good deal of controversy has arisen as to the validity of some of the findings on which it was based.

Another possible counteraction to insulin may arise in the islets themselves. As you know, these islets are made up of two separate types of cells known as alpha and beta. It is the beta cells which are believed to produce insulin, of course. Recently there have been adduced several facts which suggest the production of a secretion by the alpha cells which acts counter to insulin. The most important is that diabetes resulting from a total pancreatectomy, in which both alpha and beta cells are of course removed, requires much less insulin for control than in naturally occurring diabetes and in alloxan diabetes, in both of which the alpha cells remain intact. It has also been known for a little that insulins prepared from pancreas in certain ways produce on intravenous injection a transient hyperglycaemia, to be followed, of course, by their characteristic hypoglycaemic action, and it is believed that this hyperglycaemia may be produced by a secretion extracted from the alpha cells. It has been separated out as a protein factor present in these insulins, but it has not yet been definitely proved to originate in the alpha cells. Were these proved to be its origin, it might be that we have there the explanation for the so far unexplained magnitude of insulin dosage in most cases of naturally occurring diabetes, and, possibly, an important fact in its causation. This substance is known as the hyperglycaemic-glycogenolytic factor (H.G.F.), or as glucagon, which it was originally named by Murlin when he identified it in 1923. It has been prepared in pure crystalline form, and about a year ago a group working in the Eli Lilly Laboratories and the Indianapolis General Hospital isolated sufficient of it from commercial amorphous insulin to conduct an extensive investigation of its properties.

COMA.

Coma used to be the sword of Damocles which hung suspended over every diabetic. Every diabetic had a six to four chance of quitting this sphere without being at the time acutely aware of it – perhaps not the worst way after all, but one most unsatisfactory to the medical faculty. Approximately the same treatment was tried in all, but only a very rare case survived. Now with modern massive doses of insulin and other adjuncts, the mortality has fallen to less than 2 per cent, of all diabetic deaths, in the hands of those accustomed to the condition. I am glad to say the last case of my own I have seen die in coma was over ten years ago, and if cases are got under treatment before, or directly complete coma supervenes and there are no other serious complicating diseases, it should be possible to recover

practically all of them.

It should always be remembered that ketosis coma has no direct connection with blood sugar. You can have a blood sugar ever so high and have no tendency to coma, and you may possibly have coma present with a normal blood sugar. I find housemen, and even their seniors, often come to my laboratory in a considerable anxiety when they have a blood sugar of 500 or 600 mg. per cent, returned to them.

VASCULAR DISEASE.

If the mortality from coma has fallen so markedly since insulin appeared, that from arteriosclerosis has made up for it. Before insulin the mortality from arteriosclerosis accounted for about twenty per cent. of diabetic deaths: it now stands between seventy and eighty. The explanation is not far to seek. In 1914 the average age of diabetics at death was 44½ years. In 1946 it was 64½. Diabetics are now living on the average three times as long with diabetes as they used to, and long enough for arteriosclerosis to develop. This especially applies to persons developing the disease in youth.

Of two hundred diabetics whose diabetes had begun in childhood and had lasted more than twenty years, Priscilla White reports that 92 per cent. showed evidence of vascular disease. This state of affairs is amply confirmed by the finding in many other centres, and, as we will see, is probably due to unsatisfactory control, and so largely preventable. Analysing this vascular disease Priscilla White found that 2.5 per cent. had had cerebral vascular accidents; coronary insufficiency was present in 8 per cent.; hypertensions in 40 per cent.; 75 per cent. had calcified arteries; nephritis claimed 50 per cent.; 85 per cent. had retinal arteriosclerosis and haemorrhages.

Of 2,300 deaths among diabetic patients just under 70 per cent. were due to arteriosclerotic degenerations. Of these just under 46 per cent. were due to heart disease, just under 12 per cent. to cerebral vascular disease, 7 per cent. to nephritis and just over 3 per cent. to gangrene.

Bell has found in an analysis of fifty thousand post-mortems that 4 per cent. of all deaths from coronary disease were associated with diabetes in males and 14 per cent. in females. Gangrene, due to arteriosclerosis, was forty times as frequent in diabetics as in non-diabetics. Severe renal arteriosclerosis was one hundred times as frequent in the diabetic as in the non-diabetic group. Joslin and Wilson found that of 135 cases of diabetes beginning in childhood, dying after ten years' duration, seventy-two died of nephritis. In the Mayo Clinic arterial insufficiency in the legs of diabetics was found to be eleven times as frequent as in non-diabetics and in women arteriosclerosis obliterans was eighty times as frequent in diabetics as in non-diabetics.

From these figures and findings it will be evident that the prevention of arterial degeneration constitutes without doubt the greatest challenge in the treatment of diabetes today. It is gradually, but now almost universally, being conceded that the fault lies in failure of accurate control, and in many centres a more vigorous attempt is being made in that direction.

A good deal of attention has been paid to the renal lesions since 1936, when Kimmelstiel and Wilson pointed out a correlation between a clinical syndrome developing in diabetics – gross albuminuria, nephrotic oedema and hypertension – and a peculiar type of intercapillary sclerosis of the glomeruli in which one or more ball-like hyaline masses appear in the glomerular tuft. There is also a diffuse type, and both are often associated with frank pyelonephritis. In its typical form it is almost pathognomonic of diabetes. The hyaline material seems to be a muco-polysaccharide and to be identical with that found in the atherosclerotic arteries in association with the aneurysms found in the retina, and also, probably, with the substance deposited in the islands of Langerhans. At present a good deal of work is being carried out in investigating the nature of this substance and the factors influencing its deposition, and information of practical value may accrue, not alone in regard to diabetic arteriosclerosis, but to arteriosclerosis in general.

As in the kidney, so in the retina the lesion arising in diabetes is often pathognomonic, and the ophthalmologist can often diagnose this disease from what he sees in the fundi. It arises chiefly from the development in the capillaries of saccular micro-aneurysms which are believed to be caused by deposition of the muco-polysaccharide in the vessel walls, weakening them and so allowing pouching. Later the aneurysms are often filled with the same muco-polysaccharide as in the lesions in the kidney, and indeed the globular masses in the glomeruli may be micro-aneurysms filled with the muco-polysaccharide. The aneurysms in the retinae show an increased permeability of their walls and are often surrounded by haemorrhages and white exudates composed of protein.

For a long time no one was able to reproduce these muco-polysaccharide lesions experimentally

except in one single dog which Lukens had rendered diabetic by injection of anterior pituitary extract, and which, on being killed after five years, showed the typical Kimmelstiel-Wilson lesions. It has just recently been discovered that they can readily be brought about in rabbits by daily intramuscular injections of cortisone and of A.C.T.H. and that this can be greatly accelerated if the rabbits have previously been rendered diabetic by alloxan. Evidently there is some interaction between diabetes and increased anterior pituitary and adrenal hormones in the production of this dystrophy.

The incidence of retinal lesions parallels closely that of the intercapillary glomerulosclerosis, generally occurring like it only after about ten or more years of diabetes and in badly controlled or neglected cases.

Lens opacities frequently occur with diabetes even in young patients, but statistical evidence of their higher incidence is indefinite. It is noteworthy, though, that in Denmark, among cataracts requiring surgery, diabetes was fifteen times as expected in the age period 65-74 years, and 202 times as great as expected in the period 25-34 years.

DIABETIC NEUROPATHY.

We expect smaller or greater involvement of the C.N.S. in many diabetics, and it will not surprise most of you to know that some degree occurs in over 50 per cent. Frequently it may be the small fact of the absence of the Achilles jerks, but occasionally much more serious lesions are encountered. Sensory changes often bother the patient: sometimes it is only a matter of diminished sensitivity of the feet, but I remember a case where the patient screamed with pain every time one touched her, or when the bed on which she lay was jarred. Her diabetes had been in existence and untreated for an indefinite number of years. After about a month of control she was improved enough to do without morphia, but it was several months before she was able to get out of bed.

Severe diabetic neuropathy is found frequently in association with diabetic retinitis and nephropathy and its onset is also frequently after a similar duration of the disease. It also seems generally to be brought on by bad control of the diabetes, and an exacerbation often follows a period of complete absence of control. The conclusion is unavoidable that the neuropathy results from the abnormal metabolism of unregulated diabetes, though the exact mechanism is not clear.

There are several features of diabetic neuropathy which may sometimes not be appreciated as being of this origin. First, a typical Argyll-Robertson pupil is occasionally found. I saw an example of this quite recently in one of my patients in the Royal Victoria Hospital and have encountered three or four previously. Sometimes one finds a fully developed pseudo-tabetic condition which it may be difficult to differentiate from that of syphilitic origin, for example – Charcot joint. This seems generally to affect the tarsal and proximal metatarsal region, and is first evidenced by a thickening there. Later the joints become disorganised in the typical charcot fashion. This is an unusual complication and I can recollect only two cases. A third is an even rarer complication, urinary bladder paresis, with which a typical automatic "cord" bladder may develop. A fourth is more frequent – diabetic nocturnal diarrhoea. One sometimes sees lesser degrees of this, but occasionally it can be a most troublesome complication, with one, two or more loose motions passed almost every night; there may be incontinence. It does not generally occur during the day, for some unexplained reason. One might jump to the conclusion that it is due to a complete pancreatic lesion with resultant steatorrhoea, but this is not found to be so. I have done fat analyses on a number of these cases and obtained perfectly normal figures.

These four complications seem to arise from irreversible degenerations and very little can be done for them. The latter two can be most distressing.

TREATMENT.

The treatment of diabetes should be directed towards the production of a normal physiological environment of the tissues and anything departing from this ideal must necessarily be wrong. Since the introduction of insulin there has been a great deal of loose thinking in this matter. The almost miraculous immediate effects produced by the use of insulin, even where there is no careful adjustment of dosage and very little attempt at dieting, tempted many physicians and patients to take the cash in hand and pay very little attention to the brave music of the distant drum. No real effort was made even to try to keep the excretion of sugar within limits, and blood sugar levels were scarcely thought of. For them the chickens have come home to roost in the shape of the 92 per cent. vascular diseases in a series of diabetics of twenty years' standing who had developed diabetes at the age of 15 years or under.

The publication of this analysis has had a most sobering effect on those who have in the past been happy with an easygoing regime for their patients and has produced a considerable change of attitude. In the last edition of his encyclopaedic textbook on diabetes published just over a year ago, Joslin constantly reiterates this necessity for accurate

control, and at the first meeting of the International Federation on Diabetes held at Leyden two years ago he referred to it almost every time he got on his feet to speak. In his "Treatment of Diabetes Mellitus" he states that, while he was convinced that raised blood sugar causes overwork and degeneration of the islet tissue, he had at one time some doubt as to whether it could cause, among other things, degenerative phenomena in arteries and nerves, but that this is not so today.

He poses the question, "Does careful meticulous treatment of diabetes pay?" Stating that his opinion is based on contacts with forty thousand glycosurics in a period of fifty-four years, "He believes it does in added years of vigour and happiness" and that "those who knew most and followed the rules most implicitly were the happiest and the most comfortable." He points out that of the recipients of the Quarter Century Victory Medal awarded to those diabetics of twenty-five years' standing who were certified after examination by physicians, ophthalmologists and radiologists to be sound, with eyes and blood vessels free from degenerative changes, not one had disregarded a strict regime. He goes on to say, "We believe *a priori* that the blood sugar should be normal, because the blood sugar is the index of the disease. It is the red light which we should no more disregard than we would fail to heed the red signal at the railroad crossing."

He ends the paragraph – "Whatever may be the direct and immediate causes of the diabetic sequelae, good diabetic control will postpone or prevent these complications. "

With regard to vascular diseases, he states: "The most advanced lesions will be found in that group of patients who have been under the least careful control with diet and insulin." Again, "The frequency of angina pectoris in diabetes in middle and late life depends largely on the duration and poor control of diabetes." Wilson, Root and Marble, in an analysis of 247 patients who had had diabetes from 10-34 years, found evidence of diabetic nephropathy in 25 per cent. Not one of these 247 who had adequately controlled his diabetes by attention to a programme that included early and continued use of insulin, careful measurement of a planned diet and regular medical examination, had developed the lesion, but sixty-two patients who had had poor, or only fair control, developed the typical nephropathy. Of these last thirteen died during the year in which they were examined.

Root has made an extensive investigation into the factors influencing the development of retinopathy and found that severe retinal complications were much more frequent with patients under poor control than under fairly good control. In his series already mentioned of 247 cases examined with Wilson and Marble, he again found that no patient under good control had developed retinal changes of any importance. Of the cases with moderate to marked retinopathy all but five had had poor or only fair control. None had had excellent control. In investigating 326 cases of retinitis proliferans, the more or less end condition in severe diabetic retinitis, he found that only in three cases could it be said that dietary instructions had been closely followed with satisfactory blood and urine tests. One-third of the patients were known to have frankly given up any attempt at approximating a careful diet. A common statement of this group was that the food was carefully measured for the first few years of diabetes, and then for a period of six or more years very little, if any, dietary restrictions had been carried out. None of this group could possibly have been considered under excellent dietary control. He concludes: "Whatever the specific etiologic factors causing diabetic degenerative lesions may be, this series has demonstrated that the regulation of diabetes controls these factors. The control of diabetes thus appears more important than any other known factor, such as duration or severity of diabetes, in preventing or postponing these degenerative complications in the retina."

From Vienna also comes the opinion that vascular diseases are due to bad control.

Diabetic neuropathies also appear practically always only where there has been a failure of control. Joslin states that most diabetic cases who develop neuropathy have had antecedent periods, usually of months' or years' duration, of neglect or poorly managed and uncontrolled diabetes. Of 113 cases occurring during the year 1950 at the New England and Deaconess Hospital in no case could it be said that the neuropathy had begun at a time when diabetes was well controlled.

Many of these findings and opinions have been duplicated by Sherrill and by Jackson and his associates, and in the Mayo Clinic and elsewhere. Frederick M. Allen states that the blood sugar can nearly always be kept within the normal range (that is, not above 150 mg. per cent. throughout the twenty-four hours) without frequent hypoglycaemic troubles and without spoiling the happiness of any sincerely co-operative patient. With this control he believes that complications are absolutely prevented or, when they exist, are generally arrested. He

suggests that the reward of diabetic patients for their strict care may be a lower incidence of premature degenerations than among the general population. Dunlop, in Edinburgh, discovered that while so-called "free diets" – where no control of food was tried and no attempt made to maintain aglycosuria or normal blood sugars – did not produce many bad effects during the first five years, in the next four years the results were disastrous. After the nine years, only nine of an original fifty patients were still in good shape. As a result, from being in the opposite camp, he comes down heavily in favour of accurate control by weighed diets and frequent supervision in a diabetic clinic. He regards it as most exceptional to encounter a well-controlled patient who has been responsible for his own treatment.

This new and widespread emphasis on the necessity for accurate control confirms those of us who are specially interested in diabetes here in our opinion that it is the only real treatment of the disease and that to give the patient to understand that anything less is effective is, to put it no worse, pandering to his desire for an easy cure. Although slipshod methods will often keep him reasonably well for five or even ten years, at the end of that time he is likely to develop serious incapacity, a likelihood which will increase with the passage of each additional year of the disease. The trouble is, too, that once these degenerative complications have appeared there is no going back. Accurate control, if then instituted, may slow them down, though in my experience they steadily progress, and in any case, the existent damage can never be recovered. On looking back over my thesis for my M.D. degree presented in 1924 when insulin had been in use for two years, I find myself pointing out there that it would not be in the immediate results that the importance of accurate treatment would be seen, but rather after years, when degenerative lesions had had time to develop.

In the Metabolic Extern at the Royal Victoria Hospital we have long been aware of all this. We there see patients much more frequently than is done in most diabetic clinics, and they are seen by doctors with a good deal of experience in general medicine as well as in diabetes. We find that where exact control is instituted and maintained vascular degenerations and neuropathies rarely, if ever, appear. These patients are at least as fit as if they had not diabetes. On the other hand, when we find the record dotted with resting blood sugars of 180, 220 and suchlike figures, and notes of warnings and threats, sooner or later some serious complication begins to develop and the patient steadily progresses towards a sticky end.

Having made up our minds as to the necessity of satisfactory control, we next proceed to examine what constitutes it. Quite briefly, it means the production and maintenance of a normal physiological condition – a normal way of life with normal mental and physical exercise, kept going by a diet adequate for normal nutrition, with a constantly normal biochemical status – normal blood sugar, never exceeding 180 mg. per cent. and for the most part below 120 mg. per cent. throughout the twenty-four hours. This will generally be so if the blood sugar at four times of the day – before insulin, before the midday meal, before the evening meal and before the last meal at night – be 120 mg. per cent. or less. There may be some short intervals when 180 mg. per cent. is exceeded after the meals, but they will generally be of brief duration. In my opinion that and no less constitutes proper control and treatment of the case. In the odd patient, owing to certain difficulties it may not be completely possible, but in the great majority it is practicable and should be ensured.

To bring this about often requires a good deal of juggling of the amounts of different foods at the various meals and of both quick- and slow-acting insulins, relatively as well as absolutely. The patient must feel satisfied with his diet so as to diminish the chances of his kicking over the traces; its calorie value must be such as to maintain his weight within normal limits, and it must be balanced as to its constituents so that it will not produce a ketosis. In practice, when the diagnosis of diabetes is made, if it is of such degree as to necessitate the use of insulin, the patient is admitted to the ward. The doctor or dietitian there discovers by enquiry what the patient ordinarily eats and in what amounts. A suitable diet, based on his normal habit, is then drawn up and an experimental dose of insulin begun, to be adjusted from day to day on blood sugar results until the desired goal is reached. The patient is then discharged and attends the Metabolic Extern at intervals, longer or shorter, depending on the smoothness or otherwise of the course he runs. In large numbers of patients, especially in the older groups, where full co-operation is forthcoming, the dose can be slowly reduced, still maintaining a normal blood sugar status, and in a few eventually stopped altogether, leaving them on diet alone.

The question of the type of insulin to be used arises. There is (1) the ordinary soluble insulin which begins to act immediately and whose action only lasts for six to eight hours. It generally only gives

satisfactory control for the meal which it precedes; (2) globin insulin, whose main action lasts over a period beginning about four hours after injection, and ending about eight hours later. A dose given before breakfast will not usually control that meal satisfactorily, but will control the midday meal, and occasionally the evening meal, but not food taken at bedtime. The weight of the action is in the afternoon; (3) N.P.H. insulin, a compound with protamine zinc and phenol. This is not obtainable in this country – a great pity. Its action is a little more delayed than that of globin insulin and less so than that of (4) protamine insulin with zinc, whose action has a lag of about eight hours and is continued for a further sixteen hours or a little more. The maximum effect is often in the late evening and through the night. Recently insulins (5) semi-lente or insulin zinc suspension (amorphous), (6) lente or insulin zinc suspension, and (7) ultra lente or insulin zinc suspension (crystalline) have appeared as a result of the experiments of Hallas-Moller and his co-workers in Copenhagen. The first names, semi-lente, lente and ultra-lente are of their choice, and are used everywhere outside the British Isles, but there has been, to my mind, a most confusing attempt to adopt the second series in this country.

The elaboration of these last three insulins has been a rather interesting piece of chemistry. It has for some time been known that zinc has some important role in the action of insulin. Zinc is present in greater concentration in the islet cells than in any other tissue in the body and the liberation of insulin from them is accompanied by a simultaneous fall in their zinc content. Insulin can combine with zinc, and zinc added to insulin will enhance its action. When animals are given compounds like alloxan, oxin, or dithizone which bind zinc, the metal is taken out of action and diabetes develops.

The iso-electric point for insulin, at which it is insoluble, is 5.3, and at the pH of the body, 7.3, both ordinary insulin and insulin with small amount of zinc alone are completely soluble. As a result, both of them are what are known as quick-acting insulins. If, however, to the insulin zinc compound is added either globin or protamine the resultant compound is only slowly soluble at 7.3 and, as a result, its action is delayed.

The pH of insulin mixtures has in the past been kept right by a phosphate buffer solution. Recently Hallas-Moller and his fellow-workers discovered that if instead of using phosphate as a buffer, acetate were substituted it then was not necessary to add protamine, or any other substance, to render the insulin-zinc compound only slowly soluble at body pH. Also the insulin zinc compound could be precipitated out of solution as the pH rose from 4. Between pH 4.5 and 5.8 the deposit is crystalline with the crystals in various sizes. Outside this zone it is amorphous.

It was presently noted that when a suspension of the crystals was injected into animals rendered diabetic the amount of retardation of the insulin action was directly proportional to the size of the crystals.

A further step was the discovery that the higher the pH of the acetate buffered medium from which the insulin zinc compound was precipitated, the larger the amount of zinc which the insulin would combine with. This also enhanced the delaying action. So they now had three factors to play with in producing delay – first, the insolubility of the zinc insulin compound in acetate buffer; second, the size of the crystals, and, third, the amount of zinc in the compound. Hallas-Moller ended by producing the three suspensions of zinc insulin mentioned (5) the "amorphous," which is quick-acting – almost as quick as ordinary soluble insulin but a little longer in duration and which he designated "semi-lente"; (7) the crystalline, which is very slow-acting – rather like protamine insulin with zinc, but lasting longer than twenty-four hours, and which he designated "ultra-lente," and (6) a mixture of these two containing three parts amorphous and seven parts crystalline which he labelled "lente." This mixture, composed partly of amorphous insulin to control in the early part of the day, and partly of crystalline insulin to control in the later part of the day and through the night would, he thought, be suitable to regularise the blood sugar content of the great majority of diabetics throughout the twenty-four hours with a morning injection from one phial. It has since been claimed that this is so in 90 per cent. of cases. I have not found this claim borne out within the practical limits of dietary. If one varied diets to extreme degrees it would undoubtedly be possible to reach this high proportion, but the arrangements of food at the various meals would sometimes be far from the patients' wishes, and would produce great objections from them. The alternative is, however, often a fairly easy one. It is simply that the patient be graded on the necessary number of units of semi-lente insulin and of ultra-lente insulin before breakfast, just as one uses soluble insulin and protamine insulin with zinc. The one (perhaps doubtful) advantage over the older insulins is that whereas soluble and protamine insulin with zinc

should not be mixed in the same syringe, with semi- and ultra-lente insulin it is quite in order. It seems a small advantage to have made headlines in the daily papers and a B.B.C. broadcast over!

PREGNANCY IN DIABETICS.

Naunyn, with his wide experience in Vienna, writing as recently as 1906, stated that he had seen only one example of pregnancy in a diabetic woman. Until the appearance of insulin in 1922 it was an infrequent occurrence. The first increase followed the use of soluble insulin, and a greater increase came with the development of the slow-acting insulins which provided more complete control. Today the diabetic woman requiring investigation for sterility is the exception.

There are four matters for consideration in connection with diabetic mothers: –

1. Heredity.
2. Maternal mortality.
3. The effect of pregnancy on the course of the disease.
4. Foetal mortality.

The question of *heredity* arises prominently in the minds of diabetics and, unfortunately, with justice. Examination of a group of my cases found the presence of the disease also in a blood relation in over 40 per cent., and this agrees closely with the figure obtained by Joslin in a survey of his unique experience of forty thousand cases. He found, too, that diabetes was five times as common among relations of diabetics as it was among the general population. He regards the inheritance of diabetes as a Mendelian recessive trait. He considers that the child of a father and mother, both diabetic, is certain to develop it if he lives long enough, and that the child of one diabetic, although he may not develop the disease, may be a carrier. If a diabetic carrier marries a member of a non-diabetic family the offspring will not develop diabetes but some will be carriers. Should a diabetic marry a carrier, as many as 75 per cent. of the offspring may develop diabetes. If two carriers marry the offspring can show 25 per cent. diabetes. On this basis Joslin estimates that 25 per cent. of the population are carriers, although only about 3 per cent. develop the disease.

Similar views have been expressed by many others who have explored the matter, among them Pincus and White and, also, Buchanan in America, Cammidge and Howard in England. Von Noorden, in Germany, and Hogben, in London, considered it to be dominant rather than recessive.

In Joslin's clinic 1 per cent. of the children of diabetic mothers are known to be diabetic, whereas in the general population the incidence of diabetes in children under the age of 15 years is only 1/2,500. The high incidence when diabetes occurs in the family of the father also should entail great care to avoid, where possible, such a union.

Maternal mortality. – With proper treatment this should be no higher than in the non-diabetic. I have not seen a maternal death.

The effect on the course of the disease. – Except where vascular disease of fair degree is already present there seems to be no permanent effect. The dose of insulin is liable to vary a good deal during the pregnancy and for a short time after delivery, being usually increased, but later settles down to something like the amount necessary before the pregnancy.

Foetal mortality. – That is the big question in diabetic pregnancies. Even with the greatest care, it is undoubtedly much higher that in non-diabetic mothers. In the most carefully treated it remains at about 10 per cent., and congenital abnormalities are six times as common in children of diabetic mothers. These abnormalities do not, however, account for many of the deaths, and the exact cause is often a matter of conjecture. Ketosis, unless severe, does not seem to be a factor, nor hyper nor hypoglycaemia *at the time of the death.* At one time it was thought that hypertrophy of the foetal islets of Langerhans with over-secretion of insulin, which was used by the mother during pregnancy and produced a hypoglycaemia in the baby when born, was often the cause where death supervened a few hours after birth. This was based on the finding in such babies of blood sugars as low as 30 mg. per cent., and seemed to be the answer until it was found that the same low level was often reached in children of non-diabetic mothers. It had already been realised that giving them glucose did not increase their chances. We are driven back to the clinical finding that these babies are often big and flabby, and have a low vitality and just don't live. It is becoming more and more evident, though, that the chances of a live and viable baby are greatly increased by two things: (1) accurate control of the diabetes during the pregnancy – that is a blood sugar continuously within normal limits and a freedom from ketosis; and (2) termination of the pregnancy at thirty-seven or thirty-eight weeks, before the overgrowth and flabbiness have occurred.

Graham and Lowrey, in the Michigan Medical Bulletin of 1953, write: "Better control of diabetes in the mother is the one factor which seems to contribute to a reduction of foetal and neonatal deaths."

In the present year, Long, Hartman, Fletcher and

Eastman, from the Johns Hopkins Hospital, published their results in the Journal of Obstetrics and Gynaecology, showing 36 per cent. foetal loss in sixty-two pregnancies between the years 1942 and 1948, and 18 per cent. loss in fifty-six pregnancies between 1948 and 1952. They consider that, by adhering to two principles, (a) increased efforts at maintaining the maternal blood sugar within normal range, (b) increased use of Caesarean section before the end of the thirty-eighth week, 59 per cent. of the infant mortality over the entire period could have been prevented.

Obstetricians tell me that Caesarean section provides a greater maternal risk than does parturition per vias naturales, but I have no doubt it is best from the baby's point of view. The strain on a not very vigorous infant, further prolonged and increased by its being somewhat oversize, militates against its chances, if birth is per vaginam. This large foetus is said to occur in 80 per cent. of diabetics, and was noted as far back as 1824 by Bennewitz. In such a birth he says, "The shoulders stuck like a wedge in the vaginal outlet and would not go up or down." The infant "seemed anxious and sighed with a clear voice," but was finally still-born, "not without great difficulty." This infant, "whom you would surely say Hercules had begotten," weighed 12 lb., and "the arms were of such breadth that I could not encircle their circumference with all my fingers spread."

I am sure this description stirs up a memory in the minds of some of my older listeners.

My colleagues in the Royal Maternity Hospital used to agree with me when I suggested Caesarean section, but I notice lately a certain swing towards induction. I have not, of course, seen the cases which go wrong following Caesarean section. In any case, there is no doubt we get excellent results, and although our series is small, I think that in cases where we were able to look after the control of the mother during pregnancy, and where proper co-operation by her was forthcoming, we have probably obtained better results than any I have heard of elsewhere. We have not attempted to carry out the hormone treatment pioneered by Priscilla White in Joslin's Clinic, and it seems to me to be of doubtful value. She, too, does consider that meticulous control of the diabetes, early hospitalisation and early delivery are essential.

THE FUTURE.

We have now mentioned the past of diabetes and discussed salient points of its present. What of its future? In the past twenty-eight years since insulin became our main defensive agent, great changes have been seen. Before 1926 the outlook for a diabetes developing in the first decade of life was at most a year or so – more often about six months. These children now live twenty, twenty-five or more years from the beginning of the disease. The present life expectancy for the middle-aged diabetic is about three-quarters of that of the average individual. Pregnancies in diabetics can be brought to a successful conclusion so that these young women can live in normal family surroundings. Diabetics, apart from engine-driving, piloting aeroplanes and one or two occupations of that kind where the lives of large numbers are involved, can engage in almost any occupation. They are found in all kinds of important posts, among the ranks of scientists and as heads of large business organisations. They can participate in strenuous and competitive sports, and even compete for world championships. Many improvements can, however, still be made, even in the present state of our knowledge, and these are largely in the direction of more accurate control. As Joslin says: "Of these complications which have ravaged our diabetics, most can be explained by failure to control the disease." These result largely from vascular degeneration which we have seen is largely preventible. Many young diabetics are difficult cases, partly inherently, but partly because of lack of discipline. It is very hard to have to ask a young boy or girl to stick to accurately controlled diet and refuse so many attractive things other children enjoy, but in the more mature deviations are often not so forgivable. One often feels that the demonstration of one gangrenous foot, one uraemia, one diabetic coma, or one blind patient would make transgressions rarer.

The physician himself is often to blame. The standards set are frequently not sufficiently high, and there is often a good deal of laxity, or failure to strive after any standard at all.

I may perhaps be thought to lay too much stress on accuracy of control, but I feel that our policy here, which has always had that as its main objective, has been vindicated by the results obtained by more easygoing methods, and collected and analysed in the last few years. It is only now that these free diets and uncontrolled blood sugars have had time to produce their harvest, and it is a very sad harvest indeed.

Apart from more accurate control, it may be possible that some new and better type of insulin may be developed, though one can hardly see how this is likely. Perhaps, though, one may appear which will have continuously constant action and for longer periods, making injections less frequent.

While at the moment it seems that the only

advances may be in improvement of present methods, and that no progress to date has been made in the direction of prevention or cure, yet with the wealth of information and experience now available, one can look forward confidently to a future in which an even happier, longer, and more useful life will be possible.