MODERN TRENDS IN DIABETES*

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UNTIL the last war, the incidence of diabetes was thought to be from one-half to seven-tenths per cent of the total population, and the total number of diabetics was supposed to be not greater than one million. In 1943, Dr. Blotner,[1] then a reserve officer in the army, examined some 45,000 inductees and found that among these relatively young men, in whom diabetes is less common than in older ages, the disease had an incidence of nearly one-half of 1 per cent. This aroused Dr. Blotner's suspicion that diabetes was more prevalent than any of us had heretofore recognized. Three years later he[2] was able to examine a larger group—some 69,000 inductees—and here with more careful methods and the more liberal use of blood sugars rather than urine sugars, an incidence of 1.1 per cent was found, again in this relatively young group of people. This implied more strongly than ever that in the population at large the number of diabetics must be considerably higher than formerly believed.

In 1947 this supposition was confirmed by a careful survey conducted by Drs. Wilkerson and Krall[3] of the U. S. Public Health Service, in Oxford, Massachusetts, appropriately enough the former home of Dr. Elliott P. Joslin. Among some 3500 people who were carefully examined there were 70 diabetics in this town of approximately 5,000 inhabitants and of these 40 had previously known they had the disease and 30 had not suspected it. This then is a ratio of almost one unknown diabetic for every one who was known. Thus, instead of a million diabetics in the United States there are probably nearer two million.

It is important to find them because by bringing them under early treatment, we hope to accomplish two things: we hope to prevent mild cases from becoming severe, and we hope to prevent the more severe cases from developing complications. Please note that in expressing this hope, we are implying that by proper treatment mild diabetes can be prevented from becoming severe and severe diabetics can be prevented from having complications. This implies careful regulation of the diabetic. If this were not so, there would hardly be any point in trying to find a million unknown diabetics. In the campaign to discover the million unknown cases, special emphasis is being placed on the obese person because about 80 per cent of people with diabetes acquire their disease while they are overweight. Attention is being paid particularly also to those with a family history of diabetes because there is a definite hereditary element in the disease. We are on the look-out for people over 40

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because diabetes is predominantly, though by no means exclusively, a disease of the older age groups. The fourth category of special suspects are those who have had or are having an acute illness because acute illness often brings to light a latent diabetes.

Another development in the diabetes problem is the progress being made toward cracking the problem of what causes diabetes. Why do people get it and how do they get it? For a long time we were not even sure what organ was involved in the cause of diabetes. In the latter part of the last century Von Mering and Minkowski seemed to have settled that problem by discovering that if one took the pancreas out of a dog, the dog developed diabetes. This seemed to end at least for that time all controversy about the subject. Soon, however, it was found that patients with diseases of other parts of the body also got diabetes. Also there was a good deal of difficulty in demonstrating microscopically that the pancreas was really involved in many patients who had died after having had diabetes for a long time. Both the anterior pituitary and the adrenal cortex have now been implicated as organs if not primarily responsible for diabetes, at least as important in its causation. One can produce permanent diabetes in animals by anterior pituitary substances without touching the pancreas directly.[4] One can also produce hyperglycemia and glycosuria in animals by injections of adrenal cortical extracts without operating upon the pancreas.[5,6] Furthermore, if diabetes is produced by taking out the pancreas, the disease can be alleviated—almost cured—by removing the anterior pituitary gland[7] or the adrenal cortex.[8,9] The role of these two organs thus has assumed great importance.

The next development, however, again pointed to the pancreas. It was found[10] that when one produces diabetes by the injection of anterior pituitary extracts, the ultimate damage is to the pancreas, and the islets of Langerhans undergo characteristic changes (first over-stimulation of the beta cells, later hydropic degeneration, degranulation, hyaline degeneration, and eventually fibrosis). The same is true to a lesser extent with the adrenal cortex so that despite the importance of the pituitary and the adrenal the pancreas must still be considered as a highly important organ in the pathogenesis of diabetes.

It was found in 1943 by Dunn, Sheehan, and McLetchie[11] that the injection of alloxan into animals caused destruction of the islands of Langerhans of the pancreas. Immediately the question arose, "Is it possible that alloxan has something to do with human diabetes?" People set to work at once to find out whether there was enough alloxan in the body to be implicated. Not enough was found, so that the idea was abandoned for the moment. A couple of years later it was discovered that alloxan when injected into animals causes a definite reduction in the content of glutathione in the blood.[12] With this clue Dr. Lazarow[13] of Cleveland was the first to prove that if one injected glutathione before giving alloxan, one could prevent the diabetogenic action of the alloxan compound. Dr. Lazarow and others have expanded this further to show that other sulfhydryl-containing compounds injected into animals before alloxan would prevent the action of alloxan in producing diabetes.

Just this past year, Griffiths[14] of Australia, putting together the facts that

alloxan is closely related to uric acid and that sulfhydryl compounds including glutathione protect against the diabetogenic action of alloxan, reasoned that if the glutathione content of the blood were lowered the way might be opened for uric acid to act in the same way as alloxan in producing diabetes. Accordingly he placed rabbits on a methionine-cystine-free diet which did result in a lowering of the blood glutathione. He then gave them uric acid intraperitoneally and succeeded in producing a transient but well-defined hyperglycemia and glycosuria lasting several days. The blood sugars ranged from 200 to 250 mg. per cent. The injection of uric acid produced the same type of blood sugar curve in the first few hours following the injection as did the administration of alloxan. Both substances give rise to a tri-phasic curve, an original hyperglycemia followed by a hypoglycemic phase, and then in a few hours a permanent—more or less permanent in the case of uric acid—hyperglycemic level. This common property of the two chemically related substances is suggestive. It is important that in Griffiths' experiments the animals in which the glutathione levels of the blood were not lowered by this previous diet did not show glycosuria or hyperglycemia.

The next step and, so far as I know, the last step, was taken by Dr. Conn and co-workers[15] of Ann Arbor during the past year. Dr. Conn gave a purified preparation of adrenocorticotropic hormone of the pituitary to normal human beings and produced definite glycosuria and hyperglycemia, accompanied by a fall of blood glutathione and a considerably increased excretion of uric acid in the urine. It thus appears that the activity of the "pituitary-adrenal axis" in producing diabetes may involve, at least in part, the same mechanisms that are involved in alloxan diabetes.

One must proceed from here on grounds of speculation only. It is possible that glutathione, being protective against alloxan, is protective also against uric acid; that if one lowers the glutathione content of the blood or tissues and then presents the organism with any diabetogenic agent—an agent which will put a strain on the islet mechanism—the islets being no longer protected by an adequate amount of glutathione will then succumb and the diabetic state will supervene.

Certainly uric acid has not been demonstrated to be the cause of human diabetes. However these recent findings do open certain cracks in the wall of ignorance which has confronted us.

Another recent development has been in connection with the matter of insulin resistance, or perhaps a better term would be anti-insulin substances. It has been known for a long time that in the anterior pituitary and the adrenal cortex there do exist diabetogenic substances which may also be anti-insulin in action. This is also true of the thyroid to a somewhat lesser degree. Recently facts have been accumulating which suggest that there may be an anti-insulin substance in the pancreas itself. This would indeed be a paradox, to have the organ which produces insulin also prove to contain an anti-insulin substance as well. It is not an unprecedented situation but it is striking if true.

What are the facts to suggest that possibly the pancreas may possess an anti-insulin factor? First, in totally depancreatized dogs, as found by Drag-

stedt[16] some years ago, the requirement for insulin is less than it is in partially depancreatized dogs on the same diet. Second, the pituitary diabetic dogs of Young,[17] (the investigator who originally produced permanent diabetes by pituitary injections), required less insulin after pancreatectomy than they did when they were diabetic merely from a pituitary point of view. It should not be forgotten that the pituitary injections they had received had damaged the islet cells and that they were in the last analysis pancreatic diabetic dogs too. But the fact was that when the pancreas was removed, they needed less insulin than when the pancreas was in.

Third, if the dog made diabetic with alloxan has his insulin requirement carefully determined and is then subjected to pancreatectomy, his requirement for insulin is less after total removal of the pancreas than it was in the alloxan diabetic state.[18] Fourth, recent developments in surgery have permitted the complete removal of the pancreas in man for cancer or sclerosis of the pancreas. The remarkable thing about these patients is that with no pancreas at all, none of them has required more than 40 units of insulin a day.[19] If one contrasts this with the insulin requirement of many spontaneously diabetic patients who need 60, 80 or 100 units a day, it becomes apparent at once that in these spontaneously diabetic patients, there must be something other than a pure insulin deficiency at work.

Finally, it has been known for some time that the intravenous injection of purified preparations of insulin—at least the preparations made in this country—is followed by a transient hyperglycemic phase before the hypoglycemia supervenes. This suggested the possibility that somehow in the preparation of insulin a substance antagonistic to it also was incorporated. The latest development in this field was the announcement from McGill University during the past year to the effect that if the supernatent fluid from the first isoelectric precipitate of insulin is subjected to certain further treatment and injected into rats, the liver glycogen of the rats is reduced to one-third the normal and the blood sugar is nearly doubled.[20] It was found that there was no adrenalin present in these extracts and there was no histamine. Extracts of other organs in the hands of these investigators had no such effect. This work has recently been confirmed by Sutherland and de Duve.[21] (However, they found some similar effect from cells of the gastrointestinal mucosa.) This phenomenon was ascribed by the Montreal workers to an alpha cell hormone. For years we have been wondering what the alpha cells were doing there. Nobody could prove that they did anything. The possibility existed, of course, that they had a hormonal function of some sort. Whether the insulin antagonizing action of these extracts is actually due to an alpha cell hormone it is too early to say with finality.

Another recent development has come from the use of isotopes in the study of glycogen and fat metabolism and the function of insulin. The studies I should like to tell you about have emanated largely from the laboratory of Dr. DeWitt Stetten.[22] Dr. Stetten fed normal rats a diet containing 15 Gm. of carbohydrate per day, and labeled this carbohydrate with deuterium—heavy water. By so doing he was able to analyze various parts of the animals and

determine how much glycogen there was in each part and whether that glycogen had come from the diet or from some other source. The astonishing thing about this investigation was that from this 15 Gm. of carbohydrate in the diet per day, the rats deposited only 0.44 Gm. of liver glycogen per day. This represents only 3 per cent of their dietary intake of carbohydrate and this amount of glycogen is sufficient to supply the animal with energy needs for only thirty minutes. This casts a new light on the relative importance of glycogen in the animal economy. Dr. Stetten also was able by means of this isotopic technic to find out how much of the dietary carbohydrate was converted to fat. He found that 2 Gm. of fat were deposited per day in contrast to the 0.44 Gm. of glycogen. Thus, these normal rats made roughly five times as much fat as they did glycogen from the dietary carbohydrate, and to do this it required ten times as much carbohydrate.

What happened in the diabetic rat? The diabetic rat, instead of manufacturing 2 Gm. of fat per day from this diet, manufactured only 0.1 Gm. from these dietary sources or only 5 per cent of the normal. Thus, the absence of insulin prevented the animal from laying down or synthesizing fat at anywhere near a normal rate. This is one of the newer concepts of the function of insulin. It has yet to be elaborated but again is a highly interesting lead, and likely to revise our concepts of what insulin does and of the relative importance of fat and carbohydrate in the diabetic organism.

One of the things which we have learned in the past few years is that we must give more insulin sooner in diabetic coma. Rather than too little and too late, we had better give too much too soon. One can make up for giving too much insulin—one cannot make up for giving too little because the patient may pass beyond the stage in which insulin will be of any avail. Generally speaking, there is a rough correlation between the height of the original blood sugar in acidosis and the amount of insulin required to bring the patient out of coma. It is highly important that anyone dealing with diabetic coma have access to a laboratory in which determinations of blood sugar and carbon dioxide combining power can be performed. Many things happen to patients during coma which are not reflected promptly enough by the urinalyses. Hence the importance of a laboratory that will do the more complicated procedures cannot be overemphasized.

I think that the original dose of insulin in diabetic coma should never be less than 100 units in an adult patient. Within the first three hours the patient should receive from two to three times the original dose. How much should be given afterwards depends on circumstances so that it is difficult to lay down any general rules. The point I should like to stress is that instead of beginning with 40 units or 60 units or 80, one should begin with 100 in most cases. One need not be afraid of hypoglycemia; it may occur, but it can be corrected.

The second development in the field of diabetic acidosis has been the increasing recognition of the importance of electrolytes other than sodium. Potassium, phosphorus, and magnesium have been found to be depleted in many patients with diabetic acidosis. Many patients have been lost in coma

because of failure to recognize that these elements of blood are almost as important as those we have been used to thinking of. In 1946 Holler[23] published his brilliant observation concerning a patient with diabetic acidosis who had been successfully treated at first but a few hours afterward took a turn for the worse. The respirations became labored, muscular weakness became extreme, and Holler had the wit to recognize that this was one of the manifestations of potassium deficiency. The patient was treated with potassium chloride and recovered. Since that time, a good many cases have been reported, some with chemically proved hypokaliemia, others with conjectured hypokaliemia. Martin and Wertman[24] published in 1947 statistics on a number of cases of coma in 46 per cent of which there was a low potassium which developed during treatment. The potassium was not low in the beginning but developed as treatment progressed; the lowest value they found was 1.9 milliequivalents per liter.

Thirty-six per cent of these patients also had a chemically determined magnesium deficiency. The symptoms of potassium lack are muscular weakness, and respiratory difficulty which is in essence a respiratory paresis or paralysis and is different from the Kussmaul type of breathing. It is an effortful respiration with the accessory muscles being used freely. Finally, changes in the electrocardiogram are observed consisting specifically of a lowering of the T waves in patients whose potassium is considerably below normal. There are, of course, apt to be other abnormalities in severe diabetic coma including depression of the ST segment and prolongation of the QT. These are not specific for low potassium, may occur as a result of coma itself, may of course represent coronary disease, and must be interpreted with some caution in respect to the problem of potassium. The lowering or inversion of the T waves, if one can exclude coronary disease, is highly suggestive in the presence of the other symptoms mentioned.

The decline in potassium is probably caused by several factors. One is the depletion of serum potassium as well as other electrolytes by the profuse diuresis which patients in acidosis customarily exhibit. If one gives intravenous glucose, one serves only to accentuate this diuresis, another reason in my opinion why intravenous glucose should not be used in the treatment of diabetic coma. Second, the administration of large amounts of fluids dilutes the electrolytes. Third, there is the specific effect of insulin. Insulin injected into any organism in sufficient amounts causes lowering of the serum potassium; the large amounts which are employed in diabetic coma must necessarily have a considerable effect in this direction.

The drop in potassium does not occur early. The potassium level on the admission of the patient is usually normal or high, and it declines only some hours after treatment is begun. Should potassium be given routinely in the treatment of diabetic coma? I think not. Not more than one-half of these patients show any potassium depletion, and only a fraction of them have values low enough to be of serious significance. One has to watch for the development of suggestive symptoms, and measure potassium levels if possible. One must be exceedingly careful, however, about giving any potassium to

patients showing impaired renal function. The dose of potassium which can be given has been stated by some to be 0.6 Gm. by mouth every half hour for 6 doses, or intravenously 1.5 Gm. of potassium chloride as a 2 per cent solution. This is potentially a hazardous procedure since large amounts of potassium given to a normal person may produce damage. As a matter of fact, 2 Gm. by mouth have been shown to produce definite changes in the electrocardiogram.

Like potassium, phosphorus has been shown to decline during the treatment of diabetic coma. Whether it is as important as potassium is at this moment open to question. But certainly the phosphorus levels do decline and for much the same reasons as do the potassium levels. Franks, Berris, Kaplan, and Myers[25] demonstrated that the administration of 1.319 to 2.638 Gm. of phosphorus as sodium phosphate to patients in diabetic acidosis led to the retention of 85 to 90 per cent of the amount injected, and even this was not sufficient fully to correct the rather high degree of phosphorus depletion.

In 1900, diabetic coma caused 64 per cent of the deaths from diabetes; cardiovascular renal disease caused 18 per cent. Today diabetic coma causes death in only 3 per cent of those who die with diabetes and cardiovascular renal disease is involved in 67 per cent as the prime cause of death. The percentages are thus almost completely reversed.

In Joslin's [26] clinical experience from 1944 to 1946 there were 651 deaths with diabetes. Sixty-seven per cent of these were due to arteriosclerosis; 44.5 per cent of the total deaths were caused by arteriosclerotic lesions of the heart.

From the autopsy reports of Warren[27] we have a similar picture. Among 484 autopsies on patients dying with diabetes 30 per cent of the deaths were caused by arteriosclerosis, and of this group 57 per cent were due to cardiac causes. In 61 autopsies on patients with diabetes of fifteen years' duration or over—this is an important point—57 per cent died of arteriosclerotic lesions.

In 1947 Dolger[28] published a discouraging report. He found that of 200 regularly examined patients with diabetes up to 25 years' duration, none had escaped retinal hemorrhage regardless of age of onset, severity of the disease or method of treatment. Fifty per cent had hypertension and albuminuria at the time the first retinal hemorrhage was discovered, and in 14 per cent the patients lost their vision completely.

Equally distressing were the figures of White and Waskow[29] which appeared a little later. They had studied 200 diabetics with the onset of disease in childhood who had survived for twenty years. The incidence of vascular lesions in this group was 92 per cent. Cerebral vascular accidents had occurred in 2.5 per cent, coronary insufficiency in 8 per cent, albuminuria in 30 per cent, hypertension in 30 per cent, nephritis in 50 per cent, calcified arteries by x-ray in 75 per cent, retinal hemorrhages in 80 per cent, and sclerosis of the retinal vessels in 85 per cent. The frequency of these complications in the younger diabetics is of increasing concern to all physicians.

What causes these lesions of the arteries, the veins and the capillaries? Is it hyperglycemia, is it hyperlipemia, or is there possibly some third factor, a factor perhaps which gives rise at the same time to the tendency to have

diabetes on the one hand and the tendency of the blood vessels to be affected on the other? The answers to these questions are not at hand. Experimentally hyperglycemia has never been proved to produce vascular lesions. But one should bear in mind that so far as this point is concerned, there are probably not more than a half dozen diabetic animals in the recorded literature which have been carefully observed for long enough to determine this matter conclusively. The administration of cholesterol is well known to cause atherosclerosis in animals but has never been shown to cause retinal hemorrhages. Certainly retinal hemorrhages are part and parcel of the general vascular disease and until retinal hemorrhages as well as atherosclerosis of the larger vessels can be produced by experimental means one cannot be said to have reproduced the total vascular picture of diabetes.

In human beings the data are not conclusive. The statement is often made that degenerative complications occur regardless of the degree of control of glycosuria. That statement is, I think, difficult to support. The vast majority of juvenile diabetics—but not quite all—have not been and cannot be well controlled with our present methods. Thus the allegation that diabetics regardless of the degree of control have such complications seems to me to be rather meaningless. I think most younger diabetic patients have not been rigorously controlled over a period of many years. There is one group which is an exception, the patients of Boyd, Jackson and Allen[30] at the University of Iowa. These workers believe thoroughly in keeping the urine sugar free at all times if possible. They have taken full advantage of their unusual opportunities to follow their young diabetic patients carefully for long periods. They recently reported a study of 69 patients whose disease had begun in childhood and who returned for follow-up examinations after periods of five to ten years. Of the 69, 17 were of sub-standard height at the first examination and 13 of them resumed normal rate of growth under the strict regimen of a sugar-free urine and a normal blood sugar. There were 12 dwarfs at the terminal examination, none of them having well controlled diabetes. There were 11 with retarded maturation, none of them having been well controlled children. There were 6 examples of enlargement of the liver all of which subsided with the strict regimen Dr. Boyd employs. There were 6 examples of retinal hemorrhage all of them being related to periods of poor control. There were 6 cases with clinically demonstrable cataracts again all occurring in poorly controlled cases. About 20 patients had minor lenticular opacities none of them occurring in well controlled patients.

Thus, while the satisfactory control of the young diabetic patient is a difficult feat and is often impossible, it can be done under exceptional circumstances and when it is the results, with respect to the prevention of degenerative complications, are worth it.

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