DIABETIC ACIDOSIS *

By ROBERT F. LOEB
Associate Professor of Medicine of the College of Physicians and Surgeons of the University of Columbia.

We are dealing with a subject which forms one of the most fascinating chapters in the entire field of medicine: The history of the logical and rational development of our knowledge in relation to the disease mechanism and to the treatment of its various phases and complications, which constitutes a truly gratifying consummation of scientific endeavor. The progress which has been made in conquering the problems of this disease alone amply justifies the time, energy and financial expenditure which are being constantly directed into the channels of physiological and clinical investigation. There are other reasons why the subject of diabetes cannot be over-emphasized. First, perhaps, because of its great frequency, for as Joslin points out, in the United States alone, there are more than one million people who have or will have this disease. Finally, it is generally conceded that with proper medical attention the diabetic patient should live as long a life and be as useful a citizen as any normal individual.

In spite of this, perhaps, enthusiastic view of the situation, the recent vital statistics in New York City show an amazing and, according to some, an alarming increase in the morbidity and mortality rates for diabetes in the past decade. However, there are a number of factors which may make this an apparent rather than a real change. For example, the increase in the Jewish population has been great in the last three decades and the high incidence of diabetes in individuals of this race is well recognized. Furthermore, since the advent of insulin, there has been a much keener interest in diabetes, and physicians who formerly did not trouble to test the urine of every patient presenting himself for medical attention now appreciate the importance of this simple routine procedure

* Lecture delivered before the Puerto Rico Medical Association, San Juan, P. R., Dec. 9, 1933.

Received for publication December 9, 1933.

and apply it. In this way, innumerable cases of diabetes have been discovered among essentially symptom-free diabetics. The apparent increased incidence of diabetes in our local community has also been brought about by the fact that the determination of the blood sugar concentration is now widely applied. This test is so simple that many physicians are now able to carry it out in their own offices. They are thus enabled to detect the presence of the disease even in the absence of glycosuria. Most of the patients in whom the blood sugar is elevated without glycosuria, namely those with a high renal threshold for glucose, appear in the arteriosclerotic decades. Interestingly enough, the great increase in diabetes has been detected in this age group. Thus we see that the apparent increase in diabetes in recent years is explained in part by the increased accuracy of diagnosis. Now, just a few words as to an explanation for the alleged increase in the diabetic death rate in New York.

When sugar is found in the urine of seriously ill patients without other obvious cause for the disease picture, there is a tendency to attribute death to diabetes. That this is not an error limited to practice in the home is shown by the fact that in about 15 per cent of patients in whom death was attributed to diabetes in the Presbyterian Hospital in New York, where diagnostic aids are available, the pathologists were able to show that the diabetes was incidental to another and fatal disease. It is only fair to state that the number of deaths wrongly attributed to diabetes must be still greater in the community at large.

This emphasis upon a problem concerning vital statistics in a local community many miles from Puerto Rico has not been made merely to point out an increase in the prevalence of the disease, but in order to show how the routine examination of the urine and frequent examination of the blood have led to the discovery of an enormous number of diabetic patients whose disease some years ago escaped recognition.

Before coming to the subject matter of the title of this paper, we will review briefly the present day concepts of the physiological disturbances present in diabetes mellitus. It will be agreed that by definition we may state that diabetes results from an inadequate supply of the pancreatic hormone named insulin. Sir Edward Sharpy-Schäfer anticipated its

discovery and named it "Insulin", some years before this highly active protein was isolated chemically and used therapeutically by Banting and Best in 1922. Until very recently it has been thought that diabetes resulted from decreased activity of the pancreas, perhaps due to fibrosis of the islet tissue of the pancreas, as this pathological change is present at autopsy in many cases, although it is also found in the absence of diabetes. The histological changes seen in the pancreas are now considered secondary to the disease in a certain number of cases. In the past few years more stress has been laid upon another possibility, namely that the pancreas may secrete its normal amount of insulin or perhaps even more, but that there is some antagonist present which in some way inhibits its activity. Cori, for example, has shown that adrenalin antagonizes the action of insulin in muscles, a fact that is often taken advantage of in the emergency treatment of insulin shock. In hyperthyroidism diabetes is frequently encountered, in a severe form, and is generally ameliorated by thyroidectomy. Many years ago Harvey Cushing pointed out the common association of diabetes and acromegaly. By far the most convincing evidence produced so far in support of the idea that, at least in many cases, the apparent pancreatic deficiency in diabetes is in reality due to an antagonist, is found in the work of that brilliant South American investigator, Houssay. Houssay, as you probably all know, has shown recently that diabetes does not develop even in the depancreatized animal if the anterior lobe of the pituitary gland has first been removed. This important discovery has already received ample confirmation. Just what proportion of the cases of diabetes result from primary pancreatic disease and how many are due to an antagonism to insulin normally elaborated is a problem which must be left for the future to decide.

The known actions of insulin upon carbohydrate metabolism may be summarized as follows: First, it increases glycogen storage in the liver of the diabetic animal; second, it transports glucose to the other tissues and increases their stores of glycogen; third, it lowers the blood sugar level, and finally it increases the combustion of carbohydrate in the cells, particularly in the muscles. These actions of insulin are naturally interrelated. The lack of an adequate amount of

insulin leads to a failure of these physiological activities and the consequent development of diabetes. Now, as is generally known, if the disturbance is slight, mild diabetes results, but if it is more marked, a secondary group of physiological disorders may arise and seriously jeopardize the patient's life. These disorders result primarily from the faulty metabolism of fat.

"Fat burns in the flame of the carbohydrates." This adage is just as significant today as when it was first expressed. It implies that the failure of carbohydrate oxidation resulting from an inadequate supply of insulin leads to incomplete combustion of fat. As you know, under these circumstances fat yields aceto-acetic acid, B-oxybutyric acid and acetone, the so-called ketone bodies, instead of being completely burned to carbon dioxide and water. Dr. Palmer and Dr. Ladd showed, in 1920, that as long as the diabetic is able to burn one gram of carbohydrate for every 3 to 4 grams of fat, no ketone bodies are formed. When, however, less than one gram of carbohydrate is oxidized for this amount of fat, the flame of the carbohydrates is not sufficient for the complete combustion of fat, and ketosis results. Two of the ketone bodies, B-oxybutyric acid and diacetic acid, act as foreign acids in the body and are responsible for the disorder which we have to discuss this evening.

At the Presbyterian Hospital in New York, Dr. Atchley, Dr. Richards and the author have been much interested in the study of the chain of events which occur in the development of diabetic acidosis and in the recovery from this condition. When patients enter the hospital for treatment, the acidosis is usually so far advanced that there is little if any opportunity to follow the steps which lead up to it. Furthermore, the need for therapy in these patients is so urgent that it is impossible to institute the conditions necessary for adequate investigation. For these reasons diabetic patients were employed for investigation, the nature and purpose of the experiment first having been explained to them. The details of this study are worth relating because it seems that it is only on the basis of such tedious experimentation that we are justified in drawing any conclusions as to the nature and extent of the physiological disturbances present in this complication of diabetes. These patients were admitted to the

metabolism service and were given adequate diets and enough insulin to keep them sugar-free. After a preliminary control period of twelve to sixteen days, insulin therapy was abruptly withdrawn, the diabetes was allowed to progress in intensity, severe acidosis developing in one of the subjects. Following this, insulin therapy was again instituted and recovery was studied. Samples of the foods eaten by these patients, as well as all the urine and stools, were subjected to chemical analysis, the mineral constituents, nitrogen, ketone bodies and many other things being determined.

The more important changes which take place following the withdrawal of insulin are related in the order of their appearance. Many of them are well-known, but will be mentioned for the sake of completeness. We can divide the physiological disturbances resulting from acute diabetes, *i. e.* diabetes resulting from insulin withdrawal, into two groups. The first of these results from the failure of the carbohydrate metabolism. The second, from the development of acidosis. When the carbohydrate metabolism fails, the blood sugar naturally rises and after reaching a certain level sugar begins to be excreted in the urine. In our experiments, we found that if the sugar excretion does not exceed about 20 grams a day, no other changes of immediate importance occur. When, however, the diabetes is sufficiently severe to cause the excretion of about 120 grams of glucose a day, upon the withdrawal of insulin, other abnormalities appear. These are as follows: (1) a great increase in water excretion which, of course, is well-known; (2) a marked loss of the salts of potassium and sodium from the tissues and interstitial fluids; (3) slight loss of water and salts from the blood, and (4) a increase in nitrogen elimination signifying tissue destruction. Of these the loss of water and salts is of particular importance because, as will be seen later, this disturbance in the body starts the changes against which the treatment of diabetic acidosis must be primarily directed. The clinical picture of the neglected diabetic is characterized by emaciation and dehydration, and finds its explanation on the basis of the physiological disturbances enumerated.

We have thus far considered the results of the failure of carbohydrate metabolism alone and turn now to a discussion of acidosis and its effect upon the patient. Van Slyke has

defined "clinical" acidosis simply by stating that it is present when there is a decrease in the concentration of bicarbonate in the blood. The normal bicarbonate content of the blood is 55 to 60 volumes per cent and in severe acidosis it frequently drops to less than 10 volumes per cent. As you know, the body struggles to keep its slightly alkaline reaction at a constant level. This is essential, because even minute changes in this reaction in acid or alkaline directions result in death. One of the chief protective agencies towards the maintenance of a constant reaction or pH of the blood is its so-called bicarbonate buffer system. Translated into other terms, this merely means that bicarbonate is a chemical substance which can be replaced by various acids without changing the reaction of the solution as long as it remains in equilibrium with the proper amount of carbon dioxide gas. The lungs tend to remove excesses of carbon dioxide gas liberated when an acid introduced into the blood reacts with the bicarbonate, and as long as they succeed, the reaction of the blood remains constant and the acidosis is said to be "compensated".

When acetoacetic and B-oxybutyric acids are formed in the body of the diabetic, they must be neutralized. The bicarbonate of the blood and tissue fluids serves this purpose with a resulting decrease in the bicarbonate content of the blood and the development of clinical acidosis. When larger amounts of the ketone acids are formed, not only is the bicarbonate content of the blood reduced to almost negligible amounts, but the carbon dioxide gas is not adequately pumped out by the lungs so that an actual change in the blood reaction takes place towards the acid side and this "uncompensated" acidosis proves fatal if it is not quickly remedied.

Now, the body rids itself of these neutralized ketone acids by excreting them through the kidneys, chiefly as sodium and potassium salts. This is precisely what we found in our studies at the Presbyterian Hospital. The loss of salt from the body, which has been already referred to as a result of uncomplicated severe glycosuria, is greatly augmented when diabetic acidosis develops, sodium being given up by the blood plasma and interstitial fluids and potassium by the cells of the body. This loss of sodium and potassium is invariably associated with a great outpouring of water from the body, so that the dehydration which begins from severe

glycosuria alone is greatly increased during acidosis. The loss of sodium salts from the body is far greater than is suggested by blood analyses, because the loss of water which accompanies the excretion of salts tends to keep this concentration constant.

This state of dehydration which develops in the course of acidosis is not merely a distressing symptom to the patient, but is, in our opinion, of much more profound significance. As the tissue fluid stores become depleted, fluid is also lost from the blood plasma and when this occurs, the circulating blood volume is reduced, the result of which is what Dr. Atchley of our clinic has so appropriately termed "medical shock". The clinical picture of medical shock is characterized by weakness, collapse, falling blood pressure, rapid, thready pulse, subnormal temperature, oliguria and finally anuria. The diabetic patient who dies from acidosis, dies in the state of "medical shock". Modern text books of medicine still confuse cardiae failure with this state of shock, which is dependent upon a decreased circulating blood volume. This is a serious mistake because the principle of treatment of shock and cardiac failure are almost diametrically opposed and failure to recognize the existing conditions results in misdirected and harmful therapy.

There is one more point which I think should be emphasized in the consideration of the pathological physiology of diabetic acidosis. I have already mentioned the fact that the ketone acids are responsible for the state of acidosis and that this, if "uncompensated", will quickly result in death. It is highly probable that these substances are also "toxic" to the tissues of the nervous system and to the blood capillaries. When these ketone bodies accumulate rapidly in large amounts in the body, it seems likely that they may produce damage which cannot be repaired.

There are many other fascinating problems involved in the pathological physiology of diabetic acidosis, but from the clinical standpoint we can summarize the important changes as follows: When severe glycosuria develops, large amounts of salt and water are lost from the body. When ketone acids are produced in significant quantities, they replace bicarbonate of the blood, causing an acidosis. If this condition is progressive, it causes an actual change in the reaction of

the blood, which if at all marked results in death. The ketone bodies are excreted from the body through the kidneys and to a considerable extent in combination with sodium and potassium. When these salts are lost, water excretion is further augmented. This loss of water and salts results in further dehydration. The state of dehydration finally causes a decrease in the circulating blood volume. The end result of dehydration and decreasing blood volume is the state of shock which is probably the most important contributing factor to a fatal outcome in diabetic acidosis. Finally, we believe that the massive accumulation of the ketone bodies may actually poison the various tissues of the body.

Having discussed at some length the mechanisms involved in the production of acidosis, let us turn to the clinical considerations of this complication of diabetes. Before the advent of insulin, more than 60 per cent of diabetic deaths resulted from this disturbance. At the present time less than 10 per cent succumb to acidosis. While this represents a marked improvement in the management of this phase of diabetes, it is yet far from the end which should be attained, because diabetic acidosis, since the addition of insulin to our therapeutic armamentarium, has become a preventable complication. In our experience, severe acidosis usually develops for one of the following reasons: First, the patient oversteps the limits of his diet, frequently enjoying an orgy of eating; his carbohydrate tolerance falls and ketone bodies are rapidly formed in large amounts. Second, an acute infection develops and for reasons unknown, this causes an abrupt decrease in the ability of the body to utilize carbohydrate. Consequently, fat is not completely burned and ketosis results. Third, because of a failing appetite or because of some other illness, an insulin-treated patient reduces his insulin dosage when he lowers his food intake. This mistake frequently leads to the development of acidosis. In this connection, it is important to emphasize the fact that it is essential for a patient to continue his usual insulin dosage when diarrhea, obvious infection or loss of appetite causes him to reduce his diet, even though insulin shock may result. If patients would only recognize this rule and if they would promptly consult their physicians when such complications arise, diabetic acidosis could be prevented in most instances.

The clinical picture of diabetic acidosis is so well known that only a few particular features need be considered. One of these is the rapidity with which ketosis may develop, and which can be well demonstrated by the following case:

F. C., a boy of thirteen, who had been under treatment for severe diabetes at the Presbyterian Hospital for some years, came to the clinic one morning for routine observation. While waiting to see his physician, he became drowsy and was admitted to the ward. He was unable to void and was catheterized. His urine contained a considerable amount of sugar, but there was no evidence of ketone bodies. He became unconscious and the question arose as to whether he was suffering from acidosis or from too much insulin. Blood was taken for sugar and Co_2 determinations, and 20 grams of glucose were given intravenously, as it was felt that it would help if he were suffering from hypoglycaemia and would do no harm if he had acidosis. The reports from the laboratory showed the presence of an abnormally low blood sugar and a normal Co_2 content. Because of his slow response to glucose, he received several additional injections. He improved, but in the course of twelve hours his urine became loaded with ketone bodies, he developed an acetone breath and then had to be treated for impending acidosis.

I think this case shows adequately that the severe diabetic, particularly when slightly overweight, can, in the course of a few hours, shift from the hypoglycaemic state to a marked ketosis. In other words, the severe diabetic "skates on thin ice."

There is one symptom of diabetic acidosis which may prove almost as distressing to the physician as to the patient if he is not aware of the fact that it is frequently encountered in this condition. That symptom is severe epigastric pain associated with rigidity of the abdomen, often accompanied by nausea and vomiting. Failure to recognize this fact may lead to unnecessary and dangerous surgical intervention, particularly as there is usually a leucocytosis in diabetic acidosis, sometimes reaching 30,000 per cubic millimeter. An accurate history of the development of the symptoms is a great aid in differentiating this rather typical picture of diabetic acidosis from a surgical condition.

Hyperpnea or Kussmaul breathing is present as a rule in severe acidosis, but we have seen patients who did not present this symptom, even though the CO_2 combining power of the blood was reduced to 12 volumes per cent. In view of this fact, the absence of Kussmaul breathing does not pre-

clude the possibility of severe acidosis, and when any doubt exists, the CO_2 of the blood should be determined. On the other hand, the presence of air hunger is almost invariably associated with severe acidosis in diabetes.

The blood sugar concentration is extremely variable in acidosis. The average value in these patients is about 4.0 grams per liter, though it may be as low as 2.0 or as high as 10.0 grams per liter. The height of the blood sugar in no way reflects the gravity of the situation and is only of value clinically as a guide to therapy.

There is one deviation from the usual clinical picture of diabetic acidosis which should be discussed. When acidosis has been allowed to proceed to the state of collapse or shock, the kidneys are occasionally unable to excrete ketone bodies, in spite of high concentrations of these substances in the blood and tissues. Thus it is clear that when any question of acidosis arises we must fall back upon the CO_2 determination of the blood for accurate diagnosis. Fortunately, such cases are relatively uncommon and urine examination usually reveals the presence of large amounts of ketone bodies.

It has already been intimated that diabetic acidosis usually results from faulty treatment of the patient by himself. If patients can and will be properly impressed with the dangers of acidosis and the common errors which lead to its development, this complication should practically disappear. When, however, acidosis does develop, therapy should be instituted immediately. The longer this disturbance is allowed to progress, the more difficult is the task of treatment, and the fatal cases are practically always encountered among those patients who have been permitted to drift into complete coma. There are few medical conditions in which prompt action yields more gratifying results and in which delay is rewarded by a more disappointing termination. Procrastination means death.

We shall confine our remarks on the treatment of acidosis to severe cases, viz. those in which the CO_2 of the blood is below 25 volumes per cent. Mild cases usually respond well to the simpler forms of treatment such as rest, liberal fluid ingestion, regulation of the diet and insulin dosage.

The nature of the physiological disturbances present in acidosis has already been discussed, and I should now like to describe in detail for you the procedures we have found successful in the treatment of severe acidosis at the Presbyterian

Hospital in New York. Immediately after admission, the patient is placed between blankets and kept warm with hot water bottles. Fifty units of insulin are given intramuscularly and a specimen of urine is obtained for the qualitative determination of sugar and acetone. After a rapid physical examination, in which the measurement of the blood pressure is perhaps most important, blood is taken from an arm vein for the determination of sugar and carbon dioxide content and for blood grouping. The needle is left in the vein and an infusion of 1500 c. c. of 0.8 per cent salt solution is immediately started to combat dehydration and salt loss and to "wash out" ketone bodies. If the CO_2 content of the blood is reported as less than 25 volumes per cent, 500 c. c. of 4 per cent sodium bicarbonate solution are also infused. This is poured into the saline solution. The preparation of the bicarbonate solution is a simple matter. Five hundred c. c. of distilled water are boiled, the flame is removed and 20 grams of chemically pure, but not necessarily sterilized, bicarbonate are added. The only precaution necessary is that this solution which is quite strongly alkaline, should not be allowed to flow into tissues around the vein. Two liters of fluid are thus given intravenously in the course of one hour. If the patient has not vomited recently, he is given 100 c. c. of water and 100 c. c. of orange juice alternately every half hour. If vomiting has occurred within two hours of admission, no fluid is given by mouth for two or three hours after admission. At the end of the first busy hour, ten more units of insulin are administered intramuscularly, and this is repeated every hour until the patient is acetone- and sugar-free, as determined from the urine, each specimen voided being tested for these substances. Larger doses of insulin have no more beneficial effect. The blood pressure and pulse are recorded every hour. Four hours after admission a second infusion of saline is given, this time 1000 c. c. being injected. If the urine at this time shows little sugar but large amounts of acetone, 500 c. c. of 10 per cent glucose are added to the saline infusion in order to furnish adequate amounts of carbohydrate to burn the ketone bodies and to avoid possible insulin shock. If the blood pressure tends to fall below 100 mm. of Hg. after this, it suggests that a serious state of collapse exists and the transfusion of 500 to 700 c. c. of blood is resorted to and is occasionally repeated in 12 to 18 hours. This measure,

however, is rarely necessary. After the initial infusion has been completed the patient receives a cleansing enema and if vomiting persists, the patient is given a gastric lavage of 4 liters of water containing about 1 tablespoonful of sodium bicarbonate. When vomiting is not a serious problem, only two infusions are necessary in the treatment, as the patient will usually take between 3 and 4 liters of fluid by mouth in the first 24 hours. If, for any reason, the patient is unable to retain water and orange juice according to schedule, a 1000 c. c. infusion of 5 per cent glucose in saline may be given every 3 to 4 hours.

Most patients recover from their acidosis and become sugar and acetone free with this type of treatment within eighteen hours. The patient is then treated as a convalescent from any serious illness, and his diet is arranged accordingly for the next 24 hours. He is given toast, milk, eggs, custards, baked potato, rice, fruit juices and similar foods according to his tastes, but fat is avoided. He is given 15 to 20 units of insulin thirty minutes before each meal and each urine specimen is tested for glucose and acetone. If sugar appears, additional injections of 5 to 10 units of insulin are added. On the following day, the patient is given his maintenance diet and his insulin dosage is gradually readjusted.

When acidosis persists in spite of this therapeutic attack, one should become suspicious of complicating factors such as infections, pyogenic or respiratory, or hyperthyroidism. Infections should be treated during the acidosis if it does not yield to the measures outlined. If hyperthyroidism is an obvious complication, the administration of iodine should be started. Insulin refractory diabetes certainly exists, but fortunately this condition is so rare that it need not be considered.

There is one complication of prolonged acidosis which should be mentioned. Some patients may become sugar- and acetone-free within eighteen hours, but the state of "medical shock" or collapse with its attending low blood pressure tends to recur. It is in these cases that transfusion is of greatest value, but even this at times fails and the patient may die. It seems probable that the blood capillaries and tissues of the nervous system are poisoned by ketone bodies in these patients to a point where the damage is beyond repair.

You may have noted that nothing has been said about the use of codein, morphine, camphor, caffein, digitalis or brandy. These drugs are no longer employed by us in the routine treatment of diabetic acidosis, as it is our opinion that the picture of collapse in this disease state does not result from cardiac insufficiency. We believe that it is primarily due, as I have intimated, to the loss of water and salts from the body and that treatment should be directed toward the replacement of these substances. The elimination of ketone bodies should be brought about by increasing renal secretion and by the furtherance of oxidation through the action of insulin. The existing acidosis should be remedied by the administration of sodium bicarbonate and sodium chloride.

The foregoing is a fragmentary outline of the nature of the disorders which lead to the development of severe diabetic acidosis, and the essentially rationalistic therapy thereof, which is based upon our understanding of the physiological disturbances present in this condition.