Clinical Features of Diabetic Acidosis and Coma

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Acidosis is a reduction of alkali reserve of the blood, an acidemia due to an excess accumulation of acid metabolites. It is more the natural result of uncontrolled severe diabetes than it is a complication of this disease. As Guest[1] has emphasized, its development "is always initiated by insulin insufficiency regardless of the mechanism responsible for an increased need."

PATHOLOGIC PHYSIOLOGY

The associated events which lead to this condition are in part concurrent, but are in a constant state of change. To simplify this extremely complex chain of events into terms more readily applicable at the clinical level, we may speak of them as occurring in the following phases:

(1) Hyperglycemia occurs, producing glycosuria, which, when extreme, causes severe polyuria and dehydration.

(2) Glycogen depletion occurs, which is extreme in the liver, very slight in the skeletal muscle, and negligible or absent in the heart.

(3) Muscle breakdown occurs, resulting in increased excretion of urinary nitrogen and aggravating the already high phosphorus loss.

(4) Excess quantities of ketone bodies are formed. These metabolites are chiefly from fat and formed almost entirely in the liver, but perhaps somewhat in adipose tissue. This is a normal process which becomes abnormal when the rate of production increases excessively. Tremendous quantities of urinary ketones sometimes exceeding 100 gm. per day are recorded.[3] Three substances are especially involved. These are usually listed as *B*-hydroxybutyric acid, aceto-acetic acid and acetone, known collectively as ketone bodies. Aceto-acetic (diacetic) acid is particularly toxic. The body is incapable of oxidizing these substances above a certain limit. Beyond this limit they accumulate in the blood and tissues.

(5) Electrolytes, especially sodium and alkali, are lost in the urine with the excretion of acid metabolites.

(6) The alkali reserve of the blood falls, as reflected by the diminishing power of the blood to combine with carbon dioxide. Finally the *p*H of the blood decreases. The level of the total base commonly falls from a normal of 155 mEq/L to between 135 and 145.

(7) The level of blood fats rises; neutral fat may be extremely high and lipemia may be easily seen grossly. The blood cholesterol level is often elevated sometimes to 800 or 900 mg. per 100 cc. and occasionally to twice that level. High total blood fat may be associated with low cholesterol levels in the presence of infection. Lipoproteins are increased in the blood and the Tiselius protein pattern shows a high peak of beta and gamma globulins. In my experience, such changes as those in blood protein and fat have no clinical importance either in the prognosis or treatment of ketosis.

The exact role played by each of many factors in the production of the clinical symptoms and signs of acidosis has not been determined, but the consensus seems to be that among the most important are: 1) the direct toxic effect of ketone bodies upon the cells; and 2) dehydration. Other causes are loss of electrolytes, with loss of alkali reserves and the diminished rate of oxygen utilization by the brain. Hyperglycemia in itself appears to be relatively unimportant.

TERMS

The term "ketosis" is employed when ketone bodies have risen in urine and/or blood to abnormal levels, regardless of changes in alkali reserve. The term

From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

Presented at the Postgraduate Course in Diabetes and Basic Metabolic Problems given by the American Diabetes Association at Toronto, Canada, January 19-21, 1953.

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"acidosis" should be reserved for the state reached when ketosis has produced a fall in carbon dioxide combining power. The term "coma" properly means unconsciousness. There is little correlation between the degree of stupor and chemical findings such as blood sugar and carbon dioxide. One patient may be alert and even excited with a carbon dioxide combining power of 9, and another may be in deep stupor with a level of over 20 volumes. However, these examples are extreme. Generally speaking, severe symptoms are not present when the carbon dioxide combining power is 30 or above, but when below 15, severe symptoms are likely to exist. The validity of using the word "coma" in designating a state in which no stupor exists is controversial. Some clinicians object to it strenously. Others feel it is desirable to speak of coma in any case in which the carbon dioxide combining power is 25 or below and still others specify 20 or below. Root[13] feels that he is fully justified in using the term in cases with the lower carbon dioxide levels mentioned because it is an advantage in grouping cases for study, and it serves to call attention to the serious nature of the impending condition, though drowsiness does not exist. In addition he points out that in pre-insulin days patients in diabetic acidosis with a level of carbon dioxide below 20 almost never recovered.

There is a much closer parallelism between the concentration of ketone bodies in the blood and the degree of coma[2] although even this correlation is sometimes extremely poor. Patients have been reported mentally alert with a total blood ketone level of 123 mg. per 100 cc. as acetone and another unconscious with a level of 18.[4] The patient, however, usually becomes drowsy when the total ketone level reaches more than 60 mg. per 100 cc. and unconscious when it exceeds 100.

In considering the importance of various factors, Fisher[4] has called attention to the fact that experimentally ketone bodies cause death only when given in hypertonic solution. On the other hand Kety[14] has demonstrated that there is a striking fall in the rate of oxygen consumption by the brain in diabetic acidosis and when it falls from a normal 3.5 cc. per 100 gm. per minute to 2.1 cc., unconsciousness invariably results.

FREQUENCY

The frequency of diabetic ketosis is not known but it is certainly extremely common. Ketonuria may be detected in most diabetic patients at one time or another if they are closely followed and this is especially true in children. It is only when there is a serious acute complication that it is likely to be accompanied by symptoms. Before insulin was available for treatment, diabetic coma accounted for more than 40 per cent of deaths of all diabetic patients, but it now accounts for less than 2 per cent.

MORTALITY

The mortality rate of coma itself has been greatly reduced, but in many places it is still high. For patients in actual coma reduction of the rate to 10 per cent has probably been attained by few; apparently much higher mortality rates, from 25 to 40 per cent, still exist. A great deal can be accomplished by intensive effort and well-organized teamwork. For example, Harwood in discussing Howard's paper[5] at the 1950 American Diabetes Association meeting, stated that the mortality rate for diabetic coma had been 10 to 25 per cent at the Massachusetts General Hospital for years. Late in 1944, an effort was made to try to match the mortality rate of less than 5 per cent achieved by Joslin's group. Since that time he reported only one death in 70 cases and that was from uremia in the case of a 75 year old woman, four days after acidosis had been controlled.

ONSET

The rate at which symptoms arise may be rapid or very slow. The onset, especially in a child, may come in a few hours, no symptoms being recognized until vomiting and stupor suddenly appear and the situation is found to be critical. At the other extreme, an individual may struggle to carry on his work in spite of weakness, weight loss and severe polyuria for a year, presenting no change in symptoms over a period of weeks, and then be found to have acidosis with a carbon dioxide combining power below 20 volumes per 100 cc.

PRECIPITATING FACTORS

The factors precipitating acidosis vary greatly, but the variations are similar in the experience of physicians who see many diabetic patients. Severe symptoms may appear to be precipitated by pregnancy; a surgical operation; hyperthyroidism; or many types of stress or injury.

Infections of varied types may be responsible. Among 50 consecutive cases diagnosed as acidosis requiring hospital care, we found the common cold; bronchitis; broncho-pneumonia; otitis media; sore throat; thrush; periapical dental abscess; carbuncle; boil; cellulitis; paronychia; cholecystitis; and meningitis.

Unfortunately, there are still many patients entering our hospitals with diabetic coma with unrecognized and

untreated diabetes. It is equally tragic to find that a large number face this serious crisis because of omission of insulin treatment. This is a common error: the patient having omitted his meals because of illness concludes that he should omit his insulin not realizing that his need for it is greater than ever.

PREVENTION

The treatment of diabetic acidosis begins with prevention and this obviously entails detection and education; it also necessitates continued supervision. With regard to detection, I recommend the routine use of the blood sugar test. If blood sugar tests were done routinely by internists in all new cases, diabetes now frequently overlooked would be recognized.

By the use of routine blood sugar tests at the Cleveland Clinic, diabetes is found in 4.0 per cent of our patients. Only 2.4 per cent of the same group would be recognized to have the disease if history, symptoms and urinalysis alone were depended upon for the diagnosis.[11] We have found that routine blood sugar tests on all surgical patients have virtually eliminated acidosis postoperatively.

It is unnecessary to mention here that education of the patient is paramount: He should always continue his urine tests when an intercurrent illness supervenes, should never discontinue the use of insulin when glycosuria is present, and should promptly report loss of control of glycosuria, the appearance of ketonuria, or the occurrence of infection.

SYMPTOMATOLOGY

The symptoms of acidosis may be superimposed upon cardinal symptoms of diabetes or may appear suddenly. They may be extremely mild or exceedingly severe. With a steadily falling alkali reserve common symptoms are: Increased weakness, lassitude, and unusual need for rest; increased dyspnea on exertion; loss of appetite merging with actual nausea and vomiting; air hunger; headache; generalized aches and pains; dryness of the skin, mouth and throat; fever; and abdominal pain. The urine contains not only sugar and diacetic acid, but often albumin and casts.

If the condition is more severe the patient presents a picture of prostration, dehydration, flushing of the cheeks, rapid deep breathing, and acetone odor of the breath. He may have coffee ground vomitus. Thirst is incessant and somnolence of various degrees is seen. The eyeballs are soft. A temperature of 102° or 103° F. is common, due in part to dehydration and often aggravated by an accompanying infection. The nausea, vomiting, and abdominal pain tend to subside as stupor increases. Most patients, even in relatively severe acidosis, can be aroused.

The abdominal pain may be severe and occasionally may simulate pancreatitis, appendicitis or other intra-abdominal infection. Intra-abdominal infection may exist concurrently and be a precipitating factor. Usually, however, an hour or two of active treatment will completely relieve pain if it is due to acidosis. Leukocytosis well over 25,000 with a high neutrophil count is common with acidosis without infection, and this may make the differential diagnosis of an acute abdominal emergency a matter of concern for several hours. The sedimentation rate is also high in acidosis uncomplicated by infection.

Weakness of the respiratory muscles is often seen in severe coma. Distention of the stomach and colon may be present. The possibility of anuria should be considered.

ESTIMATION OF THE PROGNOSIS

In acidosis which is severe or prolonged, clinical evaluation is of great importance. This includes: an estimate of the degree of coma; its duration; consideration of the age of the patient; the severity of infection, if present; and, especially, a careful estimate of the cardiovascular system. The events leading to death in many cases indicate cardiac collapse with relatively acute failure often closely following falling blood pressure and evidence of peripheral vascular failure with the picture of shock. The severity index of Rabinowitch[6] may be used to considerable advantage.

INSULIN RESISTANCE

The clinician should be on the alert for insulin resistance. A need for several thousand units in the first 12 to 24 hours is not uncommon. Such relative resistance may be intimately associated with the acidosis, and the requirements may diminish to average levels rapidly. On the other hand acidosis may be controlled with 200 units per day; subsequently, more than 1000 units may be necessary, such high requirements diminishing when existing infection is brought under control. This situation is illustrated in Figure 1.

DIAGNOSIS

The diagnosis is usually not difficult. If a history of diabetes is present; if a reasonable number of the typi-

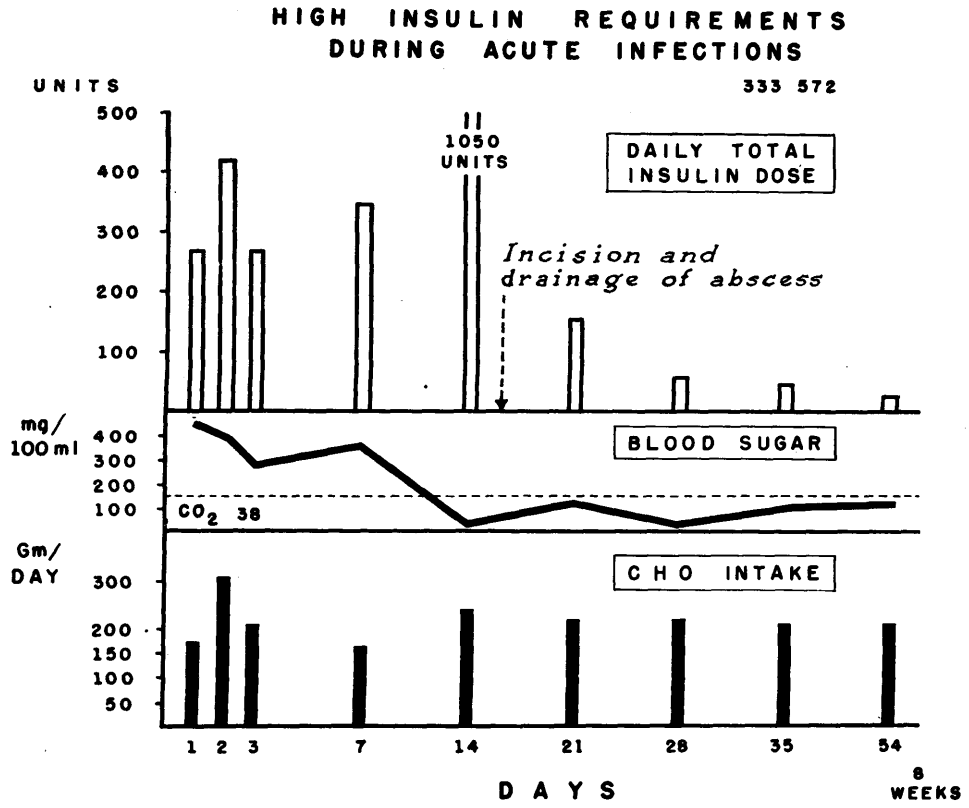

FIGURE 1. Marked insulin resistance associated with infection. The mild acidosis disappeared under treatment within a day and an abscess was drained.

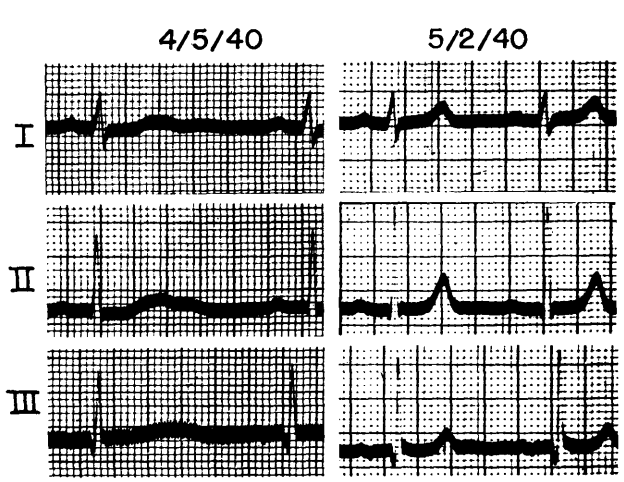

FIGURE 2. Hypopotassemia due to overtreatment with desoxycorticosterone acetate. The serum potassium content was 1.4 mEq/L on 4-5-40 and 4.1 mEq/L on 5-2-40. Prolonged Q-T interval, long flat T waves and U waves are present in the electrocardiogram on the left.

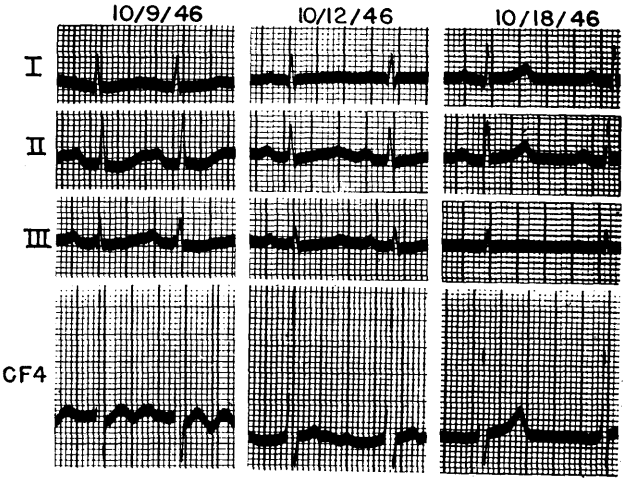

FIGURE 3. Hypopotassemia during and after diabetic acidosis. On 10-9-46 CO_2 combining power was 11.8. Serum potassium was as follows: 10-9-46—2.2; 10-12-46—2.7; and 10-18-46—5.4. Outstanding changes include low broad T waves, prolonged Q-T intervals and U waves, which are shown with particular clarity in lead CF4.

cal signs are evident; and if the urine contains a great deal of sugar and diacetic acid, the diagnosis is usually definite enough to warrant beginning treatment at once. This much evidence is necessary, but delay in therapy while waiting for extensive laboratory tests may be disastrous. In an unconscious patient with no friends or relatives to give a history, the matter is not nearly so simple.

If there is doubt, it is well to consider a number of other conditions which may be causing stupor or which may exist concurrently. These include: hypoglycemic shock; uremia; intoxication due to alcohol or drugs; shock due to trauma or hemorrhage; and also at times a number of cerebral disorders including trauma; vascular accidents; inflammation or brain tumor.

LABORATORY STUDIES

The first laboratory procedure to be done is obviously to test the urine for sugar and ketone bodies. Ketonuria may appear in various states of intoxication or starvation when diabetes is not involved, but diabetic acidosis is not usually present if the urine does not contain readily measurable amounts of diacetic acid. However, this is not always true for if acidosis is accompanied by severe renal impairment the urine may contain little or no ketone bodies.

The carbon dioxide combining power and blood sugar level should be determined at once. One may expect the blood sugar to be over 300, more commonly 600 and sometimes even over 1000 mg. per 100 cc., or more. In our practice the carbon dioxide combining power is the most useful single test in evaluating the metabolic disturbance. It indicates how close the blood is to serious depletion of alkali. A rapid test for blood ketone bodies[7] is particularly valuable for several reasons: 1) It is a good indication of the severity of acidosis. 2) It can be done quickly at the bedside. 3) It will differentiate between those cases in which blood and urine ketones are low and those in which these substances may be low in the urine and relatively high in the blood. 4) It will help to separate diabetic acidosis from uremia. Recently a test for blood ketones was made in the case of a patient who was anuric for 15 days. The carbon dioxide combining power was 29 and blood urea was 243. The blood ketone test was negative.

It would be highly desirable to know the blood *p*H and this test may be available to more clinicians in the future.

In addition it is very useful to know the blood chloride level, as indirectly it gives a good indication of the sodium levels.

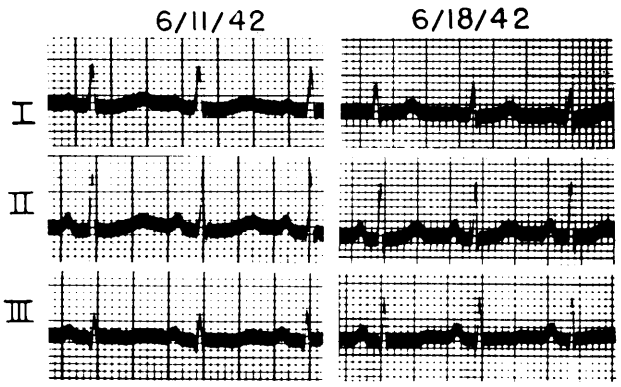

FIGURE 4. Hypopotassemia two days after beginning treatment for diabetic acidosis. CO_2 combining power was 9.0 on 6-9-42. Serum potassium mEq/L on 6-11-42 was 1.8 and on 6-19-42 was 4.1. Low rounded T waves and prolonged Q-T interval without U waves are shown in the first electrocardiogram.

A blood urea determination should be done. It may prove valuable to follow blood counts, especially if the original white cell count is elevated. Hematocrit levels will help determine hemoconcentration and should be followed serially. In diabetic acidosis it will give a reasonable estimate of blood volume.

SERUM POTASSIUM

In the past few years a great deal of attention has been given to the possible danger of low serum potassium. More complete knowledge of this subject is needed from the clinical standpoint. Several points, however, seem well established. Abnormally low serum potassium is relatively common in diabetic acidosis but usually appears after treatment is under way. In 82 cases studied by Martin[8] the serum potassium was below 2.9 mEq/L before treatment in 2 per cent of the patients. Within 48 hours after treatment was begun in the same group, the level was below 2.9 mEq/L in 14 per cent. It is well to remember that low serum potassium also may be present in chronic renal disease and may be produced by diarrhea, vomiting or constant gastric drainage.

The possibility of abnormally low serum potassium should be considered in all cases. It should be suspected where there is extreme muscle weakness, especially weakness of the diaphragm, or shock which does not respond well to usual therapy. It is commonly found where there has been a rapid fall in the blood sugar level, particularly when large amounts of fluids have been given intravenously. Hypotension; tachycardia; murmurs or cardiac dilatation; developing during the course of treatment[8] are possibly manifestations.

Changes in electrocardiograms typical of hypopotassemia are illustrated in Figure 2 (in a case in which there was overtreatment with desoxycorticosterone acetate) and in Figure 2 and 4 (cases of diabetic coma under treatment).

The earliest changes[9] due to hypopotassemia are rounding and broadening of the T-waves. Usually the T-waves are low in amplitude. The Q-T interval is prolonged depending entirely on the degree to which the duration of the T-waves is increased. Prominent U-waves are common. (In hypocalcemia. the Q-T interval is lengthened but the T-waves are normal, and U-waves do not appear.)

The level of serum potassium at which the electrocardiogram shows distinct changes is not well established. It appears to be approximately 2.5 mEq/L; and serious harm from hypopotassemia seems unlikely with levels above this range.

REFERENCES

[1] Guest, G. M.: Diabetic coma: metabolic derangements and principles for corrective therapy. Am. J. Med. 7:630-646, Nov. 1949.

[2] Root, H. F.: Use of insulin and abuse of glucose in treatment of diabetic coma. J.A.M.A. *127*:557-564, March 10, 1945, correction *127*:1068, April 21, 1945.

[3] Falta, W.: Die Zuckerkrankheit, Berlin und Wein, Urban & Schwarzenberg, 1936, p. 194. as reported by Joslin, E. P.; Root, H. F.; White, P.; and Marble, A.: Treatment of Diabetes Mellitus. ed. 9, Philadelphia, Lea & Febiger, 1952, p. 370.

[4] Fisher, P.: Role of the ketone bodies in the etiology of diabetic coma. Diabetes *1*:108-111, March-April, 1952.

[5] Howard, J. E.: Observations on therapy of diabetic acidosis. Proc. Am. Diabetes A. *10*:152-160, 1950.

[6] Rabinowitch, I. M.; Fowler, A. F.; and Bensley, E. H.: Diabetic coma (investigation of mortalities and report of severity index for comparative studies). Ann. Int. Med. *12*:1403-1428, March, 1939.

[7] Dumm, R. M.; and Shipley, R. A.: Simple estimation of blood ketones in diabetic acidosis. J. Lab. & Clin. Med. *31*:1162-1163, Oct., 1946.

[8] Martin, H. E.; Hillier, P.; and Wertman, M.: Potassium deficits in diabetic acidosis with particular reference to problems in therapy. Proc. Am. Diabetes A. *10*:161-178, 1950.

[9] Ernstene, A. C.; and Proudfit, W. L.: Differentiation of changes in Q-T interval in hypocalcemia and hypopotassemia. Am. Heart J. *38*:260-272, Aug., 1949.

[10] Story, R. D.; and Root, H. F.: Diabetic coma. J.A.M.A. *144*:86-88, Sept. 9, 1950.

[11] McCullagh, E. P.; and Zwickel, R. E.: The value of routine blood sugar tests in office practice for the detection of diabetes mellitus. J.A.M.A. accepted for publication.

[12] Lestradet, H.; and Guest, G. M.: Absence d'acetone dans le sang et les urines fraichment excrétés au cours des cétoses. Ann. Med. *53*:275, 1952.

[13] Root, H. F.: Personal communication.

[14] Kety, S. S.; Polis, B. D.; Nadler, C. S.; and Schmidt, C. F.: Blood flow and oxygen consumption of human brain in diabetic acidosis and coma. J. Clin. Investigation *27*:500-510, July, 1948.

New Knowledge Regarding Acidosis

The most important progress in the treatment of diabetic acidosis in recent years has stemmed from an improved understanding of the associated disturbances in the metabolism of water and electrolytes. Although it has long been recognized that diabetic acidosis is initiated by lack of insulin with a consequent inability of the body to utilize carbohydrates and an eventual profound depletion of salt and water, it has become increasingly apparent that even the most skillful correction of these defects does not save life in all cases, even in the absence of serious complicating illness.

From *Electrolyte Metabolism in Diabetic Acidosis,* by Randall G. Sprague, M.D. and Marschelle H. Power, Ph.D., in *The Journal* of the American Medical Association, March 1, 1953