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Pathogenesis of diabetic acidosis

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THE PATHOGENESIS OF DIABETIC ACIDOSIS

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The Plan of Thought

I. The Introduction
   A. Purpose of the Paper
   B. Incidence of Acidosis

II. History of Pathogenesis of Diabetic Acidosis
   A. History of Fatty Acid Oxidation
   B. History of the Acetone Body production

III. Pathogenesis of Diabetic Acidosis
   A. Present Concept of Etiological Factors
   B. Present Concept of Actual Etiology
   C. Electrolyte Changes Involved in the Pathogenesis

IV. Conclusion
   A. Summary of Experimental Evidence
   B. Student's Conclusions

THE PATHOGENESIS OF DIABETIC ACIDOSIS

Diabetes Mellitus is an inheritable disease of metabolism characterized by the disturbance of the mechanisms involved in the formation and utilization of sugar in the body. This results in a persistent tendency to the elevation of the glucose content of the blood; it likewise may lead to the excretion of abnormal amounts of glucose in the urine and, in the severe forms of secondary disorders of protein and fat metabolism manifested azoturia and acidosis (ketosis). It is with the complication of acidosis, more specifically its pathogenesis, with which we will concern ourselves in this paper.

When one considers the pathogenesis of acidosis one must include the etiology and also the electrolyte changes occuring in the body during acidosis in order to understand the actual development and the result in the body produced in this condition.

Diabetic Acidosis can be considered equal with Diabetes Mellitus when discussing their respective incidences as about all diabetic individuals usually have one or more episodes of acidosis. Unfortunately there are no series of figures for comparison with which we can evaluate their comparative incidences. But we can readily understand that the incidence will be very high when the various predisposing factors in producing Diabetic Acidosis are discussed later in this paper.

Diabetic Acidosis may occur solely as the result of inadequate treatment of uncomplicated diabetes or, more commonly, as a consequence of a complicating condition which temporarily intensifies the diabetes. (10)

In most cases the precipitating cause of acidosis and coma is one or a combination of more than one, of the following factors (9): 1- omission of insulin, or taking of insufficient amounts of insulin; 2- acute infection, particularly respiratory infection; 3- fracture of a bone, or other injury; 4- surgical operations; 5- hyperthyroidism; 6-pregnancy and (rarely); 7- resistance to insulin.

In a study of insulin deprivation in human diabetes Mirsky (43) and his co-workers found that in one group of patients acetonemia and increasing hyperglycemia developed rapidly and culminated in acidosis and precoma within twenty-four hours, while in the second group a significant acidosis did not develop even after one week.

Early in the history of the study of Diabetic Coma it became apparent that acidosis plays an important part in the production of this syndrome. Later it was shown that this state is due primarily to the accumulation of large amounts of organic acids in the tissues particularly Beta-hydroxybutyric and Acetoacetic acids. (44). The term "acetone bodies" and "ketone bodies" are used in their usual clinical sense. Of the three substances usually grouped under the term "ketone bodies" namely Acetoacetic acid, Beta-

hydroxybutyric acid and acetone, said Soskin and Levine (36), "the second is not a ketone, while the third represents merely a breakdown product of its more physiologically significant precursors." Magnus Levy (37) in 1910 postulated that Beta-hydroxybutyric undergoes oxidation into diacetic acid and from that Acetone is formed. Acetone can be made out of acetic acid by splitting off CO_2. As seen in the urine of diabetic patients, the ketones ordinarily are found in the following sequence:-Acetone, Diacetic Acid and Beta-hydroxybutyric acid. Due to the predominant role of the acetone bodies in the development of Diabetic Acidosis and Coma it has become of interest to determine the mechanism responsible for the formation and utilization of these acids.

It has been recognized since the work of Van Noorden et al (35) that approximately ten to thirty mgms, of Acetone may be recovered from the urine and thirty to eighty mgms. per day may be eliminated by the lungs of healthy individuals. When more than a physiological amount of acetone is present and the underlying error in metabolism that is responsible for it is allowed to continue, ketones will accumulate to a level at which diacetic acid and beta-hydroxybutyric acid can be detected in the body fluids. So it is always well to remember that ketone body production is a normal biochemical process in the body and is associated with disease only when they become excessively produced. (40).

In order to fully understand the disturbances responsible for the ultimate picture of Diabetic Acidosis one must first brief-

ly review normal carbohydrate metabolism to have a working picture of Diabetic Acidosis and also a working knowledge of the metabolic process involved in Diabetes Mellitus. Carbohydrate serves as the chief source of body energy (39). A portion of the glucose from which carbohydrate metabolism originates is converted into glycogen (glycogenesis) in the liver and muscles and is stored there to be available for the body for energy by the process of glycogenalysis. The remaining glucose is broken down by means of anerobic glycolysis to lactate and pyruvate and possibly to other 3-carbon fragments without first being converted to glycogen (41).

There are three sources of body glucose. The largest amount naturally comes from the food. The second source is liver glycogen which is derived from glucose, either ingested or synthesized by the body, and from lactic or pyruvic acid, elaborated to a large extent in the muscles. The third source is the synthesis from a number of building blocks within the body. This is termed gluconeogenesis. Gluconeogenesis appears to take place primarily in the liver from 3-carbon fragments which appear in the course of metabolism of protein, fat, and carbohydrate. According to Stetten (42) the amount of glucose made available by gluconeogenesis in the normal rat is about ten times that derived from glycogen.

The balance that normally exists between the deposition of glycogen (glycogenesis) and its breakdown (glycogenalysis) is regulated in a complex manner, but the height of the blood glucose

concentration is a most important factor. Since the available supply of insulin plays an important role in the regulatiàn of the blood sugar level, insulin also contributes to the normal homeostatic balance between glycogenesis and glycogenolysis.

Barach (34) showed that under normal conditions the balanced diet of man in the northern temperate zone obtains approximately 65% of its calories from carbohydrate, 15 to 20% from protein and 15 to 20% of its calories from fat. Acetone bodies are not demonstrable, in urine of normal individuals living on a normal diet. When, however, for one reason or another, the carbohydrate content of the diet is inadequate, or when in the absence of insulin, carbohydrate is lost to the metabolism, and the total or nearly total nutritional requirements are met by the breaking down of fat and protein, then the acetone bodies which are breakdown products of fat metabolism, make their appearance in abnormal amounts.

At the present time there are two schools of thought concerning the nature of the disturbances in carbohydrate metabolism in Diabetes Mellitus. One group led by Soskin has credited the hyperglycemia and glycosuria to "overproduction" which is assumed to result from a conversion of fatty acid to glucose and from excessive gluconeogenesisfrom protein breakdown. The other school believes that the basis for Diabete Mellitus is the under-utilization of glucose (41). It appears at the present time that under-utilization of glucose constitutes the basic disturbance in Diabetes Mellitus and that this results from the summation of three de-

fects. First, a decrease in oxidation of glucose and probably also a decrease in its utilization in amino acids and protein synthesis; second, a decrease in fatty acid formation from glucose to about 1/20 of the normal, thus making this non-metabolized glucose also available for urinary excretion; and third, a decrease in glycogen storage in the liver and muscles.

Liver biopsy specimens obtained during Diabetic Acidosis and its treatment were examined by the Gomori technic (31) for glycogen. Severe glycogen depletion was found before treatment. Restoration of glycogen content occurred after a few hours of therapy.

Ideas of how carbohydrate lack produces a ketosis have undergone many alterations. The old idea, first advanced by Geelinuydur (15), that the ketone bodies represented incomplete oxidation products of the fatty acids which required the concomittant oxidation of carbohydrate metabolism for their utilization gained many adherents (16) and the so-called "ketogeni-antiketogenic" ratio (17) which implied a quantitative relationship between the oxidation of ketone bodies and glucose became widely accepted. The old view expressed in the often quoted statement of Rosenfield that "Fats burn only in the fire of Carbohydrates" and the later remark of Woodyatt (18) that " when the mixture of metabolites oxidizing in the body contains more than three molecules of higher fatty acids to one of glucose, then the body smokes with acidosis compounds like an automobilesmokes with too much oil in the cylinder" have governed the conception of ketosis until very recently.

Lusk (19) early recognized that the ketone bodies must originate from the fatty acids of fat and possibly to a small extent from a part of some of the amino acids in protein. There is no evidence that glucose or any carbohydrate such as lactic or pyruvic acid yields ketone bodies except as they may form fat or glucose and then fat, a process in which glucose fails to take part during ketosis; Marriot (20) showed that Acetoacetic acid is generally the initial ketone body and may undergo reduction in various tissues to Beta-hydroxybutyric acid or breakdown in small amounts to form acetone. The production of Acetoacetic acid by the oxidation of fatty acids is intimately associated with the beta-oxidation theory of Knoop. It is now known that this theory cannot account for the large amount of ketone bodies which fatty acids are known to yield. A modification of Knoop's theory as discussed by McKay (21) accounts for the amount of ketone bodies formed by fatty acids and explains the discrepancies between various experimental data and the older theory.

Two new theories for the mechanism of ketone body production have been proposed. Both of them assume that all of the fatty acid molecule may be converted to ketone bodies. Hurtley (22) first proposed the "multiple alternate oxidation" theory which was elaborated on by Jowett and Quastel (23). This assumes that a fatty acid is oxidized at alternate carbon atoms simultaneously along the whole length of the chain. The C_4, C_8, C_{12}, C_{16}, and C_{20}, acids would be entirely converted to ketone bodies while the intermediate

acids would have two carbon atoms from each molecule completely oxidized at once or forming some other compound.

The other new theory of ketone body formation, based on classical beta-oxidation, was proposed by McKay (24). As proposed, it assumes that the two carbon atoms dropped from the chain by successive beta-oxidation form acetic acid. But it should be emphasized that although acetic acid appears to be a likely intermediary it is possible that some other two carbon compound is formed instead. Whether it be acetic acid or some other compound it is assumed that it condenses to acetoacetic acid. A molecule of C_{16} acid and two molecules of C_{14} acid would give four and seven molecules of ketone respectively. In the light of the present knowledge this "beta-oxidation acetic acid condensation hypothesis" seems to be the most applicable to the various observations which require explaining.

Up until the twentieth century it had been thought that ketone bodies are manufactured in all tissues of the body. The first intimation that this concept was incorrect was noted from the studies done in 1910 by Emden (44) who observed that the isolated liver was the only tissue capable of producing acetone bodies on perfusion with fatty acids. Chaikoff and Soskin (45) further showed this in 1928 when they removed the liver from the depancreatized dog which resulted in a drop in the blood acetone bodies, thus implicating the liver as the site of acetone formation in the intact animal. Edson (13) did studies on liver sl-

ices in the presence of added fatty acids and came to the conclusion that fatty acids compete with other oxidizable substrates for the oxidizing systems of the liver. Carbohydrates and their derivatives, e.g., lactose, pyruvate and dihydroxy acetone, alcohol and certain amino acids, are in anti ketogenic competition. The fatty acids also compete amongst themselves. Glycerol and sorbitol are the most powerful of the antiketogenic substances that have been examined. Substrate competition is considered to be an important factor in the regulation of hepatic ketogenesis. In 1933 Quastel and Wheatley (14) used the Warburg tissue slice method in studying the oxidation of fatty acids by guinea pig liver. They found an optimum concentration for each fatty acid exists, above which any increase in concentration leads to the production of acetone bodies. In agreement with the results of perfusion experiments all fatty acids with an even number of carbon atoms (including acetic acid) give riseto acetone (acetoacetic acid) production. Those fatty acids with an odd number carbon atoms produce little or no acetone bodies. The unsaturated acids, crotonic and isocrotonic acids, are vigorously oxidized to give rise to acetoacetic acid. Acetoacetic acid is not broken down appreciably to acetone and CO_2 in the liver; it is apparently the final oxidation product of butyric acid in this organ. They further showed that there was no evidence that glucose combines with or removes acetoacetic acid under the conditions of the experiment.

Barnes and et al (17) showed that when normal animals were

injected with beta-hydroxybutyric acid they showed no greater utilization of ketone bodies than did animals with ketosis.

Banerjie and Bhattacharya (1) further showed that diabetes produced in rabbits by the intravenous injection of alloxan is not free from ketosis. There is an early onset of acetonuria which reaches a maximum towards the end of the first week after the injection of alloxan and then falls gradually until normal levels are reached. The partial removal of the pancreas in alloxan-diabetic rabbits does not affect the course of ketosis in the animal. It is suggested that the absence of insulin alone is not responsible for ketosis in diabetes and that ketosis is probably due to some other extrapancreatic factor.

The intravenous injection of large amounts of glucose to anesthetized, nephrectomized-depancreatized dogs, to unanesthetized depancreatized dogs and phloridizinized-depancreatized dogs in all of which the presence of insulin was entirely excluded, results in a disappearance of ketone bodies. This antiketogenic action of glucose is attributed to the deposition of glycogen in the liver and a consequent cessation of ketone formation. (8)

Mirsky (5) also showed that if a correction be made for endogenous ketogenesis (initial acetone body content), it is observed that the utilization of intravenously injected beta-hydroxybutyrate by nephrectomized female rats is not influenced by fasting of feeding or by the administration of glucose. This helps to further substantiate the idea that carbohydrate does not exert

a ketolytic action and, therefore its affect in abolishing ketonuria is due to a sparing of fat or other ketogenic substances, i.e. antiketogenesis.

Acetone body utilization by the peripheral tissues has brought about considerable new experimental work. In 1928 Snapper and Gruenbaum (44) demonstrated that perfused striated muscle of normal animals utilizes acetone bodies. The studies of Chaikoff and Soskin (45) in the same year established that both normal and depancreatized dogs can oxidize acetone bodies. Later Friedmann (46), working with normal and depancreatized dogs, could demonstrate no influence of insulin on the normal rate of acetone body utilization by the muscles.

It has also been found that there is no positive correlation between the utilization of carbohydrate and that of ketone bodies by the heart-lung preparation (32). The ketolytic ratio obtained varied from zero to infinity. It has been suggested that carbohydrate is used preferentially by the heart, and that when in addition ketone bodies are made available to the cardiac muscle a competition between the substrates occurs. More recently, Mirsky et al (5) demonstrated again that sugar has no influence on the oxidation of acetone bodies by employing a technic which permitted the analysis of whole animals.

With the development of severe diabetic acidosis, almost all ingested carbohydrate is excreted in the urine in the form of glucose. In addition, virtually all sugar derived from ingested or

body protein is lost in the urine. As a result, accelerated catabolism of fat and protein occurs in an effort to meet the energy requirements of the body. Sooner or later, the rate of the formation of acetone bodies exceeds the rate of their utilization in the tissues, so that they accumulate in the body fluids and are excreted in the urine and expired air. As a result of these events, serious secondary disturbances of fluid and electrolyte economy ensue. These disturbances my be factors of major importance in the production of coma and a fatal outcome. The passage of large amounts of sugar, ketone bodies, nitrogenous products, and electrolyes into the urine provokes the excretion of tremendous quantities of water (9).

Before ketone acids are excreted in the urine they are neutralized by basic substance. A certain proportion of the ketones, because of their weak acid character, can be excreted as free acid in highly acid urine, and another fraction is neutralized by ammonia. None of these processes involves any irreversible reaction nor removes from the body any dispensable element. Up to tnis point combustion of the ketones alone will restore the normal constituition and reaction of the internal environment. The excretion of acid and ammonia may be considered as a defense against loss of body base.

This defense, however, is not perfect. A certain fraction of the ketone acids in the urine is neutralized by fixed bases. The excretion of these bases withdraws from the body, elements

which can be replaced only from extraneous sources and therefore introduces a reaction which is not automatically reversible (4).

At first ammonia serves the purpose, but in severe ketosis the rate of formation of the ketone acids is so rapid that the ammonia mechanism is soon overwhelmed. Furthermore, with the development of renal insufficiency, the ability of the kidneys to produce ammonia is impaired. There is then a continuous loss of sodium and other basic ions in the urine. An additional part of the body's reserve of base is combined in the body fluids with retained ketone acids, other inorganic acids, phosphates, and sulfates at the expense of bicarbonates.

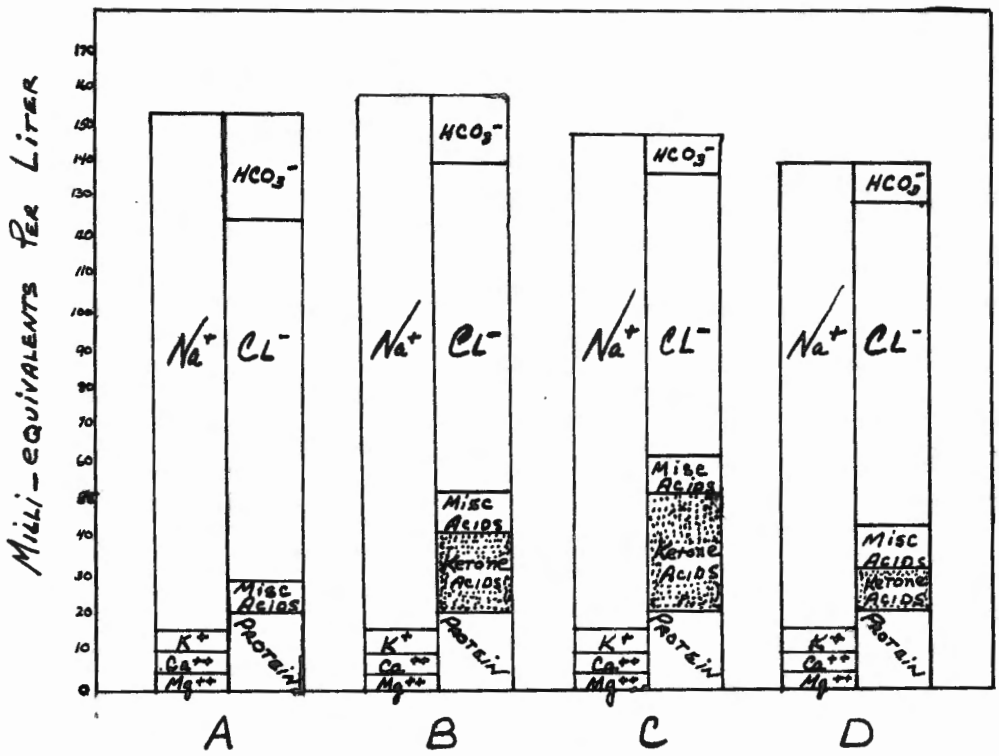
Reduction of base means reduction of the total salt or electrolyte concentration of the body fluids. To meet this, fluid is excreted with consequent dehydration. Apparently neither function, total fluid volume nor osmotic pressure, is sacrificed entirely in behalf of the other. Compromise between the two functions results in a lowered body fluid volume containing less than the normal concentration of base.

The reason for the loss of chlorides is not clear and its utility, by many investigators, seems quite questionable. In the urine, the chloride can be excreted only as the neutral salt of ammonia or some base. Loeb, et al (11) found that severe diabetics, from whom insulin had been withdrawn, excreted large quantities of chlorides in the urine even when ketosis did not develop, apparently due mostly to the diuretic effect of glycosuria alone.

Chloride depletion then may be connected less with the acidosis than with the glycosuria and dehydration which accompany it.

The foregoing disturbances are reflected in profound alterations of the acid-base equilibrium of the blood plasma and extracellular fluid. The precise pattern of these alterations varies somewhat, depending on the severity and duration of the acidosis, the presence or absence of vomiting, and the status of renal function.

The following figure is a composite of three examples which represent the acid-base composition of the blood plasma in three cases of Diabetic Acidosis compared with normal. The data are charted after the method of Gamble (3).



Values are expressed as milli-equivalents per liter of plasma. Mis-

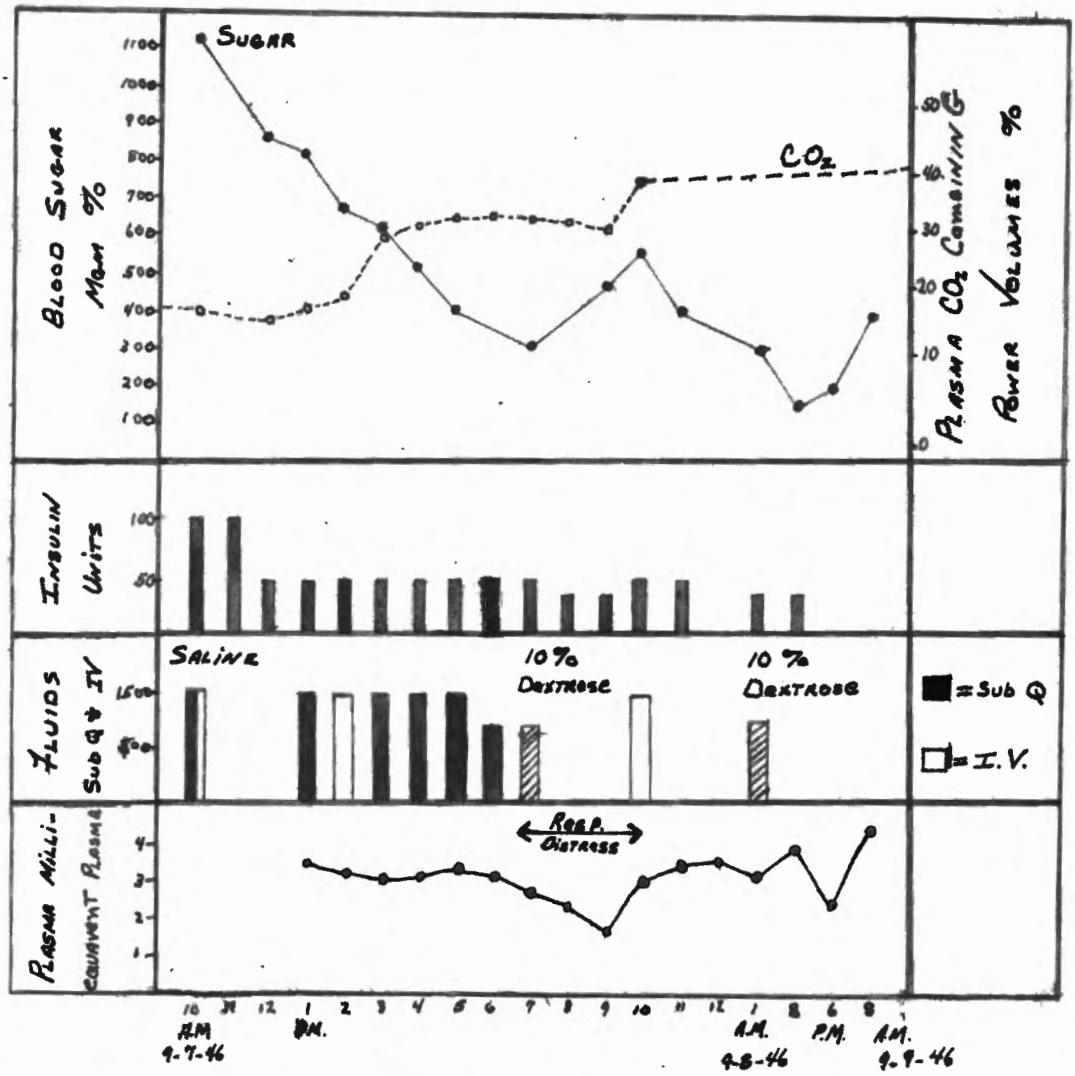
cellaneous acids include sulfates, phosphates, lactic acid, uric acid and amino acids. A is the normal patterm. B represents diabetic acidosis of a few hours' duration in a girl 14 years old. Probably as a consequence of a rapid dehydration, there has been a slight increase in the concentration of the total of the base of the plasma. There has been a marked reduction of the plasma bicarbonate, roughly corresponding to the accumulation of ketone acids in the blood. The CO_2 combining power of the plasma is 14 volumes per 100 c.c. The patient has vomited only once and the concentration of plasma chlorides has remained essentially normal. C represents aevere diabetic acidosis of at least three days' duration associated with vomiting in a boy 17 years old. Several factors have contributed to the reduction of plasma bicarbonate to a dangerously low level (plasma CO_2 combining power: 14.7 volumes per 100 c.c.). A large accumulation of ketone acids,a decrease of the total base and an increase of miscellaneous acids. The concentration of chlorides in the plasma has been reduced to 87 milli-equivalents per liter. D represents diabetes acidosis in a woman 50 years old who has been experiencing symptoms of uncontrolled diabetes for two years. Production and excretion of ketone acids probably had been in progress for a considerable period before she became critically ill. As a consequence, there has been a marked decrease of the total base and a severe reduction of the plasma bicarbonate (plasma CO_2 combining power: 17 volumes per 100 c.c.), together with a relatively small accumulation of ketones in the blood.

Atchley,D.W. et al (11) have found that the reduction in the CO_2 combining power of the blood plasma is a common feature of all instances of untreated acidosis. This is an indiresct measure of the amount of sodium which has been lost through the kidneys plus the amount which is held in combination with acid substances in the body fluids. There is always more or less accumulations of ketone acids in the blood. The behavior of the plasma chlorides is variable and seemingly erratic. When acidosis is of long standing or is associated with vomiting, the plasma chlorides are likely to be decreased. The concentration of total base in the blood plasma may be normal, increased, or diminished, depending upon the interplay of several factors, notably the relative loss of water and base.

The potassium deficiency in Diabetes Acidosis can best be illustrated by a case studied and described by Nicholson et al (25). A W/W, age 60, was admitted to Duke Hospital in September 1946. Six days before her admission her insulin syringe was broken and in order to punish her family for neglecting her she made no effort to replace it. She complained of abdominal pain and vomiting for three days before admission, and twelve hours before arrival she was found in deep coma.

Physical examination disclosed that the temperature was 98.6 degrees and the blood pressure was 60 systolic and 50 diastolic. Respirations were of the Kussmal type. There were signs of extreme dehydration and an odor of acetone on her breath. She did not respond to painful stimuli. The remainder of the examination

revealed essentially normal conditions. The urine showed a strong reaction for sugar, acetone and diacetic acid. Blood sugar level and the serum CO_2 are shown in the next diagram.



Six hours after admission the patient roused, her respiratory rate was normal and she appeared much improved. At eight hours her blood sugar level was 324 mgm/100 c.c., her CO_2 power was 34 volumes per loo c.c. and urinalysis showed traces of sugar and acetone

with no diacetic acid. One hour later her respirations became shallow, rapid and obviously difficult. She received a 10 % solution of dextrose intravenously, with further impairment of respiration. She was then given 0.6 gm of potassium chloride by mouth every half-hour until 3.6 gms had been given. Within two hours her respirations were normal and subjectively she was greatly improved. The patient made an uneventful recovery.

It is well to note that the lowest concentration of serum potassium was 1.9 milli-equivalents per liter, and at this time the patient was in respiratory distress. It must be pointed out that though the respiratory difficulty was present before the patient received dextrose, it became more pronounced afterward.

Smith (26)has reported that in dogs who are fed a diet that is low in potassium, paralysis of various muscle groups will result and, unless therapy is started, death in a state of collapse will occur. The administration of biotin will temporarily relieve these dogs, but potassium is necessary before any permanent improvement is noted. Furthermore the serum potassium concentration is low. It is believed that the severe muscular weakness that has been seen in patients who have apparently recovered from diabetic acidosis is a result of potassium deficiency.

Several factors may combine to produce the reduction in the serum potassium concentration as noted in the case above illustrated: 1-loss of potassium by diuresis and dehydration with the resultant loss of intracellular stores of water and potassium; 2-

loss of potassium is the result of the effect of insulin and; 3- the reduction of serum concentration due to dilution by parenteral fluid with no outside source of potassium.

Elkington and Winkler (27) reported that in dehydration or diuresis not due to diabetic acidosis, loss of potassium in the urine takes place. They expressed the belief that there is also loss of intracellular water and potassium. Harrop and Benedict (28) reported in 1923 that in patients with Diabetes Mellitus an injection of insulin produced a decrease of the serum potassium concentration. Briggs (29) and associates and Kerr (30) have shown that in normal dogs the administration of insulin produced a decrease in the concentration of potassium in the serum.

The concentration of the serum potassium was studied in 45 patients by Nodler (12) before and after therapy for Diabetic Acidosis. This concentration was consistently found to be normal or elevated before treatment and decreased below normal during the two to eighteen hour period after insulin therapy was instituted. These subnormal concentrations persisted until potassium or a food containing potassium was administered. A relationship was found to exist between the rate of decrease in the blood glucose concentration and the serum potassium level. Alteration of the blood pH was closely associated with the change in the serum potassium concentration, serum potassium varying inversely with the blood pH. The serum potassium level was found to vary inversely with the CO_2 combining power.

During the development of Diabetic Acidosis, Atchley et al

(11) demonstrated an increase in urinary output of phosphorous sufficient to cause a significant depletion of this element. The presence of a considerable phosphorous deficit in Diabetic Acidosis was indicated by the data of Guest and Rapaport (38).

Danowski (6) showed that the whole blood and serum of diabetic patients have been analyzed for sodium, potassium, total acid soluble phosphate, inorganic phosphate and water. At the height of Diabetic Acidosis the blood cells are extremely depleted of phosphates and base. These are slowly restored during recovery.

Peters (2) found that in severe acidosis the serum proteins are usually within or above the normal limits, but fall during recovery below the normal level. The initial high level seems to be due to hemoconcentration, the subsequent fall to restoration of normal serum volume. Both the initial high levels and the later low levels seem to bear some relation to the state of nutrition, being lower in emaciated subjects. The initial hemoconcentration is only partly due to depletion of body water, partly to loss of fluid from the vessels into the tissues. Restoration of serum volume is to a large extent independent of the replenishment of general body fluids.

When hemoconcentration and hypoproteiemia fail to respond to treatment, low blood pressure and signs of circulatory failure akin to shock are evident. Under these circumstances clinical symptoms, especially the mental state, do not improve. Clinical improvement is better correlated with the changes in serum proteins

than the blood sugar, serum bicarbonate or ketonuria. It is suggested that the state of shock and its attendant hemoconcentration may be at least contributory causes of the coma of Diabetic Acidosis.

As a further physiological alteration associated with and accompanying Diabetic Acidosis, Chang showed that during Diabetic Acidosis unaccompanied by any other known complicating factor, a well marked diminuition in the circulatory blood volume was found in 85% of the cases he studied. This diminuition was accompanied by a corresponding increase in the oxygen capacity, the cell volume remaining intact. After complete recovery from acidosis the blood volume increases to within the normal limits in a short period of time. (33)

CONCLUSION

Through many years in the experimental studies on the production of the ketone bodies in Diabetic Acidosis, it has been now shown that they are formed almost exclusively in the liver and they are a result of a faulty carbohydrate metabolism. With this faulty carbohydrate metabolism there is an increased demand on the fat metabolism. This necessitates a speed up of the oxidation of the fatty acids. Knoop's theory on the oxidation of fatty acids had been accepted in its entirety until the introduction of McKay's theory. Now parts of both theories are used to give a fairly feasible working and explainable theory.

It was formerly thought that the ketone bodies were abnormal toxic products of incomplete fat oxidation, which accumulated because of the lack of simultaneously oxidizing carbohydrate. More recently it has been found that both the carbohydrates and the ketone bodies are utilized by the extrahepatic tissues of the diabetic organism at rates comparable to those in the normal. It has further been found that it is actually an excess of these products which is the cause of the upset.

Experimental evidence has also shown that during the pathogenesis of Diabetic Acidosis there are the following electrolyte changes in the body; decrease in the serum concentration of potassium, phosphorous, and in the amounts of base present.

To the writer, the results of the many thorough investigative writings have shown the actual mechanisms in the production of the Diabetic Acidosis and in its pathogenesis the varied and important electrolyte and metabolic changes that transpire. With this knowledge and understanding, the modern practitioner has a better ability to cope with this acidosis when it is produced and can handle it with intelligence and definite plans and not in the hit and miss method the practitioner was formerly forced to use because of his lack of knowledge of the principles involved.

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