The Role of the Ketone Bodies in the Etiology of Diabetic Coma

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There is still no agreement as to the specific cause of the coma that results from uncontrolled diabetes mellitus. Differences of opinion are the natural result of conflicting experimental data on the subject.

Is acidosis itself the cause of coma? There seems to be no convincing evidence that it is, and there is much good evidence showing that it is not. Practically all recent writers share this opinion, although as recently as 1946 Peters and Van Slyke considered the acidosis itself a very important factor.

Are the ketone bodies the cause of diabetic coma? Many authorities hold this opinion. For instance Joslin, in his most recent text, states that "the clinical picture of diabetic coma (is) . . . attributable in a large part to the toxic effects of the ketone bodies." Others, including MacKay, Bertram, Baker and Brugel have denied that this is true. Evidence can be found to support both views. Recent writers, including Kety, Barach, Root, Soskin, and Best and Taylor, have given cautious, nonspecific conclusions.

There seems to be no valid evidence to refute the statements of Root and Brugel that diabetic acidosis does not exist without ketosis. Exhaustive search of the literature has failed to disclose even one case of unquestionable diabetic acidosis in which blood ketone concentration was shown to be normal.

In 1938, Schneider and Droller concluded from their own experimental work in giving sodium acetoacetate to rabbits by intravenous infusion that "diabetic coma is due in the main to a specific intoxication by the acetoacetic anion." This conclusion seems surprising in view of the disagreement that existed up to that time. An attempt was therefore made to repeat their experiments.

EXPERIMENTAL OBSERVATIONS

Schneider and Droller performed their experiments on rabbits using constant intravenous infusions and obtained blood samples for quantitative ketone analysis at the onset of signs of severe abnormality in the animal. Using the sodium salt of acetoacetic acid in isotonic concentration, they gave up to 400 cc. in one hour to each of four rabbits. No abnormalities were noted so that blood ketone analyses were not performed. They believed they were not giving "sufficient" sodium acetoacetate so they used a solution 0.4 normal—which is about 2½ times hypertonic with blood—and they produced coma readily in each of five rabbits, using quantities up to 175 cc. over similar time intervals. When one reduces their figures to grams of acetoacetate given, it is found that they gave

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as high as 5.9 grams in a one-hour period in isotonic concentration without producing apparent abnormalities, yet four rabbits given less than 5.9 grams went into coma when it was given in a hypertonic solution. There is strong reason to suspect, therefore, that the results obtained may be artefacts of the concentrations used rather than the total dosage per unit of time of the specific agent used.

Our experiment was as follows: Infusions were made into an ear vein of rabbits at a constant rate by the Schneider and Droller technic. Table 1 shows representative data. It can be seen that the volume of the solution injected was apparently not an important factor. In a control experiment one rabbit tolerated 540 cc. of isotonic saline over a period of 175 minutes without abnormal signs becoming apparent. This amount was probably over three times the blood volume of that rabbit. Large amounts of acetone were toxic, but the blood acetone concentration had to be very much higher than that found in diabetic acidosis to produce abnormalities. Rabbits given isotonic solutions of sodium acetoacetate showed no abnormalities even though high blood levels were reached. Four rabbits were given hypertonic saline solution at about the same hypertonicity of the sodium acetoacetate used by Schneider and Droller and using the same quantity of fluid at a similar rate. Each of these rabbits died or went into coma.

We reach the following conclusions from these experimental observations:

1. Hyperketonemia can be produced in rabbits in the range found in human diabetic acidosis and maintained for several hours without apparent toxic effects upon the animal.

2. Hypertonic saline solution of about three times the tonicity of plasma can cause death in rabbits when injected intravenously. Death is apparently the result of the hypertonicity itself and not the volume of fluid injected, the rate of the infusion, or the amount of sodium chloride given.

3. The toxicity noted in the experiments performed by Schneider and Droller was apparently the result of or greatly influenced by the hypertonicity of the solution injected and not necessarily the result of the specific agent or quantity of agent infused. This casts definite doubt on the validity of their conclusions.

CLINICAL OBSERVATIONS

The data obtained on 42 patients in severe diabetic acidosis who were studied at the Philadelphia General Hospital showed only limited correlation between the blood ketone concentration and the mental state before and during therapy (Tables 2 and 3). There was great individual variation. One patient with a normal mental state had a blood ketone concentration higher than the average of the group that was totally unresponsive and higher than any patient who was

TABLE 1 THE EFFECTS OF INTRAVENOUS INFUSIONS IN RABBITS

Solution Infused		Quantity Infused (ml.)	Duration of Infusion (min.)	Blood Total Ketone Concentration as Acetone* (mg. %)	Results
Saline	0.85%	540	175		Normal
Saline	2.10%	280	85		Coma at 78 min.
Acetone	1.74%†	120	44	175.9 at 50 min.	Coma at 44 min., full recovery
Sodium Aceto-Acetate	1.51%‡	150	85	63.0 at 85 min.	Normal

*Total ketone concentrations listed above are comprised almost entirely of the single agent infused. These quantities represent concentrations of the agent in excess of those generally found in human diabetic acidosis
† The value for this item in molarity is 0.3M.
‡ The value for this item in normality is 0.14N.

TABLE 2 THE RELATIONSHIP BETWEEN MENTAL STATE AND BLOOD KETONE CONCENTRATION BEFORE THERAPY

Mental State*	Number of Patients in Group	Mean Blood Total Ketone Concentration, Expressed as Acetone (mg. %)	Standard Deviation	Range	
				High	Low
1	11	60.1	26.9	123.0	34.9
2	13	73.4	24.4	111.8	25.8
3	7	85.0	35.6	117.0	21.0
4	11	109.8	37.4	154.0	47.7

*The mental state is described as follows: 1. normal; 2. lethargic; 3. unconscious, responds to painful stimuli, reflexes intact; 4. unconscious, no response to painful stimuli, reflexes absent

TABLE 3 THE RELATIONSHIP BETWEEN MENTAL STATE AND BLOOD KETONE CONCENTRATION DURING THERAPY

Patient	Interval after Onset of Therapy (hrs.)	Mental State	Blood Total Ketone Concentration, Expressed as Acetone (mg. %)
M. P.	0	1	123.0
	12	2	46.4
A. R.	0	2	80.0
	3¼	2	59.6
	8½	2	25.2
	18	2	2.8
A. M.	0	3	53.3
	3	2	72.0
	9	2	59.0
	22	2	19.0
	27	3	18.1

*Mental state is described as follows: 1. normal; 2. lethargic; 3. unconscious, responds to painful stimuli, reflexes intact

in coma with reflexes still intact. One unconscious patient had a blood ketone concentration lower than the average of the group that was normal mentally.

Follow-up data were obtained during therapy of 14 patients in an attempt to relate the changes of mental state to the blood ketone concentration after treatment was started. In 11 patients, the trend of the blood ketone concentration was toward normal as were all the metabolic abnormalities in the patients who recovered. The blood ketone change did not correlate well with the mental state in many cases. The condition of one patient appeared to be improving clinically when the blood ketone concentration rose, and then deteriorated when the blood ketone concentration decreased. Shortly before death the patient again lapsed into coma though the ketone concentration was at its lowest recorded level.

SUMMARY

There is essential agreement that all ketone bodies can cause toxic effects if given in large dosages. The question as to whether they are toxic in the concentrations found in the blood of patients in diabetic acidosis is still not definitely answered. Duration of exposure to ketosis may be as important a factor as the degree of hyperketonemia. A similar situation in regard to ether administration is well known. The fact that ketosis is an absolutely constant finding in diabetic acidosis points naturally to a strong relationship between them. But even though individual response to drugs varies greatly, if the ketone bodies themselves are the dominant factor in the production of diabetic coma, then some reasonable correlation should exist between the blood ketone concentration and the mental state. All observers agree that there is a correlation on the average, but with tremendous overlap; and in all of the reports on animal experimentation, there is poor correlation of the blood ketone concentration to the appearance of the animal. Even if there were good evidence of ketone toxicity, and even if there were good correlation of the mental state and blood ketone concentrations, the fact that a substance *can* be toxic does not necessarily mean that it *is* the cause of a particular clinical syndrome.

CONCLUSIONS

1. Acidosis per se does not seem to be the main cause of diabetic coma, though it probably plays an important role in the production of some symptoms.

2. It is very unlikely that the ketone bodies are the primary cause of diabetic coma. It seems more reasonable to view their presence as an indicator of the metabolic derangements without particular toxicity in themselves, just as the blood urea is a non-toxic indicator of uremia.

3. It has been shown frequently that many factors must contribute to the clinical appearance and prognosis of the patient in diabetic acidosis. These probably include the severity of the diabetes, the age and general health of the patient, the degree and duration of acidosis and ketosis, the serum potassium concentration, the existing complications, and so on.

4. It is possible that there is a potent factor as yet unknown that may be the dominant feature of diabetic coma.

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DISCUSSION

DR. EDWARD S. DILLON *(Philadelphia, Pa.):* We have been interested for many years in the reasons why diabetic patients, receiving inadequate treatment, go into coma and die. We clinicians are well aware that many complex chemical and physiological abnormalities appear, but in our thinking we are likely to consider these abnormalities the result of acidosis and particularly ketone acidosis.

Is death due directly to the acidosis per se? Years ago, in studying 268 coma cases, we found that the prognosis was not closely related to the degree of acidosis as measured by the carbon dioxide combining power. Furthermore, if the acidosis itself is the killing factor, why is it that alkali therapy does not play a larger and more effective role in the treatment?

Many of us are apt to feel that the acidosis is particularly noxious because it is a ketone acidosis, and that the hyperketonemia is the cause of death. The experimental data in the literature are confusing; the fact, which Dr. Fisher points out, that ketone bodies cause death only when given in hypertonic solution has not previously been pointed out, so far as I know.

Please note that in the clinical studies on 42 patients there was little correlation of the outcome with the degree of hyperketonemia.

The best correlation in any studies at our hospital was in connection with the oxygen uptake in the brain; this work done by Kety was reported at this meeting three years ago. He found that the normal oxygen consumption in the brain was 3.5 cc. per 100 gm. of brain per minute, and whenever it fell to 2.1 cc. unconsciousness invariably resulted. What does this low consumption of oxygen represent? Is it a matter of phosphorylation going on within the brain? Perhaps that is the answer. I do not know.

DR. SAMUEL SOSKIN *(Chicago, Ill.):* I think most workers will agree that there is nothing peculiarly toxic about the ketone bodies. They are just about as toxic as any other acid that produces a similar acid-base disturbance. We should not forget the work of Woodyatt and his group in the early twenties; they attempted to produce a disturbance of acid-base balance in animals with hydrochloric acid, and by and large got about the same clinical results.

On the other hand, we should clearly understand what is meant by the statement that the ketone bodies are not a specific and direct cause of diabetic coma. The fact is that there is no single cause of coma. It is the end result of a combination of circumstances or chain of events, but certainly the initiating incident is the over-production of the organic acids. Once that begins, it is not long before the loss of fluid and salt begins to introduce a shock-like state into the picture, not very much different from surgical shock. After all, people do die from surgical or traumatic shock, even when diabetes and ketone bodies are not involved.

I believe that a third factor, which enters the picture a little later, is liver failure. Diabetic dogs from which insulin is withheld develop their maximum ketosis on about the third or fourth day. From that point on to about the seventh or eighth day, when they usually die in coma, the ketone bodies fall. That is, as the animal deteriorates, he has less and less ketone bodies in the blood and urine. The same is true of other types of experimental diabetes as well as that following pancreatectomy. Biopsy of the liver of such an animal at the time when the ketones are falling but the clinical state of the animal is getting worse, or postmortem examination, reveals that the liver is a mass of fat; it is hard to distinguish any normal architecture. Indeed, if you produced that degree of liver damage by any other means, you would expect the animal to die.

So I may summarize by saying that there is a chain of events in which the final result cannot be ascribed merely to the presence of ketone bodies. Therefore, you cannot expect to find any correlation between the level of ketone bodies and the state of the patient. There is first, acidosis; second, shock; and finally, liver failure.