Diurnal Rhythm in Severe Diabetes Mellitus

The Significance of Harmoniously Timed Insulin Treatment

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In 1928, my attention was aroused by the behavior of the blood sugar and sugar excretion in a diabetic patient.[1] It was noted that the alimentary hyperglycemia almost disappeared, and that the blood sugar gradually dropped to a low level, about noon, even though food was given to the patient. To study this phenomenon more closely, a series of clinical experiments was carried out with diabetics and normal subjects receiving the same food and living under identical experimental conditions.[2] In this study as in the first case, the diurnal variations both of the glucosemia and of the glucosuria were observed to coincide more or less distinctly. Since the diurnal variations of the blood sugar coincided with those of the urine sugar, it was evident that a correct picture of the diurnal rhythm might emanate from observation of the urine sugar only.[3]

On the basis of these studies, during the first year I used a method of insulin treatment based on the diurnal variations of the urine sugar excretion.[4]

CHANGES IN EXCRETION OF KETONE BODIES

In the early phase of these studies, it was observed that the insulin treatment was sometimes not quite satisfactory, especially in cases of severe diabetes with acidosis. My attention was attracted by the behaviour of the ketone bodies, in particular by the excretion of beta-hydroxybutyric acid.[5] It was found that with unchanged food intake and decreasing insulin dosage the sugar excretion remains fairly stable, while there is a rapid rise in the excretion of beta-hydroxybutyric acid.[6] It was also noted that on fasting days without insulin, there occurred a rhythmical excretion of beta-hydroxybutyric acid, which did not coincide with the urine and blood sugar variations.[7]

The above evidence tends to show how important it is to examine every diabetic as an individual case, and to analyse this case in detail if the treatment is to be successful. The knowledge of whether or not ketone bodies are formed in a given case is essential, as is precise information as to the variations in the excretion of acids and sugar in conformity with the diurnal rhythm. If there is ketone body formation, it is also important to appraise the ammonia-forming capacity of the kidneys, as this is instrumental to the protective mechanism against acidosis and coma. If the ratio of beta-oxybutyric acid to ammonia is higher than one, the case should be considered very grave with impending danger of coma.

CLASSIFICATION OF CASES

At present, I analyse the diabetic state in patients according to the above principles. When the diabetic state is studied with such analyses, three separate types of diabetes can be differentiated, namely: (1) Diabetes characterized by ketone body excretion and sufficient ammonia formation. In these cases there is no impending danger of coma. I have termed this form *Type* A (2) Diabetes with ketone body excretion and poor ammonia formation. This is a grave type, and if insulin treatment is *not* instituted, coma will rapidly ensue. This is my *Type* O, meaning no day without insulin. (3) Diabetes without ketone body excretion. This is a mild form; there is no danger of coma. I name this form *Type* B.

The following three figures show graphs based on the average of 25 cases of different types of diabetes. The cases were selected at random and demonstrate the characteristic phenomena. Figure 1 relates to Type A. It will be seen that on a fasting day the urine sugar shows rhythmical variations, but its amount decreases gradually. The beta-oxybutyric acid excretion is not lessened and subject to marked rhythmical variations. Sufficient ammonia is being formed. The blood sugar shows no signs of rhythm. Food intake produces a rise in the urine sugar excretion, whereas ammonia and beta-hydroxybutyric acid are eliminated in unchanged amounts.

Figure 2 relates to Type O. The rhythmical variations

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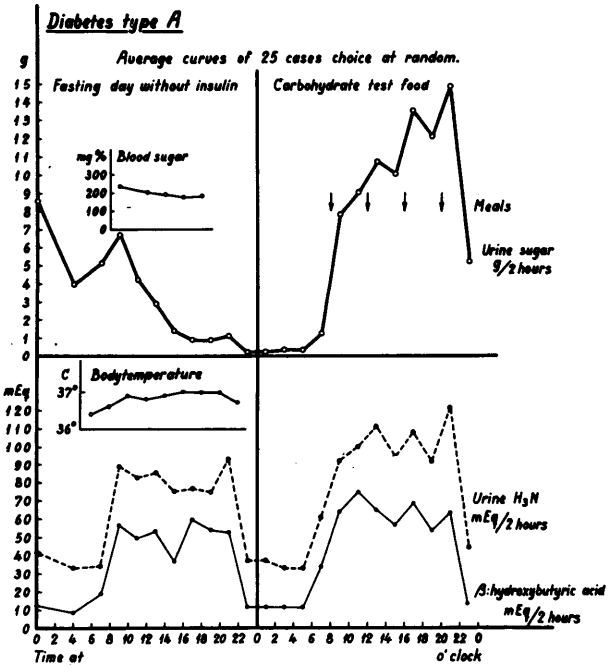

FIGURE 1. Average curves of 25 cases of diabetes TYPE A, selected at random. Diabetes with ketone body formation and satisfactory ammonia production.

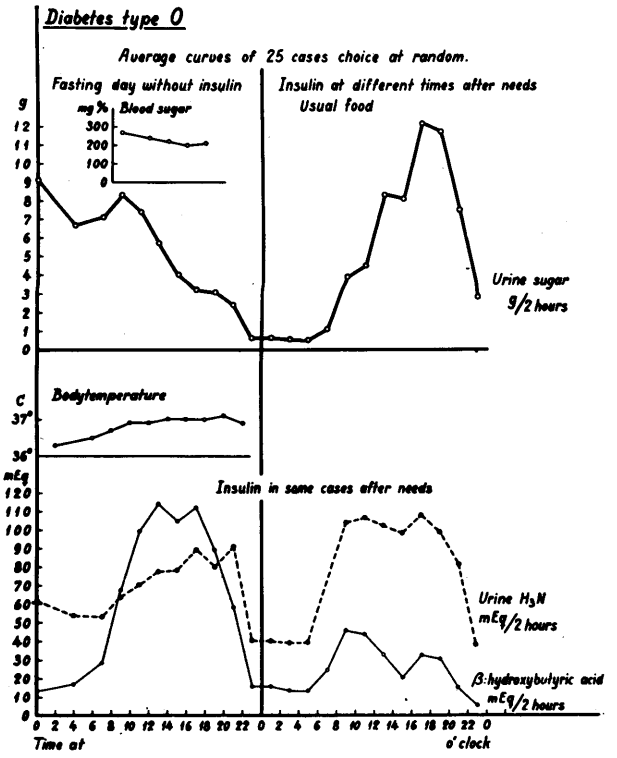

FIGURE 2. Average curves of 25 cases of diabetes TYPE O, selected at random. Diabetes with ketone body formation and poor ammonia formation.

of sugar and beta-hydroxybutyric acid appear to be the same as in Type A. Ammonia formation is here poor. There is grave danger of precoma, and *insulin must be given immediately.* It will repress the excretion of beta-oxybutyric acid and remove the danger of coma. The sugar excretion rises when food is given.

Figure 3 represents Type B. There is no excretion of beta-hydroxybutyric acid. The sugar excretion ceases on fasting days but returns when food is taken. The diurnal rhythm of the sugar excretion is well marked. The body temperature shows a rhythm similar to that of the sugar excretion.

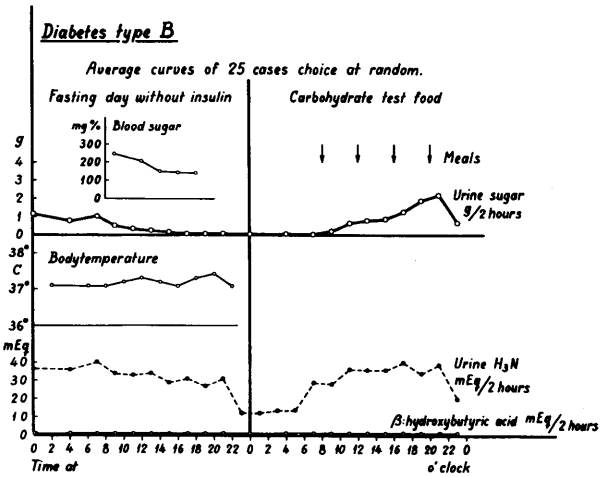

FIGURE 3. Average curves of 25 cases of diabetes TYPE B, selected at random. Diabetes without formation of ketone bodies.

During the last twenty years I have studied roughly 4,000 cases of diabetes and analysed them according to the above principles, that is, grouping them in the three groups described in the foregoing. I was interested in the incidence rates of the separate types at different ages. A statistical analysis was made of 2,116 cases. (Figure 4.) This study disclosed that Type O is frequent in childhood, while there are only a few cases in old age. The opposite is true as regards Type B; it is most common in the aged, and there are few cases among children. Type A lacks a characteristic age distribution.

CASE REPORT

Lastly I should like to give an example and to illustrate the practical application of this method of treating diabetes.

The patient was a woman, aged 46, who had had diabetes since the age of 43. For 2 years she had been

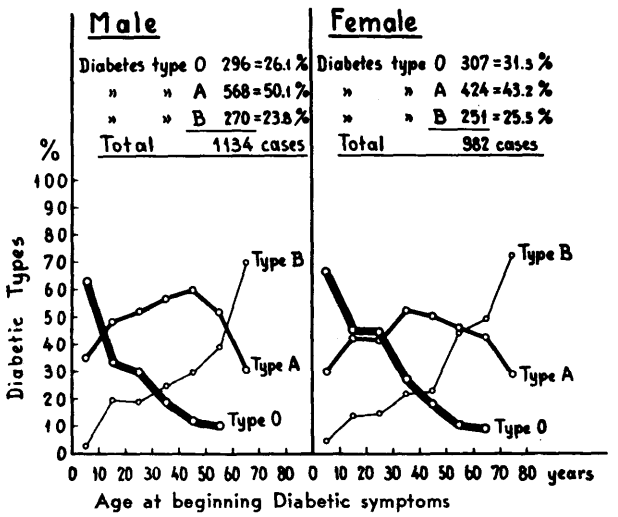

FIGURE 4. Incidences of the separate diabetes types within different age groups (age at the onset of disease).

treated with a mixture of zinc protamine and ordinary insulin, later retard insulin, *once* a day. In these years she had frequent hypoglycemic reactions but if the insulin dosage was decreased there was a tendency to acidosis. The first examination failed to disclose excretion of beta-hydroxybutyric acid. When the amount of insulin was reduced, a periodic excretion of beta-hydroxybutyric acid was found to commence. This observation is shown in Figure 5. The graph illustrates the diurnal rhythm of the beta-hydroxybutyric acid excretion, and *once this rhythm was known, correction of the treatment was easy.* The insulin administration was adapted to the rhythmical excretion of beta-hydroxybutyric acid, and two days after institution of the harmoniously timed insulin treatment, the diabetes was under perfect control. In the following days, the amount of insulin was adjusted to the needs of her normal diet and life. A few days after institution of the harmoniously timed insulin treatment, a remarkable general recovery was noted, and the patient no longer complained of lassitude and cardiac discomfort, from which she had suffered earlier. Hence it is easy to follow the changes in the need of insulin by examining day and night specimens of urine and by recording the weight.[7] My studies have shown that harmoniously timed insulin treatment also has practical advantages.

Before ending this paper I should like to recall the fact that the phenomenon of diurnal rhythm is connected with the rhythmical liver function. The diurnal liver rhythm was discovered in 1927 by the Swedish histologist, Erik Forsgren.[8] Forsgren's work was confirmed and extended by the Swedish experimental histologist, Hjalmar Holmgren, who carried out fundamental investigations. I deplore the all too early death of this dear friend. For nearly 20 years we worked in close collaboration to elucidate more clearly the diurnal rhythm governing the metabolic processes in diabetes.

SUMMARY

The diurnal rhythm of carbohydrate metabolism as manifested by periodic glycogen formation in the liver as well as by the fluctuations of the blood and urinary sugar in diabetics, is also to be observed in the production and elimination of ketone bodies during fasting,

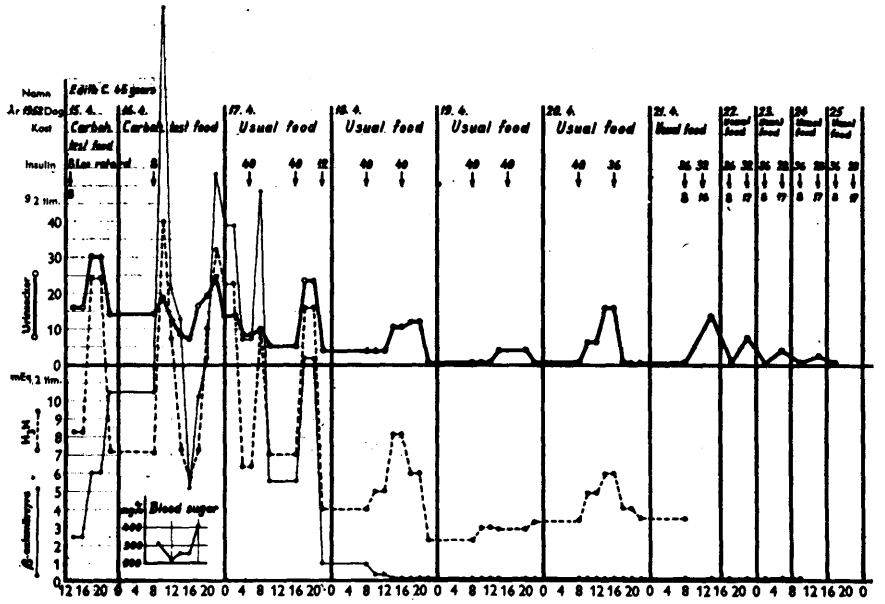

FIGURE 5. A case of severe diabetes showing the rates of urinary excretion of sugar, ammonia and beta-hydroxybutyric acid at two-hour intervals. Previous treatment (one single injection of insulin a day) disharmonious. Adaptation of a second dose of insulin to the developing wave of beta-hydroxybutyric acid resulted in harmoniously timed insulin treatment with clinical and laboratory evidence of improvement.

not paralleling the changes of glycosuria in severe cases of diabetes. To obtain a conception of the diabetic state, it is essential to know whether or not ketone bodies are formed in a given case, and whether the formation of ammonia is sufficient as a protective mechanism against acidosis and coma. Without insulin administration, three types of diabetes will be found, characterized by (a) ketone body formation with sufficient ammonia excretion during fasting; (b) no ketone body formation during fasting; and (c) ketone body formation with insufficient ammonia excretion during fasting. Individual adjustment of insulin dosage and harmonious timing of insulin injections to the waves of the periodic excretion of beta-hydroxybutyric acid are indispensable for successful treatment of severe diabetes mellitus.

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DISCUSSION

CHARLES H. BEST, M.D., (*Toronto*): In opening the discussion of Dr. Jakob Möllerström's clear presentation of the significance of harmoniously timed insulin dosage in the treatment of severe diabetes, I shall have to admit that I have probably been chosen, not because of my knowledge of this subject but because I am a friend of Doctor Möllerström. I have visited his clinic and laboratories in Stockholm and can bear witness to the devoted efforts which he has made to improve the welfare of Swedish diabetics. I am familiar with Dr. Eric Forsgren's work on the diurnal rhythm of liver function and I believe that these constitute a very interesting and real physiological problem. I did not know Doctor Forsgren personally, but I was well acquainted with Dr. Hjalmar Holmgren who did so much, along with Doctor Möllerström, to work out the details of these rhythmical changes. I had a very great respect and admiration for Doctor Holmgren and had hoped to have him spend some time in my laboratory as a Visiting Professor.

The most interesting part of Doctor Möllerström's presentation to me is the rhythmical peak in beta-hydroxybutyric acid excretion in his patients. I am informed by Dr. O. Sirek, who worked for several years with Doctor Möllerström and who is now on my staff in Toronto, that he has seen these peaks demonstrated in Doctor Möllerström's patients with great regularity and clarity. Indeed, that is what Doctor Möllerström has shown us to-day. I have gone over his data several times in Stockholm and in Toronto. As a physiologist I would, of course, like to know a lot more about the actual cause of these rhythms. I am not prepared to believe at the moment that they are caused by changes in gravitational forces or by any celestial manifestations! I feel that they merit careful biochemical and physiological study and that a simple explanation can probably be found. In the meantime, our friend Doctor Möllerström is trying to improve the treatment of diabetes by spacing his doses of insulin so that ketone body formation will be kept under control for as large a part of the day as possible. Doctor Möllerström does not use rigid dietary control in the treatment of his cases but his procedure does not come under the term "free diet." I would predict that, if we could produce a more physiological insulin which would decrease the daily sugar excretion without the threat of hypoglycemia, Doctor Möllerström would be one of the first to use it.