Original Articles

The Dawn Phenomenon, an Early Morning Glucose Rise: Implications for Diabetic Intraday Blood Glucose Variation

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Eleven insulin-dependent (type I) diabetic subjects were studied during a 24-h period to assess intraday blood glucose (BG) variation and related free insulin (FI) levels. Ten patients exhibited the dawn phenomenon, a rise in early morning fasting blood glucose (123 ± 81.1 m/dl; mean ± SD). This increase was positively and significantly correlated with the morning postprandial BG peak ($r = 0.723$; $P = 0.012$). FI/BG ratios were highest during the night (0.717 and 0.666 at 2200 and 0400 h, respectively) and lowest during the early morning (0.294 at 0800 h) ($P < 0.01$). Three of the four observed hypoglycemic episodes occurred during the period when free insulin levels were high relative to BG. We conclude that the dawn phenomenon contributed directly and significantly to the BG maximum and indirectly, in some cases, to nocturnal hypoglycemia. It thus played an important role in the intraday blood glucose variation of such patients. DIABETES CARE 4: 579–585, NOVEMBER–DECEMBER 1981.

We have previously reported a rise in morning fasting glucose levels in eight insulin-dependent diabetic subjects.[1] Interestingly, similar increments in morning fasting glucose have been detected in insulin-dependent and non-insulin-dependent diabetic patients,[2–8] but not in nondiabetic individuals.[2,9] Moreover, this glucose rise appears unrelated to food ingestion or activity for it persists after starvation,[2,4,6] alterations in feeding patterns,[5] and complete bed rest.[2]

Although the mechanism for this fasting rise in blood glucose has not yet been established, a plausible explanation for its occurrence in diabetic patients is the cortisol surge in the early morning.[1,6] However, Bright et al. found that cortisol does not account for the increase in early morning basal insulin requirements necessary to maintain euglycemia in insulin-dependent diabetes.[10] Instead of ascribing this increase in blood glucose and basal insulin requirements to any one factor, we have chosen to call it simply "the dawn phenomenon."

The purposes of this study were, first, to evaluate the contribution of the rise in early morning fasting glucose to the intraday blood glucose variation of a selected population of insulin-dependent diabetic subjects, and, second, to assess the relationship between blood glucose and free insulin variations in these patients.

MATERIALS AND METHODS

Subjects. Eleven diabetic patients were studied and all, except one (patient no. 3), were ketosis prone. All subjects were within 15% of their ideal body weight. Relevant clinical information about these patients is shown in Table 1. All patients had moderate to severe degrees of blood glucose variation, estimated by the presence of at least four of the following characteristics: (1) wide fluctuations in blood or urine glucose levels during the day, (2) marked variations in blood or urine glucose between days, (3) frequent episodes of symptomatic hypoglycemia, (4) documented hypoglycemic events, and (5) fasting hyperglycemia. In addition, repeated adjustments in insulin dosage did not improve these parameters.

Procedures. Patients were admitted for 1 day to the Pediatric Research Unit at the Johns Hopkins Hospital after informed consent was obtained. A nonthrombogenic catheter was placed in an antecubital vein and connected to a glucose monitor. A heparin lock in another vein was used for intermittent collection of blood samples for insulin determination. The monitoring periods ranged from 18½ to 27 h.

All efforts were made to maintain the same diet, timing and dosage of insulin, exercise, and hours of sleep that each patient followed before admission. A dietitian assisted the

TABLE 1
Clinical information

Patient	Sex	Age (yr)	Duration of diabetes (yr)	Percentage of ideal body weight	Insulin dose (U)
1	M	46	20	95	B 20 NPH; 10 R D 8 NPH; 4 R
2	M	25	1	100	B 12 UL; 8 SL L 6 LE D 8 SL
3	M	49	13	100	B 46 NPH
4	F	39	20	115	B 46 NPH
5	M	17	1	100	B 10 UL; 6 LE L 6 SL D 8 SL; 6 LE
6	M	12	8	85	B 7 R; 12 LE D 4 LE
7	F	65	25	95	B 12 UL; 6 SL L 8 LE D 6 SL S 6 SL
8	M	14	5	85	B 16 LE; 6 SL D 4 LE; 6 SL
9	M	20	4	100	B 14 UL; 10 LE; 10 SL D 8 LE; 8 SL
10	F	62	40	100	B 8 NPH; 6 R D 4 NPH; 6 R
11	M	36	16	95	B 36 NPH D 12 NPH

B = breakfast; L = lunch; D = dinner; S = bedtime snack; NPH = isophane; R = regular; LE = lente; SL = semilente; UL = ultralente.

patients in selecting meals that contained, as closely as possible, the patient's usual food intake. Each of the three main meals contained a similar carbohydrate content. Treadmill exercise was used to simulate the patient's daily activities. A complete description of the protocol followed during these studies has been reported.[1]

Blood glucose levels were continuously measured using a system developed by A. and D. Kowarski, as previously reported.[1] The fasting ascending segment of the morning blood glucose excursion (FAGE) was calculated as follows: the glucose nadir between 2400 and 0600 h was subtracted from the glucose value reached immediately before breakfast (at about 0800 h).

Blood glucose control was assessed by the mean blood glucose (MBG) level and by parameters of intraday blood glucose variation. MBG was calculated as the arithmetic mean of half-hourly blood glucose values during a 24-h period. Intraday blood glucose variation was assessed in two ways: the mean amplitude of glycemic excursion (MAGE) and the coefficient of variation (CV). MAGE is defined as "the arithmetic mean of the blood glucose increases or decreases (from blood glucose nadirs to peaks or vice versa) when both ascending and descending segments exceeded the value of one standard deviation of the blood glucose for the same 24 hour period" (ref. 11, appendix). CV was calculated by dividing the standard deviations of the half-hourly blood glucoses by their mean (MBG), and multiplying by 100.

Free insulin was measured by double-antibody radioimmunoassay[12] after polyethylene glycol precipitation, as described by Kuzuya et al.[13] The Wilcoxon's signed rank test was used to compare mean ratios of paired samples of free insulin/blood glucose (FI/BG). Pearson's product-moment correlation coefficients were calculated between variables. Critical values were set at $\alpha = 0.05$ unless otherwise specified. For multiple comparisons, Bonferroni's approach was used ($\alpha = 0.05$/number of all possible comparisons).[14]

RESULTS

Figure 1 illustrates values for the mean and standard error of the mean for the half-hourly blood glucose values of the 11 diabetic subjects studied. As demonstrated by this graph, glycemic excursions occurred during four periods: morning, afternoon, evening, and night, associated, respectively, with ingestion of breakfast, lunch, dinner, and the bedtime snack. The latter two, it should be noted, were relatively small when compared with the former two. Figure 1 demonstrates three findings of importance: first, the relatively large fasting component of the ascending segment of the morning glucose excursion;

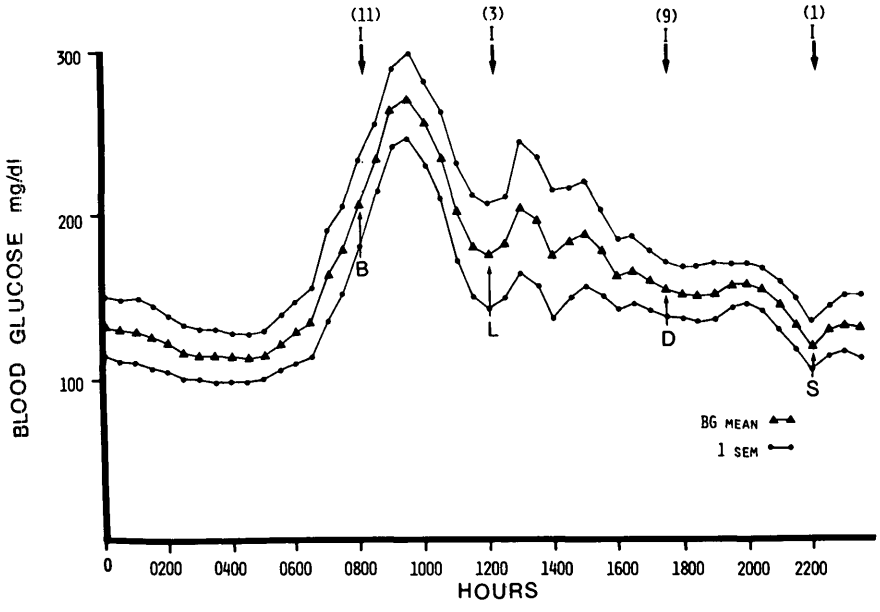

FIG. 1. Mean and SEM of half-hourly blood glucoses of 11 patients during 24 h. The numbers in parentheses indicate the number of patients taking insulin (I) at the time shown by the arrows. B, breakfast; L, lunch; D, dinner; and S, bedtime snack.

second, the midmorning occurrence of the daily blood glucose maximum; and, third, a nighttime occurrence of the daily blood glucose minimum.

A fasting ascending segment of morning excursion (FAGE) was noted in 10 of the individual patient's blood glucose tracings. The mean starting time of FAGE in these 10 patients was at 0500 h (range 0300–0730 h). The mean of FAGE in the 11 patients was 123 ± 81.1 mg/dl (mean ± SD), with values ranging from 0 to 276 mg/dl (Table 2). [This mean of FAGE values is larger than the fasting component of the ascending segment of the morning excursion noted in Figure 1 (94 mg/dl) because the two values were calculated by different methods. The latter (Figure 1) was calculated as the rise in the mean half-hourly blood glucose values, while the former (Table 2) was determined as the mean of the rise taken directly from individual patient's continuous blood glucose tracings.]

Table 2 also includes the mean blood glucose (MBG), the coefficient of variation (CV), and the mean amplitude of glycemic excursions (MAGE) for individual patients. When assessed by the magnitude of their standard deviations, the MBG varied less than the other parameters of blood glucose control in our subjects. Each patient's maximum and minimum blood glucose values, as well as the times of the four hypoglycemic events documented during the monitoring period, are also shown in Table 2. The latter are included to

TABLE 2
Parameters of blood glucose control during 24-h continuous glucose monitoring

Patient	Fasting ascending glucose excursion (FAGE)* (mg/dl)	Mean blood glucose (MBG)* (mg/dl)	Coefficient of variation (CV)*	Mean amplitude of glycemic excursion (MAGE)* (mg/dl)	Blood glucose maximum (mg/dl)	Blood glucose minimum (mg/dl)
1	210	144	60	240	330	47 (2200)†
2	65	143	26	81	203	68
3	276	166	49	245	432	72
4	110	161	36	128	336	47 (1900)†
5	60	149	42	188	308	85
6	126	197	43	126	361	85
7	170	225	68	360	445	61
8	192	165	30	137	330	71
9	44	123	36	101	190	38 (0600)†
10	103	195	25	184	290	105
11	0	112	49	102	240	32 (0200)†
Mean	123	162	42.2	172	315	64.6
SD	81.1	33.4	13.6	83.2	82.5	22.3

* See METHODS for description of calculations.
† Time of onset of hypoglycemia (h).

allow assessment of the association between the timing of the hypoglycemic episodes and the magnitude of FAGE. Note that the patients with the two lowest values of FAGE had hypoglycemia late in the night (0200 h) or early in the morning (0600 h).

The second major finding observed in Figure 1 is the mid-morning occurrence of the maximum blood glucose level (272 ± 26.0 mg/dl, mean ± SEM) based on the mean of half-hourly blood glucose values in the 11 patients. This maximum occurred at 0930 h. To assess the influence of FAGE on this daily maximum, we performed a regression of FAGE on individual postbreakfast glucose peaks. This yielded a correlation coefficient of $r = 0.723$ ($P = 0.012$).

The third finding illustrated in Figure 1 is the nighttime occurrence of the minimum blood glucose value. Although the day's discrete minimum (113 ± 15.2 mg/dl, mean ± SEM) occurred at 0400 h, more important, mean glucose achieved a plateau of minimum values between 0230 and 0500 h (range 113.4–117.7 mg/dl). Two of the four hypoglycemic episodes were detected just before or immediately after this plateau. The two remaining episodes occurred at about 1900 and 2300 h.

To determine the time of the day when blood glucose values best correlate with instability, we assessed the association between half-hourly blood glucose values and two measures of diabetic instability, CV and MAGE. Figure 2 illustrates that the highest positive correlations were found between 0900 and 1600 h for CV and 0900 and 1800 h for MAGE, periods that spanned the postbreakfast and postlunch peaks. The largest negative correlations, on the other hand, were found during the evening for both CV and MAGE. (Because each blood glucose correlated with CV and MAGE is itself included in the calculation of the two latter parameters of instability, we recalculated CV, using the following procedure: for each patient 48 different CVs were calculated, each one excluding one blood glucose value at a time. Only the calculated CV that did not include the particular blood glucose was correlated with its respective blood glucose value. Correlations so obtained were very similar to the original ones.)

To compare the availability of free insulin with blood glucose levels, we calculated the ratio of free insulin to blood glucose (FI/BG) before each meal and at 0400 h (Figure 3). Examined this way, mean FI/BG reached its nadir at 0800 h (0.294), while its highest values occurred during the night period, that is, at 2200 (0.717) and 0400 h (0.666). The differences between the mean of the FI/BG ratio at 0800 h and those of 2200 and 0400 h were statistically significant ($P < 0.01$ in both cases; Wilcoxon's signed rank test for paired samples; $\alpha = 0.05/5 = 0.01$).

DISCUSSION

Although much progress has been achieved in the quantification of diabetic instability,[11,15,16] its cause remains a matter of debate and uncertainty. Because unstable diabetic patients tend to have a total lack of endogenous insulin,[17–19] they are more susceptible to the effects of hyperglycemic factors, and identification of such factors is of prime importance. Hypoglycemia, with a consequent rebound in blood glucose, has been suggested as a possible hyperglycemic factor.[20–23] However, hormonal or metabolic factors other than hypoglycemia must play important roles since measures of blood glucose control, taken over a 48-h period, were not worsened by the occurrence of hypoglycemia in unstable diabetic patients.[24] The present study focuses on the effect of one hyperglycemic factor or cluster of factors (which we have chosen to call the dawn phenomenon) on the intraday variation of blood glucose in type I diabetic patients.

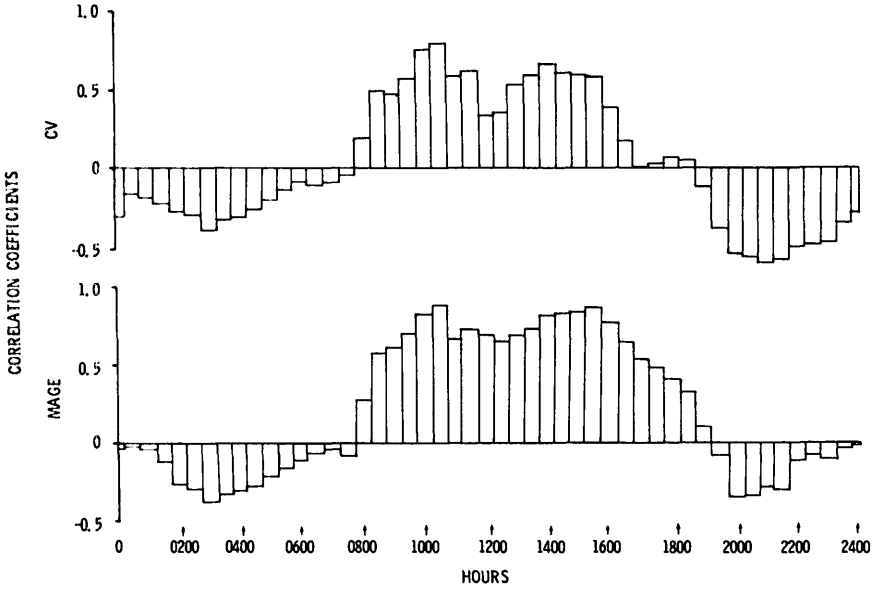

FIG. 2. Correlation coefficients of MAGE and CV with half-hourly blood glucoses during 24 h. CVs were recalculated excluding one blood glucose value at a time. Only the CV not containing that particular blood glucose was correlated with the respective blood glucose. See RESULTS for detailed explanation.

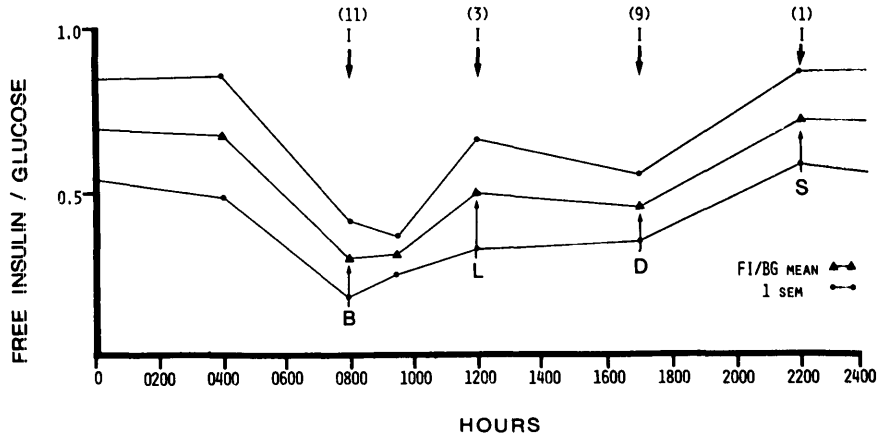

FIG. 3. Mean and SEM of ratios of free insulin/blood glucose at six different times during 24 h. Symbols are defined in Figure 1.

Why did our patients tend to have their daily blood glucose maxima in midmorning despite wide variations in their exercise, food ingestion, and schedules of insulin injection? Carbohydrate ingestion at breakfast contributes to this postprandial peak, but the carbohydrate content of all three main meals was similar in our study.[1] Thus, the carbohydrate intake during breakfast cannot alone explain the peak. Instead, the following evidence indicates that the postbreakfast peak is predominantly dependent on the dawn phenomenon. First, simple inspection of Figure 1 shows that FAGE contributes more than half of the ascending segment of the day's largest glucose excursion. This fasting glucose increment also exceeds the lunch postprandial rise in blood glucose values. Second, the individual values of FAGE correlated positively and significantly with the individual postbreakfast glucose peaks.

FI/BG ratios demonstrate that the least insulin available for a particular blood glucose was at 0800 h. By and large, the diverse insulin schedules used by our patients were unable to provide adequate insulin levels during the dawn phenomenon. Large values of FAGE and large postbreakfast blood glucose peaks resulted. It should be stressed that others have reported a fasting early morning rise in glucose and a midmorning peak of blood glucose in both insulin-dependent and non-insulin-dependent diabetic patients.[2,8]

Why did our patients tend to have their daily blood glucose nadir at night? Why did three of the four hypolycemic episodes occur between 2300 and 0600 h? FI/BG ratios show that insulin availability was greatest at 0400 and 2200 h. High nocturnal ratios suggest excessive insulin administration, predisposing to nocturnal hypoglycemia. This excess probably represents attempts by the physician to provide adequate amounts of insulin to counteract morning hyperglycemia, which, in our patients, was predominantly the result of the dawn phenomenon. In fact, the two patients (nos. 9 and 11) with the lowest values of FAGE both exhibited nocturnal hypoglycemia. This tendency toward hypoglycemia during the night period is not a finding peculiar to our study population. A recent report emphasized that nocturnal hypoglycemia is a common finding among insulin-treated diabetic patients.[25]

In summary, two undesirable effects may result from the practice of administering more insulin during the previous day in an effort to counteract morning hyperglycemia: (1) failure to suppress the morning hyperglycemia and (2) reduction of nocturnal blood glucose, not infrequently to hypoglycemic values. This analysis of the effect of treatment is based on the assumption that free insulin originated predominantly from exogenous administration. This assumption seems reasonable since all but one of our patients were insulin dependent and clinically very unstable (only patient no. 3 was not ketosis prone).

Our data suggest that the dawn phenomenon contributed importantly to the intraday blood glucose variation of our patients. Two measures of intraday diabetic instability, CV and MAGE, correlated strongly with high blood glucose values during the morning and, to a lesser extent, with low blood glucose values during the evening and night period. These findings are not surprising, as maxima and minima are two major components of intraday blood glucose variation. The glucose maxima were predominantly dependent on FAGE and the glucose minima were associated with high FI/BG ratios, which could have resulted from excessive insulin administration aimed to counteract the dawn phenomenon.

Appropriate levels of insulin and normoglycemia may be achieved by continuous insulin infusion techniques during the dawn phenomenon.[26–28] Whether adequate levels of insulin can be reached during this period by means of subcutaneous injection of insulin, without increasing the risk of nocturnal hypoglycemia, remains to be demonstrated. Some investigators have suggested an earlier injection of insulin in the morning (0500–0600 h) and others have recommended a late evening injection of intermediate-acting insulin (2200–2300 h).[2,4,29–32] We are currently involved in the planning and implementation of a randomized, double-blind clinical trial to compare the efficacy of different chronotherapeutic approaches in the treatment of the dawn phenomenon in insulin-dependent diabetes.

As already mentioned, several independent investigators[1–8] have previously reported an early morning rise in levels of blood glucose. Nonetheless, it is not yet a well-recognized entity. This study places the dawn phenomenon

within a new conceptual framework with regard to its relationship to intraday blood glucose variation. The consistency of the dawn phenomenon in our patients, despite variations in their parameters of daily living and diabetic therapy, attests to its importance for a large fraction of type I diabetic patients. However, because of the possibility of selection bias in our sample, these findings cannot yet be generalized to the total population of type I diabetic patients.

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REFERENCES

[1] Schmidt, M. I., Hadji-Georgopoulos, A., Rendell, M., Margolis, S., Kowarski, D., and Kowarski, A.: Fasting hyperglycemia and associated free insulin and cortisol changes in "Somogyi-like" patients. Diabetes Care *2*: 457–64, 1979.

[2] Hathlehol, R.: Blood sugar studies: with special regard to threshold of glycosuria in diabetes mellitus and benign chronic glycosuria. Acta Med. Scand. Suppl. *8*: 1–260, 1924.

[3] Mollenstrom, J.: The treatment of diabetes with reference to the endogenous periodicity of the carbohydrate metabolism. Acta Med. Scand. Suppl. *59*: 145–61, 1934.

[4] Hopmann, R.: Insulinbehundlung unter Berucksichtigund des 24-Stunden-Rhythmus des Diabetes Mellius. Acta Med. Scand. Suppl. *108*: 143–55, 1940.

[5] Izzo, J. L.: Diurnal (24 hour) rhythm in diabetes mellitus; diurnal variations in levels of glucose in blood and urine. Proc. Am. Diabetes A 9: 247–73, 1949.

[6] Faiman, C., and Moorhouse, J. A.: Diurnal variation in the levels of glucose and related substances in healthy and diabetic subjects during starvation. Clin. Sci. *32*: 111–26, 1967.

[7] Gale, E. A. M., Kurtz, A. B., and Tattersall, R. B.: In search of the Somogyi effect. Lancet *2*: 279–82, 1980.

[8] Gerritzen, F.: The 24-hours rhythm in diabetes. Acta Med. Scand. *111*: 212–18, 1942.

[9] Malherbe, C., Gaspara, M. de, Hertosh, R. de, and Hoet, J. J.: Circadian variations of blood sugar and plasma insulin levels in man. Diabetologia *5*: 397–404, 1969.

[10] Bright, F. M., Melton, T. W., Rogol, A. D., and Clarke, W.: Failure of cortisol blockade to inhibit early morning increases in basal insulin requirements in fasting insulin-dependent diabetics. Diabetes *29*: 662–64, 1980.

[11] Service, F. J., Molnar, G. D., Rosevear, J. W., Ackerman, E., Gatewood, L. C., and Taylor, W. F.: Mean amplitude of glycemic excursions: a measure of diabetic instabiliy. Diabetes *19*: 644–53, 1970.

[12] Morgan, C. R., and Lazarow, I.: Immunoassay of insulin two antibody system. Diabetes *12*: 115–26, 1963.

[13] Kuzuya, H., Blix, P. M., Horwitz, D. L., Steiner, D. F., and Rubenstein, A. H.: Determination of free and total insulin and C-peptide in insulin-treated diabetics. Diabetes *26*: 22–29, 1977.

[14] Harris, R. J.: A Primer of Multivariate Statistics. New York, Academic Press, 1975.

[15] Schlichtkrull, J., Munk, O., and Jersild, M.: The M-value, an index of blood-sugar control in diabetics. Acta Med. Scand. *177*: 95–102, 1965.

[16] Molnar, G. D., Taylor, W. F., and Ho, M. M.: Day-to-day variation of continuously monitored glycaemia: a further measure of diabetic instability. Diabetologia 8: 342–48, 1972.

[17] Cremer, K. E., Molnar, G. D., Taylor, W. F., Moxness, K. E., Service, F. J., Gatewood, L. C., Ackerman, E., and Rosevear, J. W.: Studies of diabetic instability. II. Tests of insulinogenic reserve with infusions of arginine, glucagon, epinephrine, and saline. Metabolism *20*: 1083–98, 1971.

[18] Reynolds, C., Molnar, G. D., Horwitz, D., Rubenstein, A. H., Taylor, W. F., and Jiang, N.: Abnormalities of endogenous glucagon and insulin in unstable diabetes. Diabetes *26*: 36–45, 1977.

[19] Shima, K., Tonaka, R., Morishita, S., Tarvi, S., Kumarhara, V., and Nishikava, M.: Studies on the etiology of "brittle diabetes." Relationship between diabetic instability and insulinogenic reserve. Diabetes *26*: 717–25, 1977.

[20] Somogyi, M.: Diabetogenic effect of hyperinsulinism. Am. J. Med. *2*: 192–98, 1959.

[21] Bloom, M. E., Mintz, D. H., and Field, J. B.: Insulin-induced posthypoglycemic hyperglycemia as a cause of "brittle" diabetes. Am. J. Med. 47: 891–903, 1969.

[22] Bruck, E., and MacGillivray, M. H.: Interaction of endogenous growth hormone, cortisol, and catecholamines with blood glucose in children with brittle diabetes mellitus. Pediatr. Res. 9: 535–41, 1975.

[23] Rosenbloom, A. L., and Giordano, B. P.: Chronic overtreatment with insulin in children and adolescents. Am. J. Dis. Child. *131*: 881–85, 1977.

[24] Molnar, G. D., Taylor, W. F., and Langworthy, A.: On measuring the adequacy of diabetes regulation: comparison of continuously monitored blood glucose patterns with values at selected time points. Diabetologia *10*: 139–43, 1974.

[25] Gale, E. A. M., and Tattersall, R. B.: Unrecognized nocturnal hypoglycemia in insulin-treated diabetics. Lancet *1*: 1049, 1979.

[26] Mirouze, J., Selam, J. L., Pham, T. C., and Covadore, D.: Evaluation of exogenous insulin homeostasis by the artificial pancreas in insulin-dependent diabetes. Diabetologia *13*: 273–78, 1977.

[27] Deckert, T., and Lorup, B.: Regulation of brittle diabetics by a planned insulin infusion programme. Diabetologia *12*: 573–79, 1976.

[28] Clarke, W., Haymond, M. W., and Santiago, J.: Overnight basal insulin requirements in fasting insulin-dependent diabetics. Diabetes *29*: 78–80, 1980.

[29] Lange, H., and Schloss, J.: Uber das Verhalten des Blutzuckers in der Nacht und den Morgenstunden. Arch. F. Exp. Pathol. U. Pharm. *139*: 274–89, 1929.

[30] Priesel, R., and Wagner, R.: Die optimale insulin verteinlung in der Behundlung des Kindlichen Diabetes Mellitus. Klin. Wochenschr. *301*, 1926.

[31] Tattersall, R., and Gale, E.: Patient self-monitoring of blood glucose and refinements of conventional insulin treatment. Am. J. Med. *70*: 177–82, 1981.

[32] Danowski, T. S., and Sunder, J. H.: Jet injection of insulin during self-monitoring of blood glucose. Diabetes Care *1*: 27–33, 1978.