Dawn Phenomenon: Its Frequency in Non-Insulin-Dependent Diabetic Patients on Conventional Therapy

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The frequency of the dawn phenomenon has been studied in non-insulin-dependent diabetic (NIDDM) patients while they continued with their conventional therapy. Plasma glucose (PG) and immunoreactive insulin (IRI) were estimated hourly from 0300 to 0900 h in 19 NIDDM patients; 9 patients were treated by diet alone (group 1), and 10 patients were treated by diet and oral hypoglycemic agents (group 2). The dawn rise of plasma glucose was demonstrated in 17 (89.5%) of the 19 patients with mean ± SE plasma glucose at 0300 h of 7.0 ± 0.5 mM and at 0800 h of 8.4 ± 0.6 ($P < .01$). IRI in all patients rose from 14.7 ± 1.3 μU/ml at 0500 h to 18.1 ± 1.8 μU/ml at 0700 h ($P < .05$). The changes in IRI levels at any time from 0300 to 0800 h in groups 1 and 2 when considered separately were insignificant. Thus, the dawn phenomenon occurs commonly in NIDDM patients taking their conventional therapy. *Diabetes Care* 10:461–65, 1987

The dawn phenomenon is a condition described in diabetic and normal subjects that is characterized by a continuous increase in fasting levels of plasma glucose, insulin requirements, or both that occurs between 0500 and 0900 h. Several alternative names have been given to this rise in blood glucose, including paradoxical glucose rise (1), early-morning glucose rise (2,3), and diurnal glucose rhythm (4). An overnight rise in blood glucose levels during fasting was noted by Hatlehol (1) as long ago as 1924, and this observation was reported by Izzo (4) in 1949. However, these findings had little influence on the management of diabetic patients, and it is only in the last few years that interest in the changes in plasma glucose during the sleeping hours has developed.

There have been many studies of these changes, but most have been in IDDM patients under situations such as conventional insulin therapy (3,5), continuous intravenous infusion (6), continuous subcutaneous insulin infusion (7–9), and a closed-loop device (10–14). In NIDDM patients, only three previous studies demonstrated the dawn phenomenon, all under unusual conditions. Patients were assessed during 4-h intervals of feeding in the first study (4), during a period of fasting for 72 h in the second (2), and while using a closed-loop device in the third (13).

The mechanisms responsible for this phenomenon have not been established. In most cases it is not a rebound hyperglycemia to nocturnal hypoglycemia (5,15). The early-morning rise of cortisol has been proposed as a possible mechanism, but metyrapone blockade (11) or dexamethasone suppression (16) did not abolish the need for increase in insulin delivery during the dawn period. A primary role for increased insulin clearance (14,17) seems unlikely because plasma insulin concentrations increase in the early morning in nondiabetic subjects (18,19) and NIDDM patients (2). Other possible causes of the dawn phenomenon, such as a relative insulin deficiency in the early morning (15) or a nocturnal surge of growth hormone (20), have been suggested. To assess the frequency of the dawn phenomenon in NIDDM patients on conventional therapy, two groups were studied from 0300 to 0900 h.

SUBJECTS AND METHODS

The subjects were 9 NIDDM patients treated by diet alone and 10 NIDDM patients treated by diet and oral hypoglycemic agents (5 on glibenclamide, 5 on chlorpropamide). Clinical information about both groups is included in Table 1. The range of glibenclamide doses was 2.5–20 mg/day, taken once or twice a day; the range of chlorpropamide doses was 100–374 mg/day once a day. The patients were selected from the general clinic population only on the basis of their

TABLE 1
Clinical details and treatment of 19 non-insulin-dependent diabetic patients

Patients	Treatment	n	Sex (F/M)	Body weight (kg)	Age (yr)	Duration of diabetes (yr)	Proteinuria	Clinical neuropathy	Retinopathy
Group 1	Diet alone	9	4/5	76.3 ± 3.9	57.9 ± 3.4	6.5 ± 1.4		1	1
Group 2	Diet + hypoglycemic agents*	10	2/8	66.7 ± 3.3	60.2 ± 2.9	10.6 ± 2.0	2		1
Total	As above	19	6/13	71.2 ± 2.7	59.1 ± 2.2	8.6 ± 1.3	2	1	2

Values for body weight, age, and duration of diabetes are means ± SE.
*100–375 mg chlorpropamide/day or 2.5–20 mg glibenclamide once or twice a day.

willingness to cooperate and entered our study if they did not have any of the exclusion criteria. The exclusion criteria were a body mass index >27.0 kg/m^2 in women or >27.5 kg/m^2 in men, a recent history of trauma, myocardial infarction, or respiratory failure or serious renal, hepatic, cardiovascular, or cerebrovascular disease. Secondary diabetes and medication that may interfere with plasma glucose (PG) and immunoreactive insulin (IRI) measurement were also exclusion criteria.

Informed consent was obtained from all patients. The usual diet and conventional therapy (where applicable) were continued during the study (last meal at 1800 h). At 2000 h an indwelling cannula was placed in the antecubital vein and kept patent with normal saline for intermittent blood sampling; hourly blood samples were taken from 0300 to 0900 h for PG and IRI. The samples were centrifuged immediately in a refrigerated centrifuge (4°C), and the plasma was stored at −20°C to be assayed by the glucose oxidase method for PG and by radioimmunoassay as described by Heding (21) for IRI. A sample for HbA_1 assessment (Boehringer chromatographic method) was taken at 0800 h. Disturbance of the patient was kept to a minimum. Breakfast and the usual medication (when applicable) were given after the 0800-h sample was taken. Statistical evaluations were performed by two-way analysis of variance and the least significant difference (LSD) test. All results were expressed as means ± SE.

RESULTS

The PG changes from 0300 to 0800 h showed a continuous rise to a maximum level at 0800 h in all 19 patients and in those on oral hypoglycemic agents (group 2) when considered separately (Figs. 1–3). For those on diet alone (group 1) a similar continuous rise in PG was found from 0300 to 0700 h, with no change in PG between 0700 and 0800 h. In group 1 the plasma glucose increased from 7.0 ± 0.7 mM at 0300 h to 7.8 ± 0.8 mM at 0700 and 0800 h ($P < .01$). In group 2 the plasma glucose increased from 7.0 ± 0.8 mM at 0300 h to 8.7 ± 0.8 mM at 0800 h ($P < .01$). When the data from both groups were pooled (19 NIDDM patients), the PG increased from 7.0 ± 0.5 mM at 0300 h to 8.4 ± 0.6 mM at 0800 h ($P < .01$).

The changes in IRI at any time from 0300 to 0800 h in groups 1 and 2 considered separately were not significant (Figs. 1 and 2), but when the groups were combined, IRI levels increased from 14.7 ± 1.3 μU/ml at 0500 h to 18.1 ± 1.8 μU/ml at 0700 h, and this reached statistical significance ($P < .05$) (Fig. 3).

The changes in the mean IRI/PG ratios at any time from

TABLE 2
Least significant difference (LSD) values and means of plasma glucose (PG), immunoreactive insulin (IRI), and IRI/PG ratios from 0300 to 0800 h in 19 non-insulin-dependent diabetic patients

Patients	0300 h	0400 h	0500 h	0600 h	0700 h	0800 h	LSD values
Group 1							
PG (mM)	7.0	7.2	7.3	7.5	7.8	7.8	0.5
IRI (μU/ml)	17.3	16.2	15.9	14.9	18.2	15.9	4.1
IRI/PG	2.5	2.3	2.2	2.1	2.5	2.2	0.7
Group 2							
PG (mM)	7.0	7.4	7.9	8.1	8.6	8.7	0.5
IRI (μU/ml)	15.8	14.8	13.7	14.9	18.0	17.0	5.2
IRI/PG	2.5	2.3	2.1	1.8	2.4	2.1	0.8
Total							
PG (mM)	7.0	7.3	7.6	7.8	8.3	8.4	0.5
IRI (μU/ml)	16.5	15.4	14.7	14.9	18.1	16.4	3.2
IRI/PG	2.5	2.3	2.1	2.1	2.5	2.1	0.5

Group treatments as in Table 1. Any rise of PG or IRI concentrations or IRI/PG ratios that exceeds the corresponding LSD value is significant at $P = .05$.

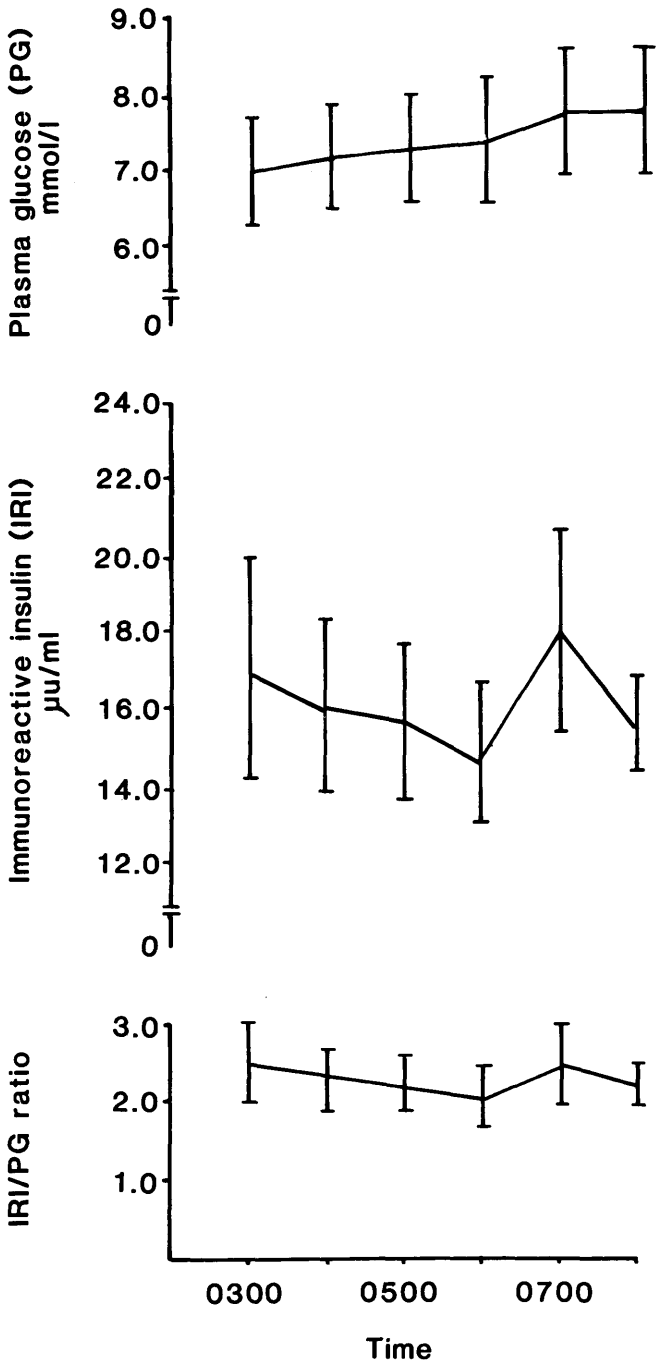

FIG. 1. Means (±SE) of plasma glucose and immunoreactive insulin concentrations and IRI/PG ratios from 0300 to 0800 h in 9 non-insulin-dependent diabetic patients on diet alone.

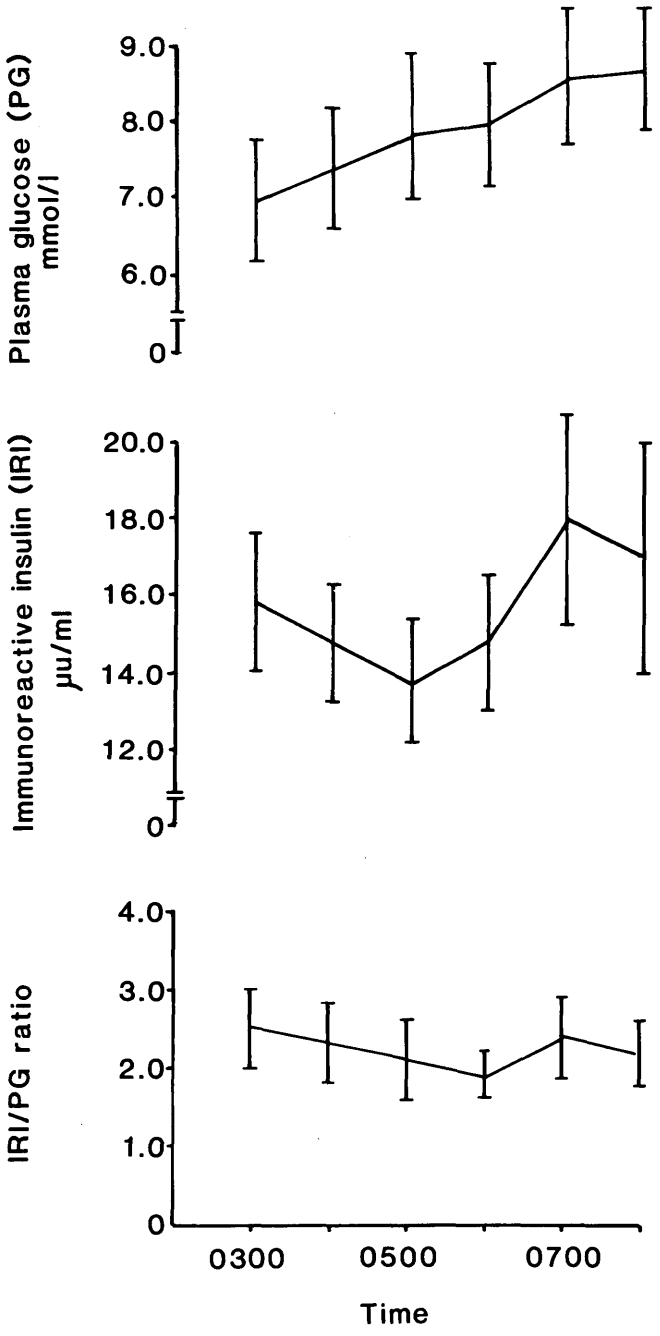

FIG. 2. Means (±SE) of plasma glucose and immunoreactive insulin concentrations and IRI/PG ratios from 0300 to 0800 h in 10 non-insulin-dependent diabetic patients treated by diet and oral hypoglycemic agents.

0300 to 0800 h in groups 1 and 2 and in all NIDDM patients together were not significant (Figs. 1–3). Table 2 illustrates the LSD values for PG, IRI, and IRI/PG ratios for all groups. Changes of the mean PG, IRI, and IRI/PG ratio at any time between 0300 and 0800 h that exceeded LSD values were considered significant at the 5% level. This confirms the significance of the changes described above. Means ± SE of HbA_1 were 8.7 ± 0.5, 9.7 ± 0.5, and 9.2 ± 0.3% for groups 1 and 2 and all NIDDM patients, respectively (normal value 6.1–7.9%).

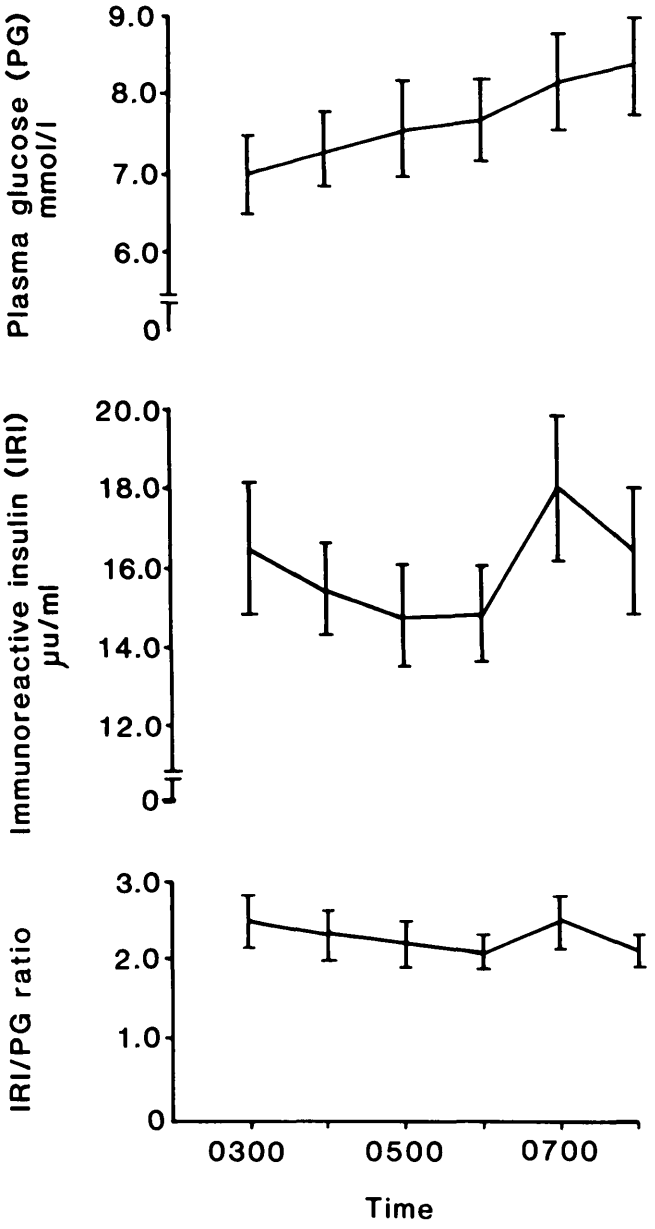

FIG. 3. Means (±SE) of plasma glucose and immunoreactive insulin concentrations and IRI/PG ratios from 0300 to 0800 h in 19 non-insulin-dependent diabetic patients (total).

DISCUSSION

Our results demonstrate that the dawn phenomenon commonly occurs in NIDDM patients on conventional therapy; this is the first time that this has been demonstrated. The reported prevalence of the dawn phenomenon has varied between 0 and 88% in patients with type I diabetes (3,4,7,9,13,14,22). There is no previous information about the prevalence of the dawn phenomenon in NIDDM patients taking their conventional therapy. The great variation in prevalence of the dawn phenomenon in IDDM patients can be at least partly explained by the lack of exact quantitative criteria for the dawn phenomenon. It may also depend on the patient population and the type of insulin therapy. If we define the dawn phenomenon as any continuous rise in early-morning (0500–0900 h) PG, then 17 (89.5%) of the 19 patients exhibited this phenomenon, with a mean rise in PG of 1.5 ± 2.0 mM. If, however, we define the dawn phenomenon as a rise in early-morning PG of >1.0 mM, then 13 (68.4%) patients demonstrated the dawn phenomenon, with a mean rise in PG of 1.8 ± 0.3 mM (Table 3).

Koivisto et al. (22) used as the criterion for the dawn phenomenon an early-morning rise of blood glucose at least twofold greater than in healthy subjects. By this definition, 16 (84.2%) of the 19 patients exhibited the dawn phenomenon. The normal physiology of early-morning PG and the magnitude of the clinically significant PG rise in diabetic patients are important factors to be considered in defining the dawn phenomenon. Neither has been fully elucidated. Conflicting results have been reported for changes in early-morning PG levels in normal controls (2,18,19,22–26), and no information is available about the magnitude of the clinically significant early-morning PG rises in diabetic patients. Therefore, we define any continuous rise in early-morning PG as being a dawn phenomenon.

In IDDM patients on conventional therapy who were ketosis prone, Schmidt et al. (3) demonstrated the dawn phenomenon in 10 (90.9%) of 11 patients. This indicates that stability and type of diabetes have no role in the cause of the dawn phenomenon but might have an influence on severity of the dawn phenomenon. Diabetic control and the type of treatment might also have a role in the severity of the dawn phenomenon. This is demonstrated in our study by the greater dawn rise of PG in NIDDM patients treated

TABLE 3
Importance of magnitude of early-morning (0500–0900 h) plasma glucose (PG) rise in determining number and percentage of non-insulin-dependent diabetic patients with dawn phenomenon

Patients	n	Patients with dawn rise of PG (n)	Patients with dawn rise of PG > 0.1 mM (n)	Patients with dawn rise of PG greater than twofold normal* (n)
Group 1	9	7 (77.7)	4 (44.4)	6 (66.6)
Group 2	10	10 (100)	9 (90.0)	10 (100)
Total	19	17 (89.5)	13 (68.4)	16 (84.2)

Group treatments as in Table 1. Numbers in parentheses are percentages.
*As described by Koivisto et al. (22).

by diet and oral hypoglycemic agents ($HbA_1 = 9.7 \pm 0.5\%$) compared with the rise in those treated by diet alone ($HbA_1 = 8.7 \pm 0.5\%$). Our study shows that the changes in the dawn period are significant in NIDDM patients and should be taken into account in assessing the overall control of their diabetes.

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REFERENCES

1. Hatlehol R: Paradoxical rise of the blood sugar concentrations in diabetes mellitus. *Acta Med Scand Suppl* 8:211–66, 1924
2. Faiman C, Moorhouse J: Diurnal variation in the levels of glucose and related substances in healthy and diabetic subjects during starvation. *Clin Sci* 32:111–26, 1967
3. Schmidt MI, Hadji-Georgopoulos A, Rendell M, Margolis S, Kowarski A: The dawn phenomenon, an early morning glucose rise: implications for diabetic intraday blood glucose variation. *Diabetes Care* 4:579–85, 1981
4. Izzo JL: Diurnal (24 hours) rhythm in diabetes mellitus: diurnal variations in levels of glucose in blood and urine. *Proc Am Diabetes Assoc* 9:247–73, 1949
5. Schmidt MI, Hadji-Georgopoulos A, Rendell M, Margolis S, Kowarski A: Fasting hyperglycemia and associated free insulin and cortisol changes in "Somogyi-like" patients. *Diabetes Care* 12:457–64, 1979
6. Deckert T, Lourp B: Regulation of brittle diabetes by a preplanned insulin programme. *Diabetologia* 12:573–79, 1976
7. Geffner ME, Frank HJ, Kaplan SA, Lippe BM, Levin SR: Early-morning hyperglycemia in diabetic individuals treated with continuous subcutaneous insulin infusion. *Diabetes Care* 6:135–39, 1983
8. Levy-Marchal C, Albisser AM, Zinman B: Overnight metabolic control with pulsed intermittent versus continuous subcutaneous insulin infusion. *Diabetes Care* 6:356–60, 1983
9. Bending JJ, Pickup JC, Collins ACG, Keen H: Rarity of a marked "dawn phenomenon" in diabetic subjects treated by continuous subcutaneous insulin infusion. *Diabetes Care* 8:28–33, 1985
10. Clarke WL, Haymond MW, Santiago JV: Overnight basal insulin requirements in fasting insulin-dependent diabetics. *Diabetes* 29:78–80, 1980
11. Bright GM, Melton TW, Rogol AD, Clarke WL: Failure of cortisol blockade to inhibit early morning increases in basal insulin requirements in fasting insulin-dependent diabetics. *Diabetes* 29:662–64, 1980
12. White NH, Skor D, Santiago JV: Practical closed-loop insulin delivery. *Ann Intern Med* 97:210–13, 1982
13. Bolli GB, Gerich JE: The "dawn phenomenon"—a common occurence in both non-insulin-dependent and insulin-dependent diabetes mellitus. *N Engl J Med* 310:746–50, 1984
14. Kerner W, Navascues I, Torres AA, Pfeiffer EF: Studies on pathogenesis of the dawn phenomenon in insulin-dependent diabetic patients. *Metabolism* 33:458–64, 1984
15. Gale EAM, Kurtz AB, Tattersall RB: In search of Somogyi effect. *Lancet* 2:279–82, 1980
16. Skor DA, White NH, Thomas L, Shah SD, Cryer PE, Santiago JV: Examination of the role of the pituitary-adrenocortical axis, counterregulatory hormones, and insulin clearance in variable nocturnal insulin requirements in insulin-dependent diabetes. *Diabetes* 32:403–407, 1983
17. Skor DA, White NH, Thomas L, Santiago JV: Relative roles of insulin clearance and insulin sensitivity in the prebreakfast increase in insulin requirements in insulin-dependent diabetic patients. *Diabetes* 33:60–63, 1984
18. Schmidt M, Lin QX, Gwynne JT, Jacob S: Fasting early morning rise in peripheral insulin: evidence of the dawn phenomenon in nondiabetes. *Diabetes Care* 7:32–35, 1984
19. Bolli GB, De Feo P, De Cosino S, Perriello G, Ventura MM, Calcinaro F, Lolli C, Campbell P, Brunetti P, Gerich JE: Demonstration of a dawn phenomenon in normal human volunteers. *Diabetes* 33:1150–53, 1984
20. Campbell PG, Bolli GP, Cryer PE, Gerich JE: Pathogenesis of the dawn phenomenon in patients with insulin dependent diabetes mellitus: accelerated glucose production and impaired glucose utilization due to noctural surges in growth hormone secretion. *N Engl J Med* 312:1473–79, 1985
21. Heding LG: Radioimmunological determination of human C-peptide in serum. *Diabetologia* 11:541–48, 1975
22. Koivisto VA, Yki-Järvinen H, Helve E, Karonen SL, Pelkonen R: Pathogenesis and prevention of the dawn phenomenon in diabetic patients treated with CSII. *Diabetes* 35:78–82, 1986
23. Holman RR, Turner RC: Maintenance of basal plasma glucose and insulin concentration in maturity-onset diabetes. *Diabetes* 28:227–30, 1979
24. Santiago J, Haymond M, Clarke W, Pagliara A: Glucagon, insulin and glucose responses to physiologic resting in normal and massively obese adults. *Metabolism* 26:1115–22, 1977
25. Taska Y, Sekine M, Wakatsuki M, Ohghawara H, Shizume K: Levels of pancreatic glucose, insulin and glucose during twenty-four hours of the day in normal subjects. *Horm Metab Res* 7:205–206, 1975
26. Mauras N, Rogol AD, Clarke WL: Failure to detect the "dawn phenomenon" in nondiabetic subjects with markedly different patterns of noctural growth hormone secretion. *J Clin Endocrinol Metab* 63:975–79, 1986