The Effectiveness of Rectal Administration of Insulin Suppository on Normal and Diabetic Subjects

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The effectiveness of insulin administration by rectal suppository was examined in normal and non-insulin-dependent nonobese diabetic subjects. A 100-U insulin suppository (mean 1.8 U/kg) given to the diabetic subjects caused four times as great a fall in plasma glucose compared with the normal subjects given the same dose (mean 1.6 U/kg). The insulin response after suppository administration demonstrated a significantly positive correlation ($r = 0.83$, $P < 0.01$) with the plasma glucose level before administration. Diabetic subjects given a 100-U insulin suppository (mean 1.7 U/kg) 15 min after meals three times daily showed a significant ($P < 0.05$) improvement in postprandial hyperglycemia accompanied by a restoration of the normal circadian profile of plasma IRI and a reduction of urinary glucose from 26 ± 5.9 to 2.0 ± 1.0 g/day. No untoward reactions were observed. These data strongly imply a unique characteristic of the insulin suppository in spite of low bioavailability. DIABETES CARE 4: 454–458, JULY–AUGUST 1981.

Insulin molecules have been shown to cross intestinal,[1–3] respiratory,[4,5] and oral mucosa[6] in normal and diabetic subjects. The insulin preparations for nonparenteral application, however, have a low efficacy compared with parenteral administration of insulin. We have already reported in animal studies that rectal application of insulin, by means of a suppository, is effective in lowering the plasma glucose concentration with a dose as low as 2 U/kg,[7] without impairments in rectal mucosae or other adverse reactions.[8] In the light of the encouraging results obtained in these studies, we decided to administer insulin by rectal suppository to normal and diabetic subjects. The preliminary studies reported here were undertaken to establish the effectiveness of insulin suppositories in regulating the hyperglycemia of diabetes in man and to assess the feasibility of its clinical application.

MATERIALS AND METHODS

Preparation of insulin suppository. The insulin suppositories were prepared according to the method previously described.[7,8] Briefly, an insulin suspension was made by mixing porcine crystalline insulin (Nordisk Insulin Laboratorium Co., Ltd., Denmark), with Witepsol H15 (Dynamit Nobel Co., Ltd., West Germany), surfactant (polyoxyethylene-9-lauryl ether, Nikko Chemicals Co., Ltd., Japan) as a suppository base, and 0.02 M HCl solution. Then the insulin suspension was solidified in a mold by cooling. The final concentration of insulin in a suppository was 50 U or 100 U/g with 3% (w/w) of surfactant and 5% (w/w) HCl solution.

The effect of rectal administration of insulin suppository to normal and diabetic subjects in the fasting state. Six normal volunteers aged 25–30 yr and five insulin-dependent diabetic subjects aged 44–60 yr took part in this study. The diabetic subjects were classified as non-insulin-dependent according to the results of a 50-g OGTT by the criteria of the Japan Diabetic Society. Two diabetic subjects were taking sulfonylurea initially, but stopped 1 day before the study. No subject had a history of insulin injection. All subjects were within 15% of ideal body weight (Metropolitan Life Insurance Company Table, 1959). None had clinical signs of autonomic neuropathy.

After an overnight fast, the six normal subjects were given a 50-U insulin suppository. At least 1 wk later, a 100-U suppository was administered to four normal and five diabetic subjects. The plastic cannula was inserted into an antecubital vein and blood samples were collected at 0, 15, 30, 45, 60, 90, 120, 150, and 180 min after administration of the suppository for plasma glucose, insulin (IRI), and C-peptide (CPR).

The effect of insulin suppository on circadian glycemia and insulin concentration in diabetic subjects. Four diabetic subjects aged 37–50 yr, within 15% of ideal weight, were admitted to the First Department of Medicine, Osaka University Hospital, or the Department of Medicine, Osaka Policemen's Hospital, and informed consent to the following investigation was obtained. After diet treatment was carried out for 1–2 wk, a 100-U insulin suppository was administered rectally 15 min after food intake three times daily for 1 day. Blood was sampled at regular intervals as shown in Figure 3 for plasma glucose, IRI, and CPR during the pretreatment control period and during the period of rectal insulin administration. Twenty-four-hour aliquots of urine were collected and daily glucose loss was calculated. The caloric content of the diet was 25–30 kcal/kg ideal body wt and was provided as three equal meals at 0800, 1200, and 1700 h.

Data analyses. Plasma glucose and urinary glucose concentrations were measured by a glucose-oxidase method using an autoanalyzer technique. Immunoreactive insulin concentration was measured by the method of Hales and Randle.[9] Plasma CPR was measured by radioimmunoassay using a kit purchased from Daichi Radioisotope Co., Ltd. (Japan). The area of increase in plasma IRI was integrated for 180 min after the rectal administration of the insulin suppository. Statistical analyses were done using a Student's *t* test.

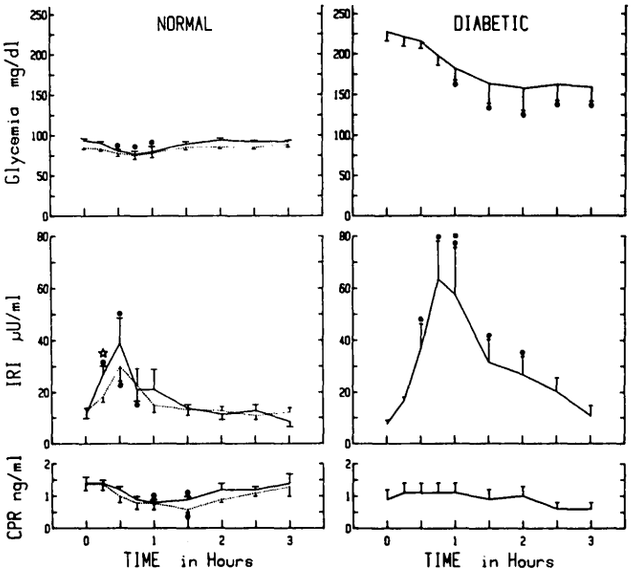

FIG. 1. Mean (±SEM) plasma glucose, IRI, and CPR responses to rectal administration of 50-U (dotted line) or 100-U insulin suppository (solid line) to normal (left) and diabetic (right) subjects. ●, Significant ($P < 0.05$) difference between each value and the prestimulated value; ☆, significant ($P < 0.05$) difference between 50- and 100-U insulin administrations; ■, significant ($P < 0.05$) difference between insulin levels of normal and diabetic subjects with 100-U insulin suppository.

RESULTS

Effect of rectal administration of insulin suppository to normal and diabetic subject in fasting state. Figure 1 demonstrates the plasma glucose, IRI, and CPR responses following the rectal administration of the 50- and 100-U insulin suppositories to fasting normal and diabetic subjects. When the 50-U insulin suppository (0.7–0.9 U/kg, mean 0.8 U/kg) was administered to normal subjects, the plasma IRI rose significantly ($P < 0.05$) to a peak of 30 ± 5.6 μU/ml (mean ± SEM) at 30 min, followed by a gradual decline to the baseline level. Plasma glucose fell by 10 mg/dl to the nadir level at 45 min and then increased to the baseline level at 90 min. Plasma CPR showed a significant ($P < 0.05$) nadir level of 0.6 ± 0.1 ng/ml at 90 min. When the 100-U insulin suppository (1.5–1.7 U/kg, mean 1.6 U/kg) was applied to normal subjects, plasma IRI increased significantly ($P < 0.05$) to the peak of 39 ± 9.7 μU/ml accompanied by a significant ($P < 0.05$) fall of glycemia to a level of 77 ± 3.8 mg/dl at 45 min and a significant reduction of plasma CPR to 0.8 ± 0.1 ng/ml at 60 min. The plasma IRI with the 100-U insulin suppository was significantly ($P < 0.05$) higher than that with the 50-U suppository at 15 min. The integrated areas of increase in plasma IRI for 180 min were 637 ± 228 or 1236 ± 308 μU·min/ml at a dose of 50 or 100 U per person, respectively. The difference was not significant ($0.1 < P < 0.05$). The coefficient of variation of insulin response against the 50- or 100-U insulin suppository was 68% or 43%, respectively.

When the 100-U insulin suppository (1.4–2.5 U/kg, mean 1.8 U/kg) was given to diabetic subjects in a fasting state, the plasma IRI rose to 63.6 ± 14.6 μU/ml at 45 min, followed by a gradual decline to the prestimulated level by 180 min. The IRI level at 120 min was still significantly ($P < 0.05$) higher than the initial level. The plasma glucose gradually fell from 228 ± 11.4 mg/dl to 158 ± 27.2 mg/dl at 120 min. A significantly ($P < 0.05$) higher IRI concentration was observed at 45 min in diabetic subjects than that in normal subjects with the same dose. Plasma CPR showed no significant change after administration.

The integrated area of increase in plasma insulin was 4151 ± 1257 μU·min/ml in the diabetic subjects. This was 3.4-fold as great as that in the normal subjects with 100 U, but not significantly different ($0.1 < P < 0.05$). The integrated area of increase in insulin was divided by a unit of insulin administration (U/kg) to give a plasma insulin response per unit of insulin administered rectally (kg·min/ml). Figure 2 demonstrates the plasma insulin responses thus calculated and plasma glycemias before administration in all subjects. Diabetic subjects with a higher glycemia showed a higher insulin response. A significantly positive correlation ($r = 0.827$, $P < 0.01$) was observed between the insulin response and the glycemic level.

Effect of rectal administration of insulin suppository on diurnal profile of glucose and insulin in diabetic subjects. Figure 3 demonstrates the diurnal excursion of plasma glucose, IRI, and CPR in diabetic subjects when the 100-U insulin suppository was administered rectally 15 min after each of the three meals. Without administration of a suppository, glycemia gradually increased from the fasting level of 191 ± 31.4

mg/dl to a peak of 388 ± 57.2 mg/dl at 1800 h. Plasma insulin showed a gradual increase to a significantly ($P < 0.05$) higher level of 19.4 ± 4.1 μU/ml at 1300 h, then slowly fell to the fasting level. This was accompanied by a significant ($P < 0.05$) rise in plasma CPR level. Urinary glucose loss for 24 h was 26 ± 5.9 g/day. When an insulin suppository was administered, a sharp rise in plasma IRI was noted 60 min after each meal. Each peak of IRI showed a similar value of about 40 μU/ml, significantly ($P < 0.05$) higher than IRI levels without suppository except at 1000 h. Fasting glycemia in the next morning was not significantly different from the initial fasting glycemia. Plasma CPR showed no significant difference whether or not the suppositories were given. Daily urinary glucose loss decreased to a level of 2.0 ± 1.0 g/day.

During suppository administration, some subjects complained of abdominal discomfort or a feeling of rectal urgency. However, these complaints were not so severe as to interrupt the experiments. No other untoward reactions were observed and hypoglycemia did not occur.

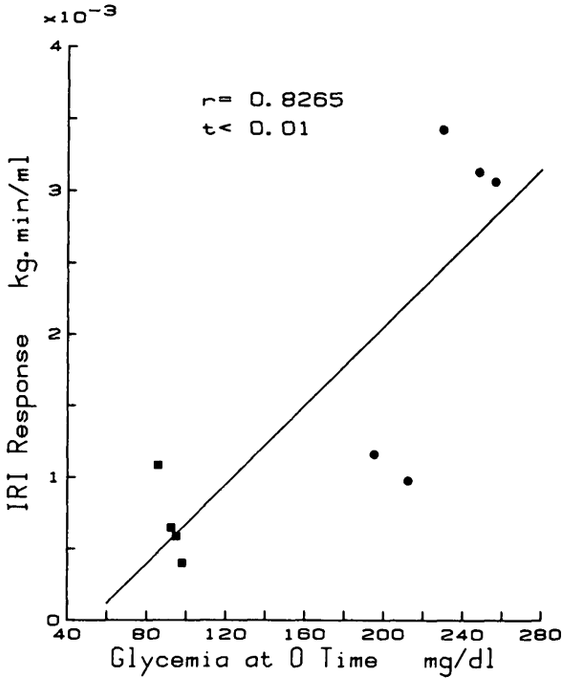

FIG. 2. The relationship between the insulin response after 100-U insulin suppository administration and the glycemic level before administration. A significantly positive relation was shown ($r = 0.827$, $P < 0.01$). ●, Diabetic patient; ■, normal subject. The insulin response (kg·min/ml) was calculated as the integrated area of IRI increase for 180 nm (μU·min/ml) divided by the insulin dose (U/kg).

DISCUSSION

During recent years, studies from our laboratory have focused attention on the possibility that diabetes can be controlled by orally administered insulin. With the intrajejunal administration of water-in-oil-in-water insulin emulsions[10] or micells,[11] we carried out the successful short-term treatment of alloxan-diabetic rats. However, it was also delineated that their bioavailability still remained at a low level, around 4% that of intramuscular insulin injection. We therefore turned to a rectal administration of insulin by means of a suppository. A preliminary report[7] suggested an improvement of bioavailability and the possibility that rectal absorption of insulin was increased in depancreatectomized dogs compared with normal dogs. The short-term treatment of alloxan-diabetic dogs with the rectal administration of insulin suppositories for 6–9 days assessed a reasonable coefficient of variation of glycemic response against suppository, as little as 13–15%,[8] and neither untoward reactions nor pathologic changes in rectal mucosae were recognized. In the light of the encouraging results obtained in these studies, the effect of the administration of insulin suppository to man was examined in normal and diabetic subjects.

The studies on the fasting normal subjects demonstrated that a small dose of insulin per rectum, as little as 0.8 U/kg, was significantly effective in raising the plasma IRI by 17 μU/ml and lowering the plasma CPR from 1.4–0.6 ng/ml. At a dose of 100 U, normal subjects showed a significant reduction of glycemia by 17 mg/dl at 45 min concomitant with a significant change in plasma IRI and CPR levels. Diabetic subjects who received the 100-U insulin suppository showed an integrated insulin response three times as great as that of normal subjects. A significant fall of glycemia by 36% of the prestimulated level observed in diabetic subjects was thought to be mainly due to the effect of insulin absorbed from the rectum, because a spontaneous glycemic fall was observed to be only 15% for 3 h in untreated diabetic subjects with a similar glycemic level.[12]

The insulin response after rectal administration of insulin was positively correlated with the prestimulated glycemic level. This positive correlation was not indicated in the oral insulin preparations[1,2,10–12] nor in the other nonparenteral insulin preparations.[4–6] The decreased degradation rate of insulin[13] or the decreased clearance rate of insulin[14,15] would explain the greater insulin response in diabetic subjects. However, because these changes in insulin kinetics were as subtle as 5–30%, they could account in part for the phenomenon in which the insulin response was increased by 200% in diabetic subjects. A second explanation is that the total amount of insulin absorbed was increased in diabetic subjects. The observations that the intestinal absorption was increased in diabetic subjects[16] and the intestinal transport of sugers and amino acids was augmented in the diabetic rat[17,18] were comparable to the increased insulin response observed in diabetic subjects. Olsen and Rosenberg also indicated that the augmented intestinal transport was reduced by insulin treatment.[17] Therefore, the positive correlation between the glycemia level before suppository administration and the insulin response thereafter might imply that the greater insulin response in diabetic subjects is reduced according to a normalization of the diabetic state. This characteristic of an in-

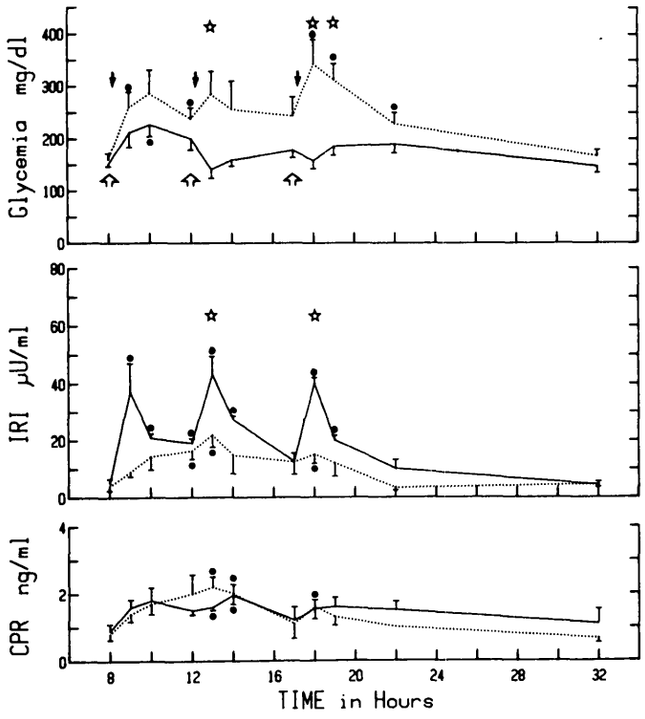

FIG. 3. Diurnal plasma glucose, IRI, and CPR excursions in diabetic subjects with insulin suppository (solid lines) and without insulin suppository (dotted lines). Data were expressed as mean ± SEM. Insulin suppository of 100 U was administered (⇓) 15 min after each meal (⇑) three times daily. The meal was given at 0800, 1200, and 1700 h. ●, significant ($P < 0.05$) difference between each value and the fasting value at 0800 h; ☆, significant ($P < 0.05$) difference between the responses with and without insulin suppositories.

sulin suppository seems to be unique and useful for its possible clinical application because oral sulfonylureas exert a similar or more intensive effect on normal subjects compared with their effect on diabetic subjects. However, the possibility that the total amount of insulin absorbed is increased in diabetic subjects remains to be established.

An approximately flat glycemic excursion was shown throughout 24 h in four diabetic subjects fed regular meals, when the insulin suppository was applied three times daily after each meal. The postprandial rise in glycemia observed with diet treatment was lessened after breakfast and significantly reverted to a reduction after lunch and supper with additional insulin suppositories. Plasma IRI showed a peak of around 40 μU/ml at 1 h after each meal followed by a gradual decrease to a slightly higher level than the fasting level before meals. The pattern and magnitude of the diurnal insulin excursion thus obtained was similar to that in normal subjects.[19–21] Plasma CPR showed no significant changes between the experiments with and without insulin suppositories. The daily urinary glucose loss reduced to a negligible level of 2.0 ± 10 g/day. These data clearly demonstrated that the attenuation of the glycemic rise after meals with a marked reduction of the urinary glucose loss was mainly due to insulin absorbed from the rectum in spite of the residual endogenous insulin secretion.

Rectal insulin administered after meals was not effective in reducing fasting hyperglycemia significantly. This is consistent with the glycemic control of insulin-dependent diabetic subjects with s.c. bolus injection of crystalline zinc insulin four times daily in which fasting hyperglycemia above 200 mg/dl was observed after the bedtime s.c. injection, in spite of the restoration of normal glycemic excursion during the day.[22] They also showed that the constant s.c. crystalline insulin infusion or s.c. Lente insulin injection combined with s.c. crystalline bolus insulin injection could normalize fasting glycemia. These data suggested that a long-acting insulin suppository might improve fasting hyperglycemia in diabetic subjects, since the present insulin suppository is as short-acting as an intramuscular injection.[23]

Rectal administration of insulin is a more physiologic route for applying insulin to diabetic subjects than the conventional parenteral administration because some portion of insulin absorbed enters into the portal vein directly. We showed that the insulin level in the portal vein was three times as large as the peripheral insulin level after rectal administration of insulin in normal subjects (data not shown). These data allow us to estimate by means of an insulin dynamic model[24] that about 30% of insulin absorbed from the rectum is assigned directly to the portal vein. The lymphatics as a possible route of disposal of rectally absorbed insulin also remains to be clarified quantitatively. Although it is known that liver degradates about 50% of insulin delivered,[25] the increment of portal insulin concentration is shown to intensify the magnitude of the net hepatic glucose uptake induced by portal glucose infusion.[26] An open-loop portal insulin delivery study applied to the pancreatectomized unrestrained dogs fed regular meals[27] demonstrated less hyperinsulinemia than that observed in a peripheral infusion study.[28] These data indicate the importance of portal insulin delivery in normalizing both glycemia and insulinemia postprandially. The insulin suppository also attenuated the postprandial glycemic rise in diabetic subjects, and the peripheral insulinemia was similar to that in normal subjects after meal. These observations presented a possibility that insulin suppository could control the postprandial glycemia in a more physiologic manner than conventional insulin therapy, because the substantial amount of insulin absorbed from the rectum enters directly into the portal vein.

After rectal administration of a suppository, a few subjects complained of abdominal discomfort for a while. Even though no other adverse effects were noted in these acute studies, the possibility that bacteria might be absorbed through surfactant-treated rectal mucosa should be clarified before long-term clinical applications. We have already shown that no pathologic changes were demonstrated in the rectal specimens of alloxan-diabetic dogs controlled with insulin suppositories for 6–9 days.[8] However, these data were not sufficiently encouraging to proceed with the long-term treatment by insulin suppository. Additional studies to improve the efficacy and dependability of delivery and confir-

mation of safety with long-term use would be required before consideration for clinical use.

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REFERENCES

[1] Murlin, J. R., Gibbs, C. B. F., Romanosky, M. J., Steinhausen, T. B., and Traux, F. L.: Effectiveness of per-oral insulin in human diabetes. J. Clin. Invest. *19*: 709–22, 1940.

[2] Crane, C. W., and Luntz, G. R. W.: Absorption of insulin from the human small intestine. Diabetes *17*: 625–27, 1968.

[3] Galloway, J. A., and Root, M. A.: New forms of insulin. Diabetes *21* (Suppl. 2): 637–48, 1972.

[4] Wigley, F. M., Londons, J. H., Wood, S. H., Shipp, J. C., and Waldman, R. H.: Insulin across respiratory mucosae by aerosol delivery. Diabetes *20*: 552–56, 1971.

[5] Shin-Wei, L., and Sciarra, J. J.: Development of an aerosol dosage form containing insulin. J. Pharm. Sci. *65*: 567–72, 1976.

[6] Earle, M. P.: Experimental use of oral insulin. Isr. J. Med. Sci. *8*: 899–900, 1972.

[7] Shichiri, M., Yamasaki, Y., Kawamori, R., Kikuchi, M., Hakui, N., and Abe, H.: Increased intestinal absorption of insulin: insulin suppository. J. Pharm. Pharmacol. *30*: 806–808, 1978.

[8] Yamasaki, Y., Shichiri, M., Kawamori, R., Morishima, T., Hakui, N., Yagi, T., and Abe, H.: The effect of rectal administration of insulin on the short-term treatment of alloxan-diabetic dogs. Can. J. Physiol. Pharmacol. *59*: 1–6, 1981.

[9] Hales, C. N., and Randle, P. J.: Immunoassay of insulin with insulin-antibody precipitate. Biochem. J. *88*: 137–46, 1963.

[10] Shichiri, M., Kawamori, R., Yoshida, M., Etani, N., Hoshi, M., Izumi, K., Shigeta, Y., and Abe, H.: Short-term treatment of alloxan-diabetic rats with intrajejunal administration of water-in-oil-in-water insulin emulsions. Diabetes *24*: 971–76, 1975.

[11] Shichiri, M., Kawamori, R., Goriya, Y., Kikuchi, M., Yamasaki, Y., Shigeta, Y., and Abe, H.: Increased intestinal absorption of insulin in a micellar solution; Water-in-oil-in-water insulin micelles. Acta Diabetologica Latina *15*: 175–83, 1978.

[12] Shichiri, M., Etani, N., Kawamori, R., Goriya, Y., Shigeta, Y., and Abe, H.: Experimental treatment of alloxan-rats with water-in-oil-in-water insulin micelles. J. Japan Diab. Soc. *19*(Suppl.): 101, 1976 (in Japanese).

[13] Stimmler, L.: Disappearance of immunoreactive insulin in normal and adult-onset diabetic subjects. Diabetes *16*: 652–55, 1967.

[14] Navalesi, R., Pilo, A., and Ferrannini, E.: Kinetic analysis of plasma insulin disappearance in nonketotic diabetic patients and in normal subjects. A tracer study with ^{125}I-insulin. J. Clin. Invest. *61*: 197–208, 1978.

[15] McGuire, E. A., Tobin, J. D., Berman, M., and Andres, R.: Kinetics of native insulin in diabetic, obese, and aged men. Diabetes *28*: 110–20, 1979.

[16] Vinnik, I. E., Kern, F., Jr., and Sussman, K. E.: The effect of diabetes mellitus and insulin on glucose absorption by the small intestine, in man. J. Lab. Clin. Med. *66*: 131–36, 1965.

[17] Olsen, W. A., and Rosenberg, I. H.: Intestinal transport of sugars and amino acids in diabetic rats. J. Clin. Invest. *49*: 96–105, 1970.

[18] Younoszai, M. K., and Schedl, H. P.: Intestinal amino acid transport and tissue concentrations in diabetes. Am. J. Physiol. *223*: 828–31, 1972.

[19] Macherbe, C., de Gaspara, M., de Hertogh, R., and Hoet, J. J.: Circadian variation of blood sugar and plasma insulin levels in man. Diabetologia 5: 397–404, 1969.

[20] Hansen, A. P., and Johansen, K.: Diurnal patterns of blood glucose, serum free fatty acids, insulin, glucagon and growth hormone in normals and juvenile diabetics. Diabetologia 6: 27–33, 1970.

[21] Hanna, A. K., Zinman, B., Nakhooda, A. F., Minuk, H. L., Stokes, E. F., Albisser, A. M., Leibel, B. S., and Marliss, E. B.: Insulin, glucagon, and amino acids during glycemic control by the artificial pancreas in diabetic man. Metabolism *29*: 321–32, 1980.

[22] Nelson, J. D., Marliss, E. B., Albisser, A. M., and Zinman, B.: Role of continuous component in subcutaneous "open-loop" insulin delivery. Lancet *1*: 1383–86, 1980.

[23] Guerra, S. M. O., and Kitabchi, A. E.: Comparison of the effectiveness of various routes of insulin injection: insulin levels and glucose response in normal subjects. J. Clin. Endocrinol. Metab. *42*: 869–74, 1976.

[24] Tiran, J., Avruch, L. I., and Albisser, A. M.: A circulation and organs model for insulin dynamics. Am. J. Physiol. *237*: E331–39, 1979.

[25] Röjmark, S., Bloom, G., Chou, M. C. Y., and Field, J. B.: Hepatic extraction of exogenous insulin and glucagon in the dog. Endocrinology *102*: 806–13, 1978.

[26] Berman, R. N., and Bucolo, R. J.: Interactions of insulin and glucose in the control of hepatic glucose balance. Am. J. Physiol. *227*: 1314–22, 1974.

[27] Goriya, Y., Bahoric, A., Marliss, E. B., Zinman, B., and Albisser, A. M.: Glycemia regulation and insulin clearance in unrestrained diabetic dogs portally infused with a portable insulin delivery system. Diabetologia *19*: 452–57, 1980.

[28] Goriya, Y., Bahoric, A., Marliss, E. B., Zinman, B., and Albisser, A. M.: Glycemic regulation using a programmed insulin delivery device. III. Long-term studies on diabetic dogs. Diabetes *28*: 558–64, 1979.