Determination of Insulin Requirements in Brittle Diabetic Patients by the Artificial Pancreas

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SUMMARY

An extracorporeal system (called the artificial pancreas) infused insulin and/or glucose at rates regulated by feedback control of the continuously monitored blood glucose. This system was capable of restoring the circadian blood glucose profile of 11 brittle diabetics to within a physiologic range. These patients made two stays of one week each in the hospital, during which the M-value and the MAGE index (used as indexes of blood glucose control and of glycemic fluctuations) were measured. The first stay was just before their connection to the artificial pancreas, while the patients were being given their usual insulin dosage; the second stay occurred one to nine months later. The day after connection of the artificial pancreas, the patients received a new insulin regimen, calculated according to the daily insulin profile infused by the artificial pancreas, consisting of two daily injections of a mixture of short-acting and intermediate-acting insulins. This regimen was essentially characterized by an increased proportion of regular insulin in the daily dose of from 31.2 ± 5.8 per cent (mean ± S.E.M.) before to 56.1 ± 3.0 per cent after artificial pancreas, $p < 0.01$, and a reduction of the percentage of the dose given in the morning of from 68.1 ± 5.9 to 52.6 ± 2.8 per cent, $p < 0.025$. These changes of insulin dosage caused a noticeable decrease of the M-value, from 69.5 ± 8 to 53.1 ± 4.4 ($p < 0.02$), but the MAGE index was not significantly affected (187 ± 20 versus 162 ± 14). Thus, the artificial pancreas could be helpful in the clinical management of brittle diabetics by providing a more precise estimate of the patient's insulin needs (particularly those of short-acting insulin), leading to a better control of blood glucose. DIABETES 27:825-33, August, 1978.

Continuous blood glucose monitoring[1-7] has shown that the rapid and important fluctuations of blood glucose concentrations characteristic of brittle diabetes are mostly consequent to food ingestion and physical exercise. Three subcutaneous injections of insulin a day controlled glycemia in stable diabetics,[8] but they could not prevent marked blood glucose fluctuations in unstable diabetics.[9] Thus, these patients remain exposed to hypoglycemic episodes and are prone to develop complications like microangiopathy, the appearance of which seems to be facilitated by a poor metabolic control.[10-16]

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After the pioneer work of Kadish,[17] several attempts were made to construct devices able to simulate the physiologic insulin secretion by delivering adequate small amounts of the hormone intravenously. Two types of such devices have been used so far: a computer-controlled apparatus (usually called artificial pancreas) infusing insulin according to the concentration of blood glucose,[18-21] and less sophisticated systems consisting essentially of a pump delivering insulin at different rates depending on the period of the day.[8,22-25] Blood glucose could be maintained within normal limits, both in fasting and postabsorptive states, in diabetics connected to these devices during a period that usually did not exceed a few days and was often limited to 24 hours.

The artificial pancreas developed in our laboratories also proved to be capable of maintaining normoglycemia, even in the most unstable diabetics, by delivering insulin and/or glucose at rates regulated by

feedback control from the continuously monitored blood glucose. The purpose of the present study was to examine whether the circadian profile of insulin administration by the artificial pancreas to 11 brittle diabetics could be used to determine the most appropriate scheme of daily insulin injections in these patients.

MATERIALS AND METHODS

Artificial pancreas. This device has been described in detail elsewhere.[26] Briefly, it consisted of three parts: an on-line system for glucose analysis and hematocrit measurement, a computer-controller unit, and pumps for insulin and glucose delivery. The analyzer for continuous glucose monitoring is based on a glucose electrode containing glucose oxidase immobilized between two porous membranes. This glucose sensor met the necessary requirements of low drift and fast response time using whole blood diluted about 1:10 with a heparin solution. The glucose analyzer, adapted for continuous measurement from commercially available equipment (Glucose Analyzer 23A, Yellow Springs Instruments, Scientific Division, Ohio), was calibrated every four to six hours and eventually adjusted by comparing the recorded blood glucose with that measured at the same time by the AutoAnalyzer method.[27] Usually the drift did not exceed 10 mg./100 ml. per four hours. A second electrode, developed in our laboratories,[26] measured (with an electrical impedance method) the hematocrit of the mixture of blood and heparin solution so that the true blood glucose was instantaneously known. The digital computer (PDP 11-45 DEC), remotely located, controlled the various subsystems, determined (in connection with preprogrammed safety measures) the optimal insulin or glucose requirements, and activated the infusion pumps. By the use of various control algorithms derived from those previously published by Albisser et al.,[18,19] insulin (or glucose) infusion was not only a function of the actual blood glucose concentration but also of a projected glycemia. Control algorithms used a hyperbolic tangent function that related the respective rates of insulin and glucose infusions to the measured glycemia. The blood glucose concentrations at which half-maximum infusion rates occurred were set at 70 and 150 mg./100 ml. for glucose and insulin infusions, respectively. Furthermore, a projected blood glucose was calculated by adding a difference factor DF to the actual glycemia; DF was defined by the formula: $DF = K_1 (\exp A/K_2 - 1)$, with K_1 adjusting the magnitude of DF, and K_2 representing its sensitivity to changes in A, which was the rate of change of blood glucose. K_1 and K_2 values were usually fixed at 40 and 4, respectively, during the day hours so as to increase the sensitivity of the system, thus permitting a greater rate of insulin delivery as soon as blood glucose rose after a meal. During the night, K_2 was increased to a value of 8 to 12 in order to minimize fluctuations of blood glucose caused by the system.

Two peristaltic Perpex pumps (Werner Meyer, Lucerne, Switzerland), controlled by the computer through an interface, infused insulin (measured concentration of 400 mU. Novo Actrapid per milliliter normal saline) or glucose (a 30 per cent solution) at a rate ranging from 0 to 2 ml. per minute. The data are printed out at the bedside in real time at intervals of one minute. These included the blood glucose concentration (in milligrams per 100 ml.), the rates of insulin (in milliunits per minute) and glucose (milligrams per minute) infusions as well as the total amounts of insulin and glucose administered during the preceding 15 minutes and hour. Blood was withdrawn from the jugular vein through a two-lumen catheter. A heparin solution (40 U. per milliliter saline) circulated at a rate of 25 to 30 ml. per hour from the outer lumen to the tip of the catheter, where it mixed with blood before entering the inner lumen, thus avoiding systemic heparinization. The length of tubing between the patient and the glucose sensor was about 1.5 m., which allowed the patient to sit and, eventually, to leave the bed; however, they usually remained immobile during the test, which lasted 24 to 27 hours. Less than three minutes elapsed from the time blood entered the two-lumen catheter to when the computer reacted by modifying the insulin or glucose infusion rate. The total blood losses amounted to about 75 ml./24 hr. Insulin and glucose solutions were infused into a contralateral forearm vein through a nonthrombogenic cannula. Most patients felt well, and no complications of any kind were encountered during or after our studies.

Patients. Eleven brittle diabetics (nine males and two females) were studied, all of whom gave their informed consent. They were referred to our department of internal medicine by their physicians because of the extreme difficulty they had in achieving fair blood glucose control. The main characteristics of these subjects are shown in table 1. None of the patients was actually ill from intercurrent disease at the time of the study. Their mean age was 45.3 years with an average duration of diabetes of 14.8 years. Two

TABLE 1

Individual data of 11 brittle diabetics

Case	Sex	Age (yr.)	Height (cm.)	% of ideal body weight	Duration of diabetes (yr.)	Neuropathy	Retinopathy*	Insulin/kg. body weight (U.)	Blood urea (mg./100 ml.)
1	F	47	167	93	26	+	+	1.28	51
2	M	54	169	113	9	0	0	0.65	33
3	M	40	172	95	5	0	0	1.16	25
4	M	26	167	115	16	0	0	0.85	30
5	M	39	169	103	4	0	0	0.69	43
6	F	65	157	120	16	0	0	1.28	37
7	M	46	174	100	14	+	0	0.69	38
8	M	51	174	128	25	+	+	0.86	84
9	M	34	166	97	22	+	++	0.93	36
10	M	48	171	95	17	+	0	0.66	42
11	M	48	182	96	9	0	0	0.72	41
Mean		45.3	169.8	105	14.8	5/11	3/11	0.89	41.8
S.E.M.		3.1	1.9	3.6	2.3			0.07	4.7

*On first hospital day. + = Background retinopathy; ++ = proliferative retinopathy.

patients (cases 6 and 8) were overweight (at least 20 per cent above the ideal body weight). All but one subject (patient 8) had normal renal function. Five patients had neuropathy, as assessed by clinical examination and electromyography; three of them had developed retinopathy. Before connection to the artificial pancreas, their average daily insulin requirement amounted to 0.89 U. per kilogram body weight (range: 0.65 to 1.28). Each patient was hospitalized twice for one week: the first week just before the day of extracorporeal regulation of blood glucose, and the second time at intervals ranging from one to nine

TABLE 2

Comparison of the insulin doses before and after connection to the artificial pancreas

		Before				Months between two clinical examinations	After			
Case		Repartition*	% a.m.	%AR	Total (U./day)		Repartition*	% a.m.	%AR	Total (U./day)
1	a.m.	24 AR + 20 NL	65				16 AR + 8 MT	46		
	p.m.	14 AR + 10 NL		56	68	2	10 AR + 18 MT		50	52
2	a.m.	12 AR + 20 MT	70				12 AR + 6 MT	36		
	p.m.	14 MT		26	46	4	12 AR + 20 MT		48	50
3	a.m.	12 AR + 24 SL	50				20 AR + 20 SL	50		
	p.m.	12 AR + 24 SL		33	72	3	20 AR + 20 SL		50	80
4	a.m.	30 SL	50				26 AR + 6 MT	42		
	p.m.	30 SL		0	60	9	28 AR + 16 MT		71	76
5	a.m.	45 RT	100				16 AR + 10 MT	50		
	p.m.	—		25†	45	5	16 AR + 10 MT		62	52
6	a.m.	20 AR + 30 MT	64				36 AR + 10 MT	58		
	p.m.	14 AR + 14 MT		44	78	1	16 AR + 18 MT		65	80
7	a.m.	10 AR + 30 NL	87				28 AR + 12 NL	69		
	p.m.	6 NL		22	46	5	10 AR + 8 NL		66	58
8	a.m.	34 AR + 40 MT	100				30 AR + 20 MT	60		
	p.m.	—		53	64	8	14 AR + 20 MT		52	84
9	a.m.	12 AR + 13 IPZ	45				18 AR + 10 MT	52		
	p.m.	15 AR + 15 IPZ		49	55	1	14 AR + 12 MT		59	54
10	a.m.	24 SL	60				16 AR + 10 MT	57		
	p.m.	16 SL		0	40	5	10 AR + 10 MT		57	46
11	a.m.	14 AR + 16 SL	58				16 AR + 16 MT	59		
	p.m.	4 AR + 18 SL		35	52	9	4 AR + 18 MT		37	54
Mean			68.1	31.2	56.9	4.7		52.6	56.1	62.4
S.E.M.			5.9	5.8	3.8	0.9		2.8	3.0	4.3

*Abbreviations: AR = Novo Actrapid, NL = Novo Lente, SL = Novo Semi-Lente, RT = Novo Rapitard, MT = Novo Monotard, IPZ = Insulin protamine-zinc. Also listed are the percentages of the daily dose given in the morning (% a.m.) and as short-acting insulin (% AR). The generic equivalents in the United States of NL and SL insulins are Lilly Lente Iletin and Semilente Iletin. The durations of the hypoglycemic action of AR, RT, and MT insulins are about 6, 16, and 20 hours, respectively.

†Percentage of AR present in RT.

months later (table 2). During the two stays in the hospital, the patients received a regular diet of 1800 to 2000 calories (of which about 40 per cent was carbohydrates) divided into three meals and two snacks. They were asked to keep a similar diet at home. During the first week in the hospital, the patients were given their usual insulin dose. Subcutaneous insulin was withheld on the day of the test and for the period of connection to the artificial pancreas, but the prescribed diet of each patient was continued. Between the two stays in the hospital and during the second week of observation, the patients received the insulin treatment determined on the basis of the indications given by the artificial pancreas (see RESULTS

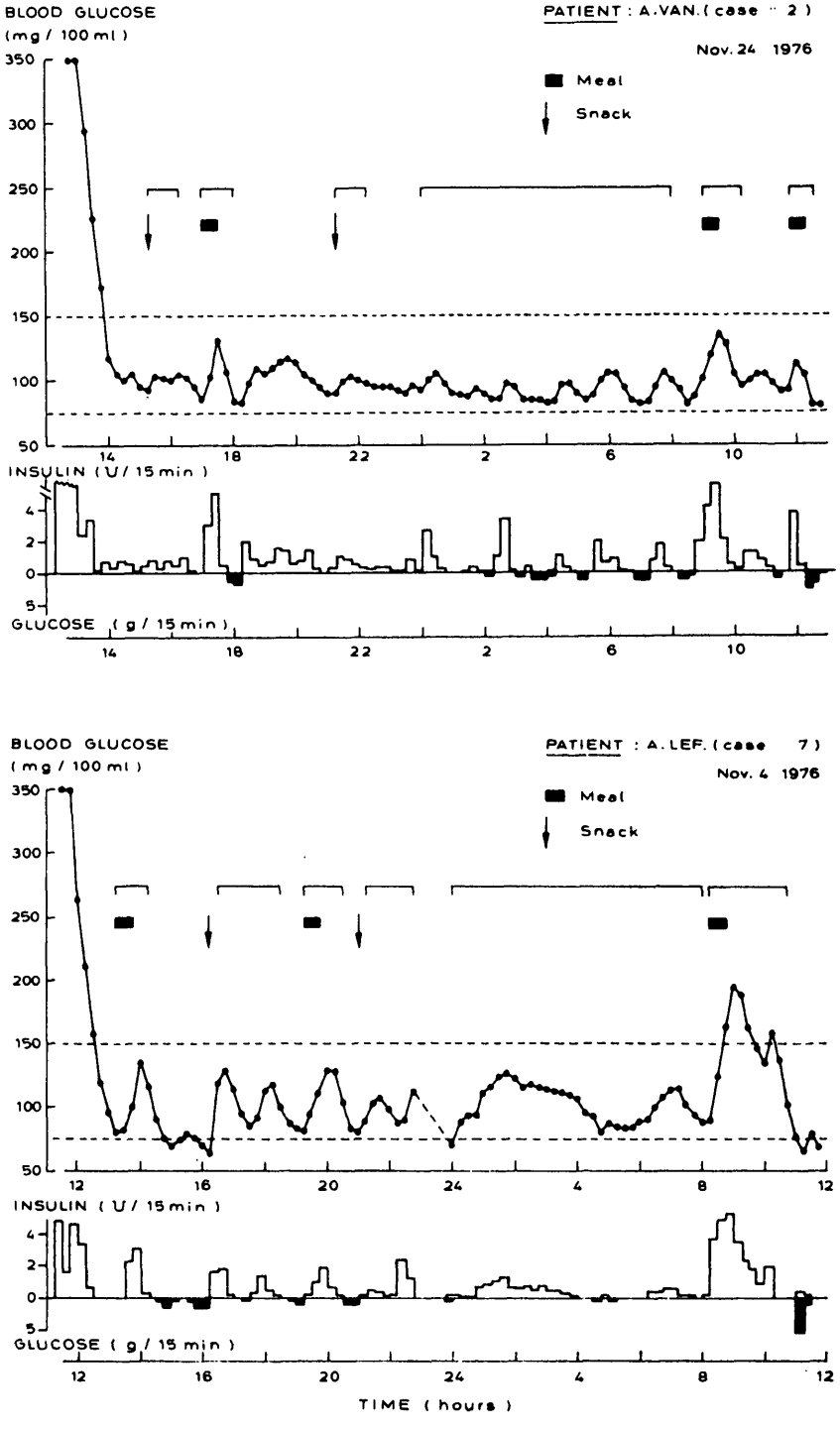

FIGURE 1

Blood glucose profiles of two unstable diabetics during connection to the artificial pancreas for a 24-hour period. The amounts of insulin (open bars) and glucose (black bars) administered to the patients are also illustrated. The horizontal brackets delineate the periods considered for the calculation of subcutaneous insulin requirements.

section). The average weight of the subjects was not modified significantly at the time of the second clinical examination. Capillary blood was taken seven times a day (i.e., just before and two hours after each meal and at midnight) during each hospital day for glucose determination by the AutoAnalyzer method.[27] The M value was used as an index of blood glucose (BG) control. This index, calculated according to Schlichtkrull et al.,[28] was equal to $M^{BG} + M^{W}$, where M^{BG} was the average of all M^{BG}_{BG} values defined by the formulas $M^{BG}_{BG} = [10 \times \log BG/120]$ and $M^{W} = W/20$, in which W was the difference between the maximum and minimum blood glucose values during the period concerned. The mean amplitude of glycemic excursions (MAGE) served as a measure of diabetic instability. This index, defined by Service et al.,[29] was calculated by a slightly modified method, in which it represented the mean of three consecutive blood-glucose swings in the same direction (i.e., peak to nadir or nadir to peak) that exceeded the value of one standard deviation of all blood glucose levels recorded during the clinical examination. Statistical comparisons were made by the paired *t*-test.

RESULTS

Figure 1 is a record of two blood sugar profiles (cases 2 and 7) regulated by the artificial pancreas during a 24-hour period. Both patients received their last subcutaneous insulin injection (see table 2) the day before at 7 p.m. In both cases, blood glucose exceeded 400 mg./100 ml. (402 and 445 mg./100 ml.) at the beginning of the test. Return of blood glucose to the normal range was achieved within 1.5 hours, requiring 26 U. insulin in patient 2 and 15 U. in patient 7. The amounts of insulin infused during the remaining time (± 23 hours) amounted to 72 and 62 U. in patients 2 and 7, respectively. An accidental disconnection of the catheter occurred between 22.45 and 23.45 hours (during patient's sleep) in patient 7. From the data shown in figure 1, it is evident that the artificial pancreas was capable of maintaining blood glucose homeostasis of unstable diabetics within a nearly physiologic range. Few relative hypoglycemic values were recorded, the amount of glucose delivered being 19 to 20 gm. per 24 hours in both patients. Expected rises of blood glucose were observed in the postprandial periods, but glycemic fluctuations independent of food ingestion were also noted in all patients studied, particularly during the early morning hours. Among these glycemic oscillations, two features are worth mentioning: first, a blood sugar rise, variable in amplitude but noted in most cases, occurred between 6 and 8 a.m.; and second, the highest blood sugar peak and the largest insulin delivery were observed after breakfast. From the day immediately after the period of automatic regulation of blood sugar, all patients were placed on two daily injections of a mixture of short-acting (Novo Actrapid) and intermediate-acting (Novo Semi-Lente, Monotard, or Lente) insulins. As shown in table 3, the estimation of subcutaneous insulin requirements was based on the amounts of insulin delivered by the artificial pancreas

TABLE 3

Method of calculation of insulin requirements according to the data obtained from the artificial pancreas (AP) (see figure 1)

Meal	Period of the day considered (hr.)	Elapsed time (hr.)	Glucose given by AP (gm.)	Insulin given by AP (U.)	Insulin dosage* after AP (U.)
		Case 2			
Breakfast	9.00 - 10.15	1.25	0	12.6	a.m.: 12 AR + 6 MT
Lunch	11.45 - 12.30	0.75	0.2	4.3	
Snack	15.15 - 16.15	1	0	2.4	
Supper	17.00 - 18.00	1	0	8.5	p.m.: 12 AR + 20 MT
Snack	21.15 - 22.15	1	0	3.3	
None	0 - 8.00	8	10.2	19.0	
Total		13.00	10.4	50.1	24 AR + 26 MT
		Case 7			
Breakfast	8.15 - 10.45	2.5	0	27.0	a.m.: 28 AR + 12 NL
Lunch	13.15 - 14.15	1	0	6.0	
Snack	16.30 - 18.30	2	0.5	6.0	
Supper	19.15 - 20.30	1.25	0	4.3	p.m.: 10 AR + 8 NL
Snack	21.15 - 22.45	1.5	0	4.7	
None	0 - 8.00	8	2.6	10.0	
Total		16.25	3.1	58.0	38 AR + 20 NL

*Abbreviations: AR = Novo Actrapid; NL = Novo Lente; MT = Novo Monotard.

during six periods of the day, namely, after each meal or snack (usually from the beginning of food ingestion until blood glucose returned to 100 mg./100 ml.) and during the night (from midnight to 8 a.m.). The amounts of insulin administered after breakfast, supper, and bedtime snack were converted into the nearest even figure of Actrapid insulin given before breakfast and supper, respectively. Similarly, the amounts of insulin infused after lunch and afternoon snack and during the night were converted into the corresponding doses of intermediate-acting insulin.

The results summarized in table 2 show the comparison of the daily insulin doses used before and after the artificial pancreas in the eleven brittle diabetics studied. Before the study, two patients (cases 5 and 8) received a single daily injection of insulin; the treatment of two others (cases 4 and 10) comprised no short-acting insulin. The total dose averaged 57 U. per day with about one-third (range: 0 to 56 per cent) being regular insulin. After connection to the artificial pancreas, the percentage of the daily dose given as short-acting insulin was increased in eight patients, this increment usually affecting both morning and evening injections. It was slightly diminished in only one subject (patient 1). The mean proportion of short-acting insulin was increased markedly to 56.1 ± 3.0 per cent ($p < 0.01$). The total amount of insulin was not significantly different after the test (mean: 56.9 ± 3.8 U. vs. 62.4 ± 4.3 U. per day), while the morning dose was significantly reduced (from 68.1 ± 5.9 to 52.6 ± 2.8 per cent; $p < 0.025$).

Table 4 is an illustration of the blood glucose profiles of these brittle diabetics. The wide swings of blood glucose as well as the hypoglycemic episodes were particularly evident in most patients before their connection to the artificial pancreas. The changes in insulin dosages introduced after the artificial pancreas appeared to diminish blood glucose fluctuations, thus leading to an improvement in diabetic control. These data were confirmed by those shown in table 5, evidencing a diminution of the M-value in nine patients and a significant decrease in the mean M-value (69.5 ± 8.0 vs. 53.1 ± 4.4; $p < 0.02$). The MAGE index was relatively high in all subjects, thereby confirming the marked fluctuations of blood sugar in these patients, and it was not significantly affected by the new insulin program (table 5).

DISCUSSION

Brittle diabetes, characterized by great difficulties of management and extreme variability of blood glucose, remains one of the most frustrating problems of

TABLE 4

Blood glucose profile on the third hospital day and the extreme blood glucose concentrations recorded during the two clinical examinations before and after connection to the artificial pancreas

Case		Blood glucose (mg./100 ml.)							BG min*	BG max
	Time (hr.)	8	10	12	14	18	20	0	(mg./100 ml.)	(mg./100 ml.)
1	before	178	387	246	66	52	439	411	31	687
	after	121	290	225	126	113	312	280	41	474
2	before	82	211	118	243	431	491	121	27	499
	after	119	228	190	157	227	198	39	39	346
3	before	363	296	178	111	84	210	116	40	462
	after	319	383	196	88	179	261	97	55	385
4	before	202	432	200	230	153	227	56	28	441
	after	47	214	104	138	156	357	149	38	378
5	before	96	186	123	170	80	127	129	41	258
	after	101	212	75	140	76	95	103	52	272
6	before	405	311	264	236	176	214	80	31	573
	after	152	243	277	241	154	185	72	67	349
7	before	221	368	186	112	72	163	44	37	456
	after	76	321	162	91	139	178	223	72	443
8	before	360	465	354	303	98	133	258	38	471
	after	112	346	291	158	94	137	37	37	369
9	before	72	165	134	107	46	178	42	36	178
	after	57	228	185	117	84	205	80	52	337
10	before	382	529	351	267	165	89	44	40	529
	after	294	363	235	187	242	319	117	99	363
11	before	112	246	193	106	115	228	162	56	386
	after	67	148	125	167	109	196	131	60	369

*BG min = minimum blood glucose; BG max = maximum blood glucose.

TABLE 5

Comparison of M and MAGE values before and after the connection to the artificial pancreas

Case	M value		MAGE value	
	Before	After	Before	After
1	120.3	68.9	328	250
2	92.6	67.1	171	151
3	61.8	68.5	249	188
4	78.0	49.2	158	144
5	29.6	24.6	132	157
6	89.2	50.6	195	119
7	69.0	64.5	159	197
8	74.3	64.4	234	222
9	36.4	42.7	102	109
10	69.0	42.5	212	141
11	44.0	40.7	121	100
Mean	69.5	53.1	187	162
S.E.M.	8.0	4.4	20	14
	< 0.02		< 0.10	

clinical diabetology. The present study, confirming and extending previously published reports,[19,30,31] demonstrates that the artificial pancreas effectively maintained blood glucose of unstable diabetics within a physiologic range. The early morning elevation of glycemia and the important insulin requirement after breakfast have already been reported.[8,9,22,24,25] They can reasonably be attributed to the morning rise of plasma cortisol concentration as well as to the relatively high carbohydrate content of the breakfast.

The ample and frequent fluctuations of blood glucose, variable from patient to patient and often underestimated without continuous blood glucose monitoring, render a precise determination of insulin dosage in brittle diabetics difficult, even during a prolonged stay in a specialized unit. The analysis of the circadian insulin profile during extracorporeal regulation of blood glucose by the artificial pancreas confirmed that the hormone is infused mainly during the postprandial periods, especially after breakfast and supper. The calculation of subcutaneous insulin doses has taken into account empirically, therefore, only the amounts of insulin delivered after food ingestion and during a part of the night (as an estimate of the basal needs). Equally empiric were the choice of two daily injections of a mixture of short-acting and intermediate-acting insulins and the conversion of the amounts of infused hormone into units of each insulin type, depending on the period of the day.

During the second stay at the hospital, most of the subjects studied showed a noticeable improvement of diabetes control, as evidenced by the diminution of the average M-value, which still did not reach, however, a level considered by Schlichtkrull et al.[28] to reflect good metabolic control. All but one patient (case 9) reported a marked reduction in the frequency and severity of hypoglycemic attacks as well as a decrease in the daily excretion of urinary glucose after his connection to the artificial pancreas, but no attempt was made to quantify these data. The MAGE index was not affected significantly, a finding that is not surprising in view of previous studies showing that this index remained unabated in brittle diabetics treated with four daily doses of regular insulin.[29] It has recently been reported that diabetic patients controlled for several days by pulses of intravenous insulin or for shorter periods by the artificial pancreas could temporarily be improved *after* disconnection from these systems.[23,30] These data were tentatively explained by assuming some transient recuperation of the beta-cell function, as suggested by increased circulating levels of endogenous insulin[23] and C-peptide.[30] Since the improvement of metabolic control was still noticed in our patients several weeks or months after the artificial-pancreas study, it is likely secondary to the modifications of insulin dosage rather than to some hypothetic endogenous cause. The most remarkable change of insulin program introduced after the artificial-pancreas study was the increased proportion of short-acting insulin in the two daily injections, reflecting the relatively high insulin requirements of these patients after breakfast and supper. It should be mentioned, however, that no strict correlation appears to exist between the change in percentage of Actrapid insulin and the diminution of the M-value. Indeed, patient 1 exhibited a marked improvement of the M-value concomitantly with a reduction of the dose of short-acting insulin, whereas the metabolic control of patients 3 and 9 appeared to deterioriate somewhat in spite of an increased dose of short-acting insulin.

Several criticisms can be raised against our method of calculation of insulin dosage, the least not being that it assumes a relatively constant circadian blood glucose and insulin profile in a given patient with standardized diet and physical activity. Available studies in which blood glucose was continuously monitored for two successive days[32] suggest that this might in fact be the case in stable diabetics. In brittle diabetes, glycemic profiles were less parallel from day to day, although they usually followed a similar pattern. It may also be argued that the total amount of insulin infused by the artificial pancreas during 24 hours was higher than the daily dose prescribed thereafter and that the patients were kept in a somewhat

artificial environment since they were, in particular, unable to perform any significant physical exercise. It is conceivable, however, that their relative immobility increased the insulin needs, such increment not being required during the subsequent ambulatory treatment.

Nevertheless, the method of calculation of subcutaneous insulin doses, based on the amounts infused by the artificial pancreas, appears to improve the metabolic control in brittle diabetes. It could thus be helpful by providing a rapid and more precise estimate of insulin requirements. The clinical experience with insulin doses based on the profiles of insulin infused by the artificial pancreas suggests that a reasonable compromise between treatment efficiency and patient comfort in the long-term management of unstable diabetics would consist of two daily injections of a mixture of short-acting and intermediate-acting insulins comprising at least 50 per cent of the total dose given as regular insulin.

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