

TABLE 1. Clinical characteristics of the pancreas recipients 1 year after transplantation

Sex (m/f)	30/23
Duration of diabetes (yr)	25.5±0.9
Age at transplant (yr)	38.2±1.1
Segmentary/total	16/37
Cold ischemia time (min)	557±42
Weight (kg)	62.6±1.4
Prednisone (mg/day)	10.1±0.2
Cyclosporine (mg/day)	335±14
Azathioprine (mg/day)	64±4
Creatinine (mg/dL)	1.3±0.1

for a metabolic assessment that consisted of the following procedures: 24-h metabolic profile ($n=51$) that consisted of sampling every 2 hours plasma glucose, serum free-insulin, and c-peptide concentrations. During the profiles, the subjects received an isocaloric diet fractionated in a breakfast, lunch, and dinner of their choice.

IVGTT. Forty-eight subjects underwent an IVGTT as previously described (0.3 g/kg of dextrose administered as an intravenous bolus followed by a rapid sampling of serum insulin concentrations), and the peak incremental insulin response was used as an index of insulin secretion.

Euglycemic hyperinsulinemic clamp ($n=14$). Briefly, a prime-continuous infusion of crystalline human insulin (Actrapid HM, Novo Nordisk, Copenhagen, Denmark) was administered at the rate of 1 mU·kg⁻¹·min⁻¹ for 2 hours to achieve and maintain an increment in plasma insulin concentrations of approximately 430 pmol/L. The plasma glucose concentration was maintained at the basal concentration by determining it at 5-min intervals with a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA) and by periodic adjustment of a 20% glucose infusion on the basis of a negative feedback principle. The M value was calculated from the rate of glucose infusion necessary to keep euglycemia in the second hour of the clamp, corrected for changes in glucose concentration and urinary glucose losses (12). To correctly estimate the whole-body glucose disposal during hyperinsulinemia, the calculation of the M value assumes that the endogenous glucose production is completely suppressed. This assumption was previously tested in a subset of the recipients with the aid of glucose tracers, and the results in these subjects have been published (13).

Analytical methods. The aliquots of blood for the measurement of glucose were placed into tubes that contained lithium heparin and lithium iodoacetate and immediately centrifuged, then the plasma was decanted and refrigerated at 4°C until the assay with the hexokinase method (Boehringer Mannheim, Germany) (14). The blood aliquots for free-insulin and c-peptide were prepared as previously described and were measured by standard RIA methods (15).

Follow-up. Table 2 shows the individual durations of the follow-up. The return to the diabetic state was defined by fasting plasma glucose >140 mg/dL coupled with HbA_{1c} >6.5% and/or initiation of insulin therapy. Six subjects dropped out for reasons independent from the pancreas (cerebral bleeding, neoplasm, or abdominal surgery). Fourteen patients experienced the return to the diabetic state. The failure of the pancreatic function was definitive in 13 of these subjects, and only transient in one patient. In the third year, this recipient (#31) had an episode of acute uveitis that was treated with an increased dose of steroids. He also underwent surgery for bilateral cataracts immediately before the metabolic tests. He recovered in a few months and had a satisfactory pancreatic function in the following 2 years. This subject was defined free of diabetes at the end of the observation period.

Statistical analysis. The daily mean, minimum, maximum, and the maximum excursion on the day of the profile were calculated for plasma glucose, serum free-insulin, and serum c-peptide concentrations. The contribution to the risk of returning to the diabetic state

of these variables in the profiles of the M value in the insulin clamp and of the incremental insulin response in the IVGTT was evaluated by Cox proportional hazards regression analysis. Kaplan-Meier survival curves were used to show the survival of the pancreatic function in the recipients. Analysis with receiver operating characteristic (ROC) methodology was used to evaluate the contribution of mean daily glucose in the profiles and of the insulin response in the IVGTT to predict pancreatic failure at 4 years.

RESULTS

The subjects were followed for 4.8 ± 0.3 years. The individual data in the profiles, in the IVGTT, and in the clamp are reported in Table 2 with the duration and the outcome of the follow-up.

24-h metabolic profiles. The variables derived from plasma glucose were significantly associated with the risk of returning to the diabetic state (daily mean, $P=0.0004$; minimum, $P=0.0007$; maximum, $P=0.0005$; and excursion, $P=0.0012$). The mean glucose had the greatest association with the hazard function: an increment of 1 standard deviation (30 mg/dL) in the mean glucose increased the risk of returning to the diabetic state 1.645 (range, 1.25 to 2.17) times. The risk increased briskly in the top quartile of the distribution of the mean glucose concentrations, corresponding to a cutoff value of 127 mg/dL. The top panel of Figure 1 shows the Kaplan-Meier survival curve of pancreatic function based on this cutoff. The mean survival time in the subjects whose mean daily glucose was ≤ 127 mg/dL was 7.52 ± 0.37 years, whereas in the subjects whose mean daily glucose was >127 mg/dL, the mean survival was 3.07 ± 0.30 years ($P<0.00001$ with log-rank test). The bottom panel of Figure 1 shows the relationship between survival of the pancreatic function at 4 years and mean daily glucose in the subjects who were transplanted at least 4 years previously. ROC analysis showed that the cutoff value of 127 mg/dL predicted a 4-year survival with a 93% specificity and a 100% sensitivity. In contrast to glucose, the variables derived from insulin and c-peptide concentrations were not associated to the hazard function.

Insulin clamp. The M value calculated during the euglycemic clamp was not associated with the risk of returning to the diabetic state. The top panel of Figure 2 shows that there was no difference in the function survival of the subjects with the M value in the lowest quartile compared to the others. The bottom panel of the figure shows that there was no relationship between survival of the pancreatic function at 4 years and M value in the subjects who were transplanted at least 4 years previously.

IVGTT. The peak incremental response in insulin concentration was significantly associated to the risk of returning to the diabetic state ($P<0.001$). The top panel of Figure 3 compares the survival curves of the pancreatic function in the subjects with the response in the lowest quartile (<24.7 μ U/ml) to those with a higher response. The mean survival time was 4.2 ± 0.76 years in the subjects with a response in the lowest quartile, and 6.51 ± 0.26 years in the others ($P<0.0002$ with log-rank test). The bottom panel of Figure 3 shows the relationship between survival of the pancreatic function at 4 years and insulin response in the subjects who were transplanted at least 4 years previously. ROC analysis showed that a cutoff value of insulin delta peak <32 μ U/ml

TABLE 2. Values derived from metabolic profiles and insulin clamp 1 year after the transplant

subject id	24-h profiles												IVGTT c-pep (ng/ml) delta peak	Clamp M value (mg/kg/min)	Follow-up yr							
	p-Glucose (mg/dL)				f-iri (μU/ml)				c-pep (ng/ml)						1	2	3	4	5	6	7	8
	avg	min	max	delta	avg	min	max	delta	avg	min	max	delta										
1	—	—	—	—	—	—	—	—	—	—	—	—	39.3	5.10	0	0	0	1	1	1	1	1
2	—	—	—	—	—	—	—	—	4.1	2.1	9.0	6.9	20.6	5.22	0	0	0	0	0	0	1	1
3	—	—	—	—	—	—	—	—	—	—	—	—	−0.4	7.38	0	0	0	0	1	1	1	1
4	137	84	276	192	35.3	10.8	81.5	70.7	5.4	3.0	9.6	6.6	31.3	6.10	0	1	1	1	1	1	1	1
5	114	77	195	118	92.2	23.6	168.7	145.1	9.4	3.9	15.0	11.1	68.5	3.51	0	0	0	0	0	0	—	—
6	108	84	139	55	26.1	18.0	52.8	34.8	3.3	2.0	5.9	3.9	60.4	3.93	0	0	0	0	0	0	0	—
7	287	146	505	359	26.7	13.3	42.6	29.3	1.1	0.5	2.9	2.4	4.0	6.19	0	0	0	1	1	1	1	1
8	110	74	161	87	19.4	5.8	41.1	35.3	3.1	1.4	6.3	4.9	49.3	6.75	0	0	0	0	0	0	0	0
9	96	76	122	46	20.9	5.3	49.0	43.7	—	—	—	—	26.7	6.38	0	0	0	0	0	0	0	0
10	117	98	153	55	30.7	14.3	50.9	36.6	6.1	3.7	9.9	6.2	30.2	4.93	0	0	0	0	1	1	1	1
11	108	61	200	139	29.1	15.2	49.9	34.7	—	—	—	—	—	5.56	0	0	0	0	1	1	1	1
12	127	80	203	123	36.9	21.1	54.2	33.1	—	—	—	—	43.0	—	0	0	0	0	0	0	1	1
13	141	89	243	154	20.3	5.5	45.3	39.8	3.6	2.1	6.3	4.2	22.9	—	0	1	1	1	1	1	1	1
14	96	66	148	82	14.1	2.0	31.3	29.3	3.2	1.2	5.5	4.3	36.2	—	0	0	0	0	—	—	—	—
15	163	114	222	108	37.0	11.2	83.2	72.0	3.7	2.2	5.3	3.1	7.2	—	1	1	1	1	1	1	1	1
16	134	92	261	169	26.0	13.5	48.1	34.6	5.2	2.7	8.5	5.8	13.1	—	0	0	0	0	—	—	—	—
17	104	85	130	45	35.8	12.6	72.5	59.9	—	—	—	—	132.1	—	0	0	0	0	0	0	0	0
18	130	84	246	162	39.8	15.7	153.3	137.6	5.9	2.9	16.8	13.9	43.0	—	0	0	0	1	1	1	1	1
19	125	98	210	112	54.0	12.0	164.7	152.7	7.9	4.2	14.1	9.9	90.9	—	0	0	0	0	—	—	—	—
20	90	74	113	39	16.9	5.9	41.2	35.3	5.9	3.6	8.8	5.2	71.9	3.31	0	0	0	0	0	0	0	0
21	99	87	139	52	19.1	6.2	88.7	82.5	6.5	4.0	12.4	8.4	70.4	—	0	0	0	0	0	0	0	0
22	107	82	166	84	31.8	9.4	97.1	87.7	4.8	1.8	12.0	10.2	35.9	5.24	0	0	0	0	0	0	0	0
23	111	84	155	71	44.1	18.3	108.0	89.7	4.3	2.6	7.7	5.1	75.9	—	0	0	0	0	0	0	0	0
24	94	69	112	43	44.7	16.8	88.3	71.5	4.4	2.5	6.3	3.8	128.9	6.57	0	0	0	0	0	0	0	0
25	103	82	182	100	37.1	14.3	75.6	61.3	5.0	2.3	9.4	7.1	68.2	—	0	0	0	0	0	0	0	0
26	97	65	151	86	70.2	2.8	192.1	189.3	12.1	4.6	23.0	18.4	123.1	—	0	—	—	—	—	—	—	—
27	105	83	138	55	42.6	14.1	92.4	78.3	4.9	2.3	8.0	5.7	132.5	—	0	0	0	0	0	0	0	0
28	176	127	242	115	26.5	17.9	42.3	24.4	2.2	1.6	3.0	1.4	0.3	—	1	1	1	1	1	1	1	1
29	109	88	162	74	43.1	17.6	92.4	74.8	4.4	2.3	8.0	5.7	84.8	—	0	0	0	0	0	0	0	0
30	92	66	122	56	17.3	7.3	32.6	25.3	2.5	1.8	3.9	2.1	107.0	—	0	0	0	0	0	0	0	0
31	112	79	190	111	45.5	15.7	104.6	88.9	7.1	2.3	12.7	10.4	—	—	0	0	1	0	0	0	0	0
32	113	53	277	224	33.2	8.5	101.0	92.5	—	—	—	—	14.7	—	0	0	0	0	0	0	0	0
33	106	84	154	70	48.9	18.1	120.8	102.7	—	—	—	—	209.3	—	0	0	0	0	0	0	0	0
34	97	77	127	50	41.1	17.3	90.0	72.7	6.3	3.0	11.4	8.4	128.0	—	0	0	0	0	0	0	0	0
35	132	84	212	128	46.5	12.9	123.3	110.4	5.1	2.4	8.0	5.6	12.4	—	0	0	0	1	0	0	0	0
36	105	85	156	71	36.5	10.6	69.7	59.1	4.3	1.5	6.6	5.1	29.3	—	0	0	0	0	0	0	0	0
37	129	82	247	165	27.4	10.3	70.1	59.8	3.5	1.6	6.3	4.7	40.7	—	0	0	0	0	0	0	0	0
38	104	74	172	98	32.7	14.0	54.8	40.8	5.2	3.0	9.1	6.1	107.2	—	0	0	0	0	0	0	0	0
39	101	74	148	74	60.8	14.3	190.2	175.9	5.7	2.9	11.3	8.4	97.4	—	0	0	0	0	0	0	0	0
40	116	80	197	117	—	—	—	—	5.5	3.2	10.3	7.1	50.4	—	0	0	0	0	0	0	0	0
41	138	102	235	133	26.7	11.2	44.3	33.1	4.3	2.2	6.8	4.6	—	—	0	0	0	0	0	0	0	0
42	109	85	167	82	46.2	12.2	143.4	131.2	4.8	2.9	12.9	10.0	122.3	—	0	0	0	0	0	0	0	0
43	—	—	—	—	58.1	22.9	166.4	143.5	4.1	2.8	10.6	7.8	46.1	—	0	0	0	0	0	0	0	0
44	128	78	206	128	75.0	35.2	203.1	167.9	4.0	1.9	8.5	6.6	8.4	—	0	0	0	0	0	0	0	0
45	105	79	149	70	46.1	11.2	122.8	111.6	4.8	1.8	9.1	7.3	—	—	0	0	0	0	0	0	0	0
46	119	84	230	146	17.4	2.1	76.0	73.9	5.2	2.1	13.1	11.0	53.3	—	0	0	0	0	0	0	0	0
47	131	89	179	90	28.3	11.2	54.8	43.6	7.3	4.0	14.4	10.4	2.4	—	0	0	0	0	0	0	0	0
48	99	77	141	64	15.2	3.1	26.9	23.8	3.2	1.3	4.9	3.6	—	—	0	0	0	0	0	0	0	0
49	114	73	159	86	31.8	10.1	71.2	61.1	9.9	4.5	18.4	13.9	67.6	—	0	0	0	0	0	0	0	0
50	103	72	123	51	—	—	—	—	—	—	—	—	110.4	—	0	0	0	0	0	0	0	0
51	112	68	161	93	22.0	2.8	69.4	66.6	—	—	—	—	8.7	—	0	0	0	0	0	0	0	0
52	106	80	144	64	29.8	6.6	57.8	51.2	—	—	—	—	28.7	—	0	0	0	0	0	0	0	0
53	122	87	158	71	103.1	22.6	250.6	228.0	—	—	—	—	199.7	—	0	0	0	0	0	0	0	0
mean	118	83	184	101	37.7	12.6	90.6	78.1	5.1	2.6	9.6	7.0	61.5	5.44								
se	4	2	9	8	2.7	0.9	7.5	7.1	0.3	0.1	0.7	0.5	7.3	0.33								
n	49	49	49	49	48	48	48	48	41	41	41	41	48	14								

The table reports the daily mean, minimum, maximum, and excursion of plasma glucose, serum free-insulin (firi), and c-peptide (c-pep) in the profiles, the insulin peak in the IVGTT, and the M value in the second hour of the euglycemic clamp performed 1 year after transplantation. A value 0 in the follow-up indicates free from diabetes; 1, relapsed; and —, lost to follow-up for reasons independent from the pancreas.

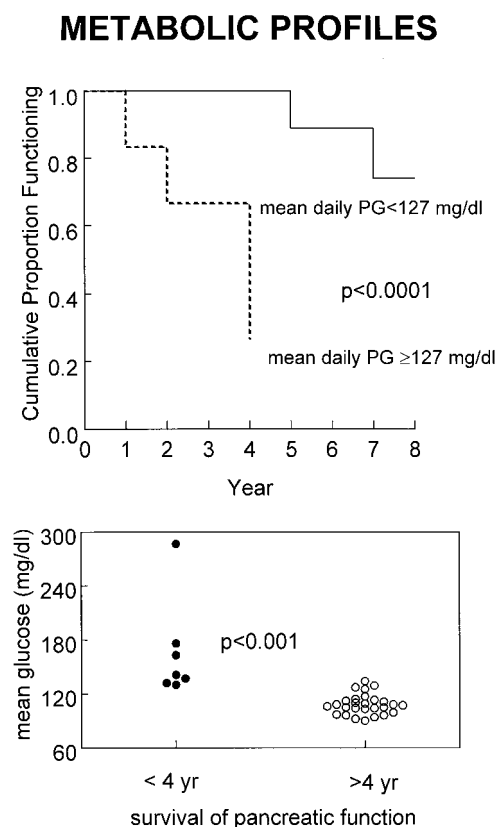


FIGURE 1. Top, An increased mean daily glucose in the profiles 1 year after transplantation was associated with a shorter duration of the pancreatic function. The figure shows the duration of pancreatic function in the subjects in the top quartile compared to the others. Bottom, The mean daily glucose was significantly increased in the subjects who lost the pancreatic function in the first 4 years.

predicts the return to the diabetic state within 4 years from transplantation with a 75% specificity and a 75% sensitivity.

DISCUSSION

This study showed that it is possible to predict with reasonable accuracy the return to the diabetic state for any cause in patients with type 1 diabetes who received a combined kidney and pancreas transplant. The best predictive index was the mean daily glucose concentration 1 year after transplantation, even though the minimum and the maximum daily glucose and the glycemic excursion had similar predictive powers. The subjects who could keep low their glucose concentration and could limit their daily glucose excursion had the best chances to remain free of diabetes after pancreas transplantation. The power of glucose profiles to predict failure in the long term may be surprising. Nonetheless, we also analyzed the predictive power of the metabolic profiles that the same subjects underwent 1 month after transplantation, and we achieved similar results (data not shown). These findings suggest that the reasons for pancreas failure are not contingent and the life span of the pancreas graft is at least in part already determined at the time of transplantation.

The ability to control glucose profiles depends both on insulin secretion and on insulin sensitivity. In regard to

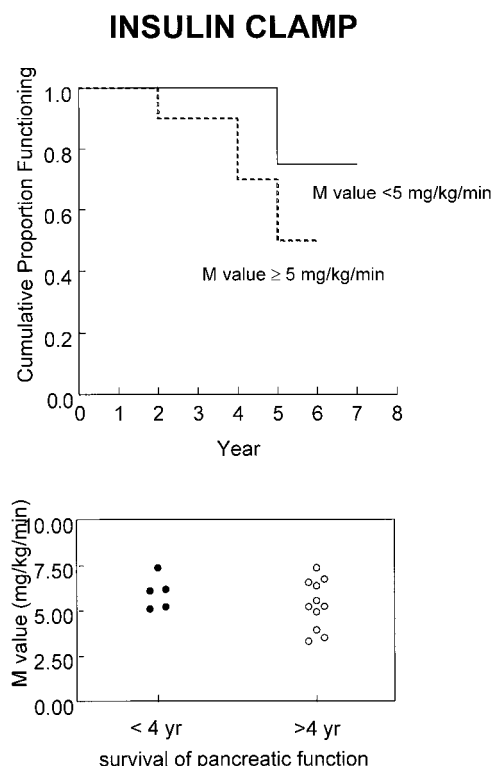


FIGURE 2. Top, A decreased M value in the clamp, an index of insulin sensitivity, 1 year after transplantation was not associated with the duration of the pancreatic function. The figure shows the duration of pancreatic function in the subjects in the lower quartile compared to the others. Bottom, The M value in the clamp was not decreased in the subjects who lost pancreatic function in the first 4 years.

insulin secretion, none of the indexes derived from the profiles of insulin and c-peptide was associated with the hazard function. The subjects with an earlier return to the diabetic state were not particularly insulinopenic or hyperinsulinemic, and they had insulinemic excursions comparable to the other subjects. The concentrations of the c-peptide showed a similar behavior. It is possible that the indexes derived from the insulin and the c-peptide daily profiles in this study lacked the sensitivity to detect defects in insulin secretion. In contrast, the IVGTT studies showed that a defective insulin response to intravenous glucose is associated with a return to the diabetic state. These data suggest that neither insulinopenia nor gross alterations in insulin secretion are significant early determinants of the return to the diabetic state. However, subtle defects such as the loss of the first phase of insulin secretion or altered insulin auto-feedback (16) may be involved in the early derangement of the glucose profiles and the subsequent return to the diabetic state.

There is no doubt that insulin sensitivity is another important factor in the derangement of glucose tolerance and the development of diabetes. Insulin resistance predicts the development of type 2 diabetes (17, 18), and it is also invariably associated with type 1 diabetes (19). We have previously shown that 1 year after transplantation, pancreas recipients are mildly insulin resistant for glucose metabolism (13). The posttransplant insulin resistance is at least in part caused by immunosuppression, and some predisposed subjects may be

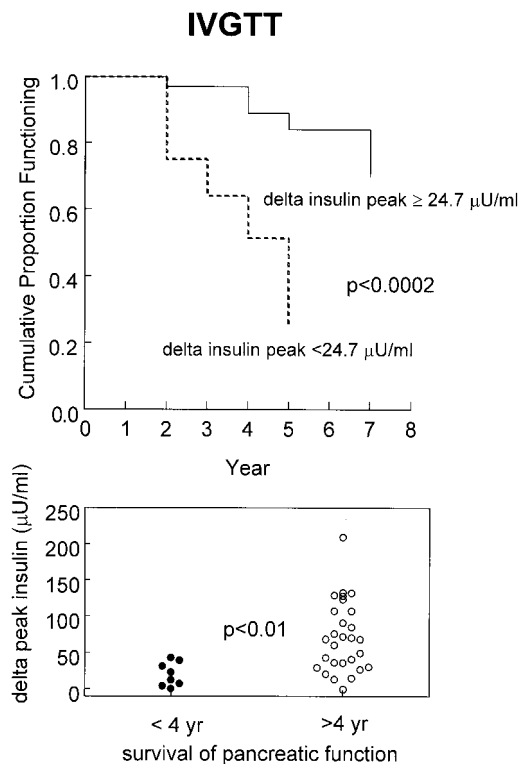


FIGURE 3. Top, A decreased peak insulin response to the IVGTT 1 year after transplantation was associated with a shorter duration of pancreatic function. The figure shows the duration of pancreatic function in the subjects in the lower quartile compared to the others. Bottom, The peak insulin response to the IVGTT was significantly decreased in the subjects who lost pancreatic function in the first 4 years.

particularly sensitive to the detrimental action of the steroids (20). Another reason for insulin resistance in heterotopic pancreas transplantation may relate to the peripheral site of insulin secretion (21). Nonetheless, insulin sensitivity in the recipients was devoid of predictive value for the return to the diabetic state. The small sample size ($n=14$) limited the power for the statistical inference; however, the subjects who relapsed before 5 years from transplant had M values well within 1 standard deviation of the distribution of the M values. Thus, it is unlikely that a larger sample could have shown that the M value is valuable for the long-term prediction of returning to the diabetic state.

Various reasons may explain why insulin resistance cannot predict the return to the diabetic state in the long term. Many factors that may affect the insulin sensitivity of recipients, including changes in the dose of the immunosuppressive drugs (20), infections (22, 23), the renal function (24), aging (25), and hyperinsulinemia (26), may change over time. We have previously shown that, as a consequence, the degree of insulin sensitivity changes over time after transplantation, presenting a steady improvement with fluctuations (13). Thus, insulin resistance cannot be considered *per se* an early risk factor, although it is an important last common pathway for many factors that determine the return to the diabetic state.

An additional explanation for the scarce value of measures of insulin sensitivity in predicting the long-term pancreatic

function can be found in the close relationship that exists between insulin sensitivity and insulin secretion. Interestingly, in this study, the M value (an index of insulin sensitivity) was negatively associated with the mean concentration of c-peptide, which is an index of insulin secretion (Spearman rank-order correlation coefficient = -0.6242 , $P=0.0480$). Insulin resistance and hyperinsulinemia are often associated. Insulin resistance, either primary (17) or secondary to steroid administration (27), can cause compensatory hyperinsulinemia. Conversely, hyperinsulinemia *per se*, either by systemic diversion of the pancreatic drainage or by inappropriate insulin secretion, can cause insulin resistance (21, 26). In contrast, a decreased insulin secretion can initially increase insulin sensitivity (28, 29). However, in the long term, both insulin resistance and an increased and a decreased insulin secretion can equally lead to a decreased glucose tolerance. Thus, it is not surprising that neither insulin secretion nor insulin resistance were univocally associated to the mean glucose values in the profiles and to the risk of losing the pancreatic function in the long term.

Irrespective of the causes of increased glucose concentrations in the recipients predisposed to pancreatic failure, our data suggest that hyperglycemia could adversely affect the outcome of the graft. The idea that chronic hyperglycemia *per se* impairs both insulin secretion and insulin sensitivity has been proposed several years ago (30), and it has been substantiated by a lot of experimental evidence (31–34). In the light of the present results, we propose to intensively monitor the subjects with a daily mean glucose concentration >125 mg/dL 1 year after transplantation, because these individuals have a high risk of returning to the diabetic state within 4 years. These are at-risk subjects who could benefit from aggressive programs for the early detection and treatment of pancreas rejection (2) and infection (35) and from the use of positive modulators of insulin action.

In conclusion, the return to the diabetic state is at least in part determined at the time of pancreas transplantation. Mean daily glucose concentrations are a good predictor of the return to the diabetic state, which is also associated to defects in insulin secretion and not to insulin resistance. Mean daily glucose concentrations 1 year after transplantation may be used to identify the recipients that could benefit from aggressive diagnostic and therapeutic protocols to prevent the recurrence of diabetes.

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Received 27 December 1999.

Accepted 12 September 2000.