Evaluation of Insulin Secretion after Pancreas Autotransplantation by Oral or Intravenous Glucose Challenge

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Segmental pancreatic autotransplantation is accompanied by surgical alterations to the pancreas that may have consequences for carbohydrate metabolism. Four mongrel dogs were evaluated before operation and sequentially until 40 weeks after total pancreatectomy and autotransplantation of the splenic lobe of the pancreas with bolus intravenous and oral administration. Intravenous glucose tolerance test (IVGTT) (0.5 g/kg) revealed maintenance of fasting euglycemia for as long as 40 weeks after operation. Peak glucose and integrated glucose values did not show significant changes as a result of autotransplantation. Following transplantation, a delayed peak insulin response was seen; however, basal, peak, and integrated insulin values were largely unaltered. Only K values, a measure of glucose disposal, showed severe alterations (2.44 ± 0.21 before operation to 1.24 ± 0.30 at 40 weeks after operation). Oral glucose tolerance tests (OGTT) (2.0 g/kg) demonstrated an increased peak hyperglycemic response after autotransplantation with increased integrated glucose responses. Insulin levels remained at those levels seen before operation, and glucose-dependent insulinotropic polypeptide (GIP) responses were unchanged during the OGTT as late as 20 weeks after operation. In conclusion, pancreas autotransplantation after total pancreatectomy results in significant metabolic alterations that the IVGTT fails to detect with absolute glucose or insulin levels. However, K values are significantly lowered, which indicates alterations in cellular glucose transport. The OGTT demonstrates hyperglycemia without increased insulin or GIP levels, which suggests an altered beta cell response to the enteric stimulus of insulin release. These changes are nonetheless well tolerated by animals that have remained clinically healthy and euglycemic in the basal state.

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CLINICAL PANCREAS TRANSPLANTATION has been employed with increasing frequency since its initial use in 1967.[1] Transplantation of beta cell mass has encompassed islet cell, segmental gland and, most recently, whole gland transplantation. Clinical results continue to favor optimism about long-range success; however, there are many aspects of postoperative pancreatic function that remain unknown. Specifically, the effect of such surgery on the integrity of pancreatic regulation of carbohydrate metabolism needs evaluation. Initial enthusiasm for segmental transplantation has been bolstered by reports of postoperative fasting euglycemia and "improved" insulin secretion.[1,2]

Hormonal regulation of insulin secretion and peripheral glucose metabolism is not completely understood, even in the normal organism. Recent investigation has demonstrated the importance of the insulinotropic hormone, GIP, in postprandial insulin secretion and the necessity of ambient hyperglycemia for GIP's optimal effect.[3–5] For this reason, GIP has been renamed glucose-dependent insulinotropic polypeptide and appears to be an integral part of the "enteroinsular axis," by which insulin secretion is regulated by enteric factors.

Segmental pancreas transplantation might be expected to have measurable and possibly undesirable effects on carbohydrate metabolism, as it can result in reduced beta cell mass, systemic drainage of insulin, and pancreatic denervation. For these reasons, the integrity of the enteroinsular axis may be altered, whereby postprandial enteric hormonal secretagogues of insulin release would be affected by the surgical alteration of transplantation. We therefore studied segmental pancreas transplantation in dogs specifically to document the stability of the transplant over a prolonged postoperative period. In addition, we tested the hypothesis that the combined effects of systemic release of insulin and pancreatic denervation would alter

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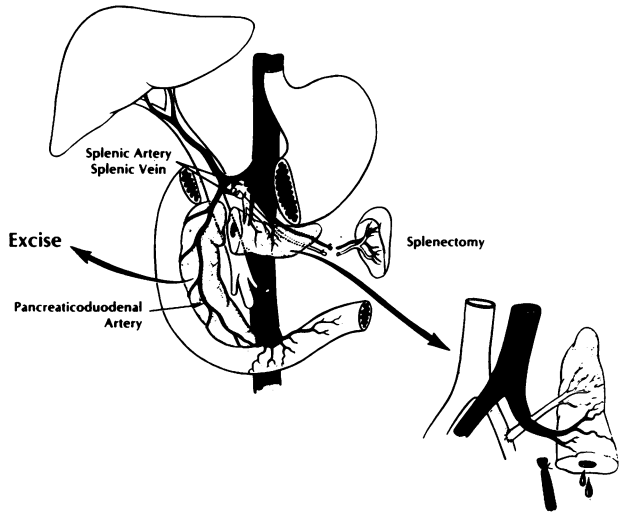


FIG. 1. The segmental pancreas autotransplant model. A total pancreatectomy is performed preserving the pancreaticoduodenal artery. The splenic lobe of the pancreas is anastomosed to the iliac vessels as pictured. Splenectomy is performed.

hormonal regulation of insulin release by the insulinotropic hormone GIP.

Materials and Methods

Pancreatic Autotransplantation (Fig. 1)

Mongrel dogs weighing 15–20 kg were fasted for 18 hours before operation. After induction of endotracheal inhalational anesthesia (halothane), a midline incision was made. Proximal pancreatectomy completely removed the pancreatic substance from the mesenteric side of the duodenum. Careful dissection of the pancreatic capsule with individual ligation of small branches of the pancreaticoduodenal artery was begun distally and carried proximally to the celiac axis. A constant avascular attachment was identified in this area, and the pancreas was transected. All pancreas on the duodenal side of this incision was removed, resulting in removal of 25–30 g of tissue.

Attention then turned to the splenic lobe of the canine pancreas. The splenic artery was identified at the celiac axis, and the splenic vein at its junction to the portal vein. Vascular loops were placed on the artery and vein, and all other lymphatic and nervous structures were divided. After complete isolation of the remaining pancreas, splenectomy was performed. An 18-gauge needle was then placed in the distal splenic artery for perfusion of the pancreas during completion of the anastomosis. During that time, distal intra-arterial infusion was performed with chilled normal heparinized saline containing 1% bovine albumin. The venous anastomosis was performed in an end-to-side fashion into the iliac vein with interrupted 7–0 monofilament sutures.

On completion of the venous anastomosis, the perfusion was stopped and attention turned to the arterial anastomosis, which was performed in an end-to-end fashion with 7–0 monofilament interrupted sutures. The vascular clamps were then released, and the graft was attached to the lateral abdominal side walls.

The animals were maintained on a liquid diet for the first 2 or 3 postoperative days. No animal received steroid, insulin, or glucagon therapy. At approximately the second and third postoperative day, all dogs began receiving Viokase® (1.4 g) supplements daily.

Intravenous and Oral Glucose Tolerance Tests

Oral glucose tolerance tests and intravenous glucose tolerance tests were performed on each animal before operation and between 2 and 4 weeks, 4 and 6 weeks, 10 and 20 weeks, and 30 and 40 weeks.

Intravenous Glucose Tolerance Test (IVGTT). IVGTT was performed by the rapid infusion of 20% glucose (0.5 g/kg body weight). After basal samples were taken, serum glucose samples were drawn at 2, 5, 10, 15, 20, 40, 60, 90, and 120 minutes and rapidly chilled on ice. These were centrifuged, and glucose determination was performed with the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Each serum sample was saved for insulin determination using the standard radioimmunoassay techniques performed by the University of Virginia Core Radioimmunoassay Laboratories.

Oral Glucose Tolerance Test (OGTT). Preoperative and postoperative OGTT were performed at the intervals described above. A bolus of 20% glucose (2 g/kg body weight) was delivered *via* a #18 French Salem feeding tube that was placed in each animal's mouth to ensure uniformity of the delivered dose. After basal samples for glucose, insulin, and gastric inhibitory polypeptide were taken, sequential samples at 30, 60, 90, 120, and 180 minutes were drawn. Serum glucose values were immediately gauged with the Beckman Glucose Analyzer II, as described above. Sequential insulin samples were measured as well. Samples for gastric inhibitory polypeptide were saved on Trasylol (Sigma Chemical, St. Louis, MO), using the GIP assay of the State University of New York Downstate Medical Center in Brooklyn, New York.[6]

Statistical Analysis

Data were analyzed using the SAS statistical package on a DEC VAX-751 computing system (Digital Equipment Corp., Maynard, MA).[7] Integrated time-compensated values were calculated for the glucose, insulin, and GIP response curves on the IVGTT:

$$\text{INT GLUC} = \frac{\sum_{i=n}^{i=2}\left[\left(\frac{\text{GLUC}_i + \text{GLUC}_{i-1}}{2}\right) \times (T_i - T_{i-1})\right]}{(T_n - T_1)}$$

$GLUC_i$ = glucose at each point of analysis; $GLUC_{i-1}$ = glucose at the previous time of analysis; T_n = length of test; and T_1 = first time point of analysis. INT INS and INT GIP were calculated with the same formula.

K values were calculated *via* a linear regression model of the 5- to 45-minute segment of the response curve plotted against the natural log of the dependent variable (glucose) to time:

$$K\ value_{5\to45} = 100 \times (SLOPE_{5\to45}),$$

where the $SLOPE_{5\to45}$ is obtained from the regression line of the natural log of the glucose values *versus* the time during the 5- to 45-minute period of the IVGTT response curve.

Glucose, insulin, and gastric inhibitory polypeptide values were grouped according to postoperative time and individually compared to the preoperative group with a Student's paired t-test.

Results

Clinical Status

Four female mongrel dogs underwent pancreatic autotransplantation (as described above) after completion of OGTT and IVGTT. All animals maintained preoperative body weight and eating habits with daily Viokase supplements.

Microscopic Analysis

Figures 2A and B show microscopic views of a segmentally transplanted gland 24 months after operation. Individual islets are identified in the absence of acinar architecture. No acute inflammation is seen. Peri-islet fibrosis is apparent without evidence of active inflammation.

Intravenous Glucose Tolerance Test

Table 1 details the IVGTT on normal preoperative animals as well as at 2–4, 10–20, and 30–40 weeks after operation. Normal preoperative animals had a fasting glucose value of 73 ± 4 mg/dl with an initial peak glucose value of 370 ± 43 mg/dl in response to 0.5 g/kg of rapid glucose infusion. After 120 minutes, an integrated glucose response of 219 ± 8 with a K value of 2.44 ± 0.21 was calculated. After operation, fasting euglycemia was demonstrated each time IVGTT was repeated. The integrated glucose values at each of the three postoperative periods were unaltered from preoperative values. K values, however, were significantly decreased: 1.66 ± 0.49 at 2–4 weeks, 1.22 ± 0.23 at 10–20 weeks, and 1.24 ± 0.30 at 30–40 weeks.

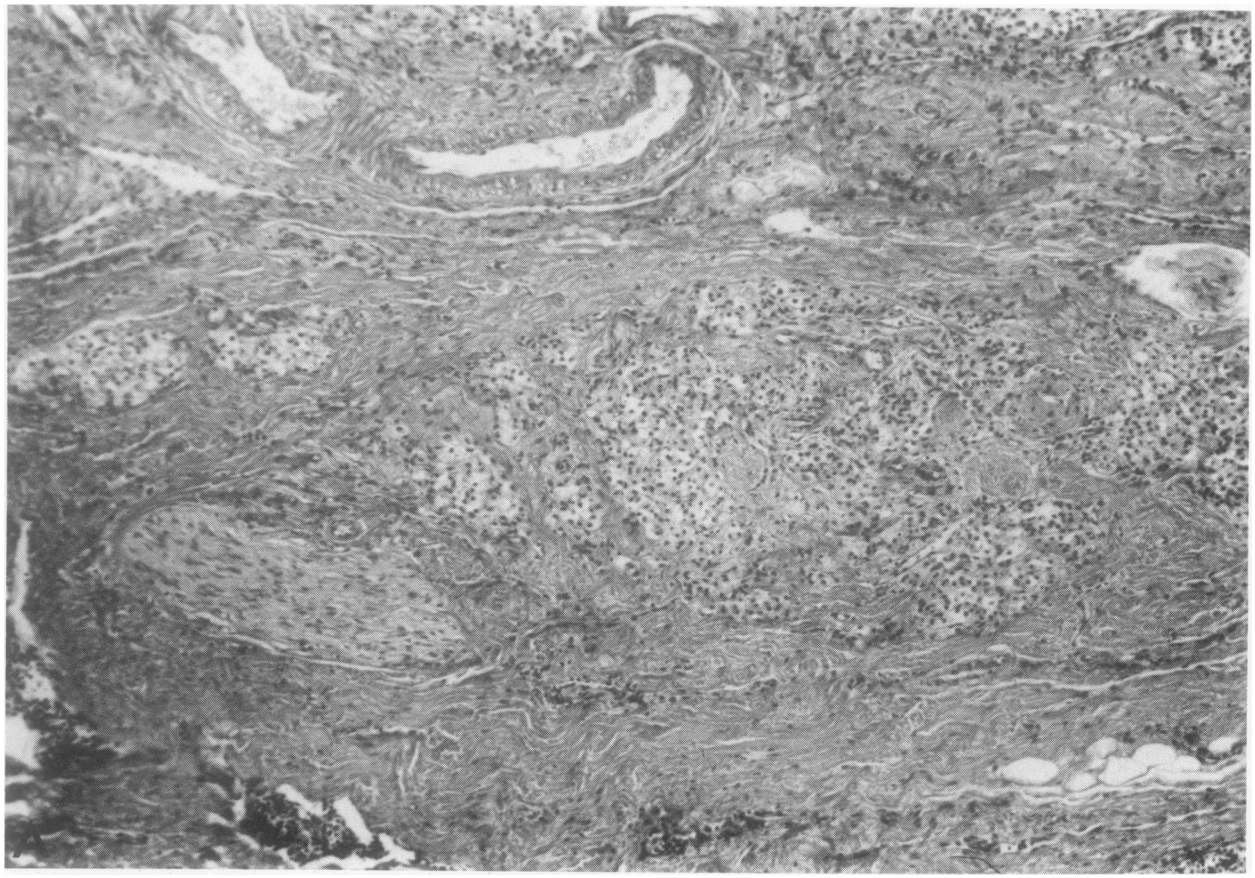
Insulin data in response to IVGTT are also presented in Table 1. Normal preoperative animals had a basal insulin value of 14 ± 4 μU/ml, which rapidly elevated to 52 ± 5 and 58 ± 6 μU/ml at 2 and 10 minutes, respectively. The integrated insulin value was 28 ± 3 μU/ml for the preoperative tests. At 2–4 weeks, a basal insulin value of 11 ± 2 μU/ml was obtained. Peak values of 61 ± 24 and 63 ± 20 were obtained at 2 and 10 minutes, respectively. The integrated insulin value of 26 ± 5 μU/ml was not statistically different from that obtained in normal preoperative animals. The 10- to 20-week and 30- to 40-week insulin values showed unaltered basal insulin values. The peak insulin at 10–20 weeks occurred somewhat later in the test (49 ± 15 μU/ml at 20 minutes); however, the integrated insulin response (29 ± 6) remained statistically unaltered from normal preoperative values. In the 30- to 40-minute period, the peak insulin value of 43 ± 10 μU/ml was demonstrated at 5 minutes; however, again, the integrated insulin value of 24 ± 4 μU/ml was not statistically different from that in normal preoperative animals.

Oral Glucose Tolerance Test

Table 2 shows the glucose, insulin, and gastric inhibitory polypeptide responses in normal preoperative animals after oral ingestion of 2 g/kg of glucose and again at 2–4, 4–6, and 10 –20 weeks after operation. Normal preoperative animals had a fasting glucose value of 78 ± 7 mg/dl with a peak glucose value of 115 ± 14 at 30 minutes after ingestion. The integrated glucose value was 87 ± 4 mg/dl. At 2–4 weeks, hyperglycemia was documented by 30 minutes; at 60 minutes, it reached a peak level of 244 ± 29 mg/dl. The integrated glucose value was statistically elevated at 191 ± 19 mg/dl. This effect was also documented at 4–6 and 10–20 weeks after operation. The peak glucose value occurred at 60 minutes for the tests at 4–6 weeks and at 90 minutes at 10–20 weeks. However, the integrated glucose response had stabilized at 150 ± 7 mg/dl (4–6 weeks) and 156 ± 3 mg/dl (10–20 weeks).

Insulin secretion in response to the OGTT is also presented in Table 2. Before operation, animals had an insulin response to oral glucose tolerance that peaked at 60 minutes at values of 61 ± 20 μU/ml. The integrated insulin response was 30 ± 4 μU/ml. At 2–4 weeks after operation, the basal insulin value of 14 ± 4 μU/ml was not statistically altered from that in preoperative animals. Peak insulin values occurred at 30 minutes after ingestion, and the integrated insulin response was 30 ± 9. Neither was statistically altered from control values. At 4–6 weeks and again at 10–20 weeks, fasting insulin values were not statistically altered from those of preoperative controls. As in the IVGTT, peak insulin levels occurred later after ingestion, but the integrated insulin response was not statistically different from that of preoperative animals (33 ± 6 at 4–6 weeks and 32 ± 8 at 10–20 weeks).

Data for the GIP in response to OGTT are also presented. Preoperative animals had fasting GIP levels of 450 ± 137 pg/ml, which peaked at 60 minutes at 1600 ± 389



FIGS. 2A and B. Microscopic evaluation of the pancreas autotransplant 24 months after operation reveals intact islet cells with surrounding fibrosis. No active inflammation or evidence of acinar architecture was demonstrated. Figure 2B is on opposite page.

pg/ml. The integrated GIP response for the normal preoperative animals was 1259 ± 182 pg/ml. At 2–4 weeks after operation, fasting GIP levels were not statistically altered from those in preoperative controls. Peak GIP levels occurred at 30 minutes, and the integrated value was not statistically different from that in normal controls (1015 ± 293). At 4–6 weeks and at 10–20 weeks, fasting GIP levels were not statistically altered from those of preoperative controls, and the integrated GIP response had stabilized.

Discussion

Pancreas transplantation has received increased attention as an attractive alternative to chronic insulin therapy for the treatment of diabetes. Despite recent enthusiasm for cadaveric whole pancreas allotransplantation, much of the current clinical experience has been with segmental pancreas transplantation either in living, related individuals or with cadaver donors. Sutherland's most recent report of the University of Minnesota experience includes 86 pancreas transplants in 75 patients.[1,2] The results of IVGTT studies in that group of patients suggest that K values, a measure of the rate of glucose metabolism, improved from a preoperative mean value of 0.58 to 2.19 6 months after transplant. Oral glucose tolerance data suggest fasting euglycemia 6 months after segmental transplantation in 12 patients. The data presented for several individual patients show what appears to be fasting hyperinsulinemia of more than 40 μU/ml. More detailed studies are lacking in this population, however.

Few reports analyze the stability of the endocrine function of segmental pancreas transplants over extended postoperative periods or provide a precise evaluation of the effects of this procedure on glucose metabolism. Segmental transplantation results in three important alterations in the pancreas: reduction of beta cell mass, systemic drainage of insulin, and denervation. The model of canine segmental autotransplantation allows analysis of the effects of complex surgical alteration of the gland on postoperative endocrine function in the absence of immune alterations of pancreatic function. We therefore evaluated the response of the segmental pancreas transplant to IVGTT and OGTT, as well as the morphologic features

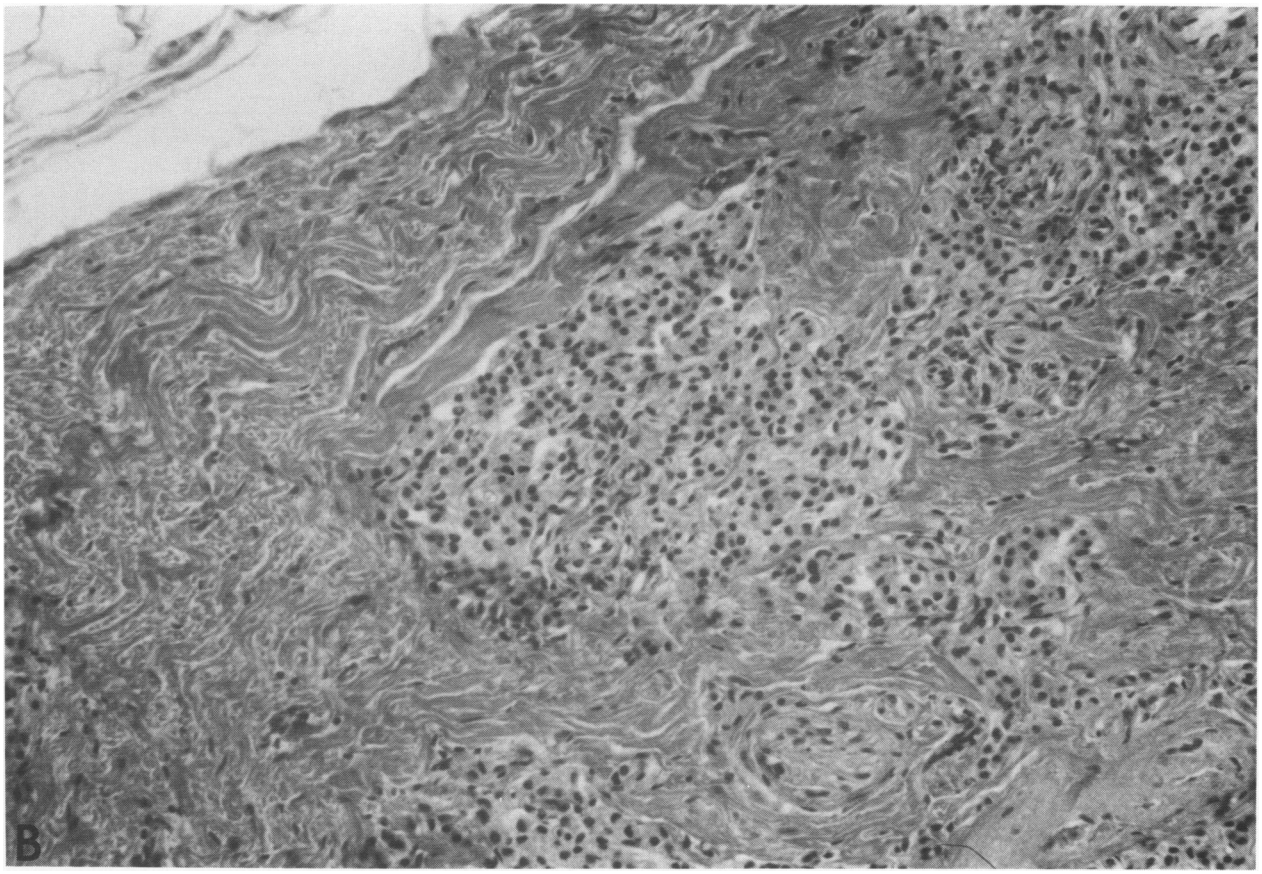


FIG. 2. (*Continued*)

and physiologic stability of the transplanted gland over an extended postoperative period.

Munda and colleagues examined segmental canine pancreas autotransplants microscopically at 37–43 days after operation and documented extensive graft fibrosis with residual intact islet architecture.[8] We corroborated these findings on microscopic examination of our freely draining, open-duct, pancreas autotransplant at 2 years (as shown in Figs. 2A and B). All acinar tissue was replaced by fibrosis, and intact islets are identified. Each surgical specimen weighed 25–30 g; therefore, we would approximate an 80% reduction in islet cell population, assuming all islets survived in the postoperative autograft.

The IVGTT is the standard method for the evaluation of the handling of an intravenous glucose load both clinically and in laboratory animals. Fasting glucose values of 80–90 mg/dl elevate to peak glucose levels of over 300 mg/dl after a 600-mg/kg bolus in normal animals.[9-10] Fasting insulin values of 8–12 μU/ml rapidly increase to 40 to 50 μU/ml after an intravenous glucose load of 600–1000 mg/kg. The K value for IVGTT and the integrated response for glucose and insulin measure separate parameters. Classically, the K value measures the slope of disappearance of rapidly infused glucose and hints at peripheral glucose disappearance that may or may not be modulated by insulin. We evaluated the IVGTT and OGTT using time-compensated integrals for glucose, insulin, and GIP (for OGTT). Those calculations give a more sensitive measure of appearance in the periphery than the standard basal and peak values.

Using IVGTT in an animal model similar to ours, Munda and associates demonstrated fasting euglycemia, peak glucose levels, and basal insulin values that were unaltered by transplantation.[8] In allotransplantation models, Kyriakides et al. reported "normal" glucose and insulin values after IVGTT, whereas Bewick and colleagues reported hyperinsulinemia.[11,12] Our data indicate that, in spite of comparable systemic insulin levels after intravenous glucose challenge, the rate of overall glucose metabolism (K value) is significantly impaired after segmental transplantation and remains abnormal for a prolonged period.

To assess the effects of the reduction in beta cell mass *per se* on glucose metabolism, Mizumoto et al. studied

TABLE 1. *Intravenous Glucose Tolerance Test (IVGTT)**

	Glucose (mg/dl)								
	Basal	2 min	5 min	10 min	20 min	40 min	120 min	Int G	K
Preop	73 ± 4	370 ± 43	267 ± 16	222 ± 11	146 ± 11	99 ± 7	86 ± 3	129 ± 8	2.44 ± 0.21
2–4 wk	80 ± 8	302 ± 43	242 ± 22	219 ± 16	177 ± 12	136 ± 14	93 ± 9	131 ± 10	1.66 ± 0.49†
10–20 wk	79 ± 10	325 ± 37	244 ± 19	219 ± 10	208 ± 15	157 ± 17	85 ± 9	142 ± 14	1.22 ± 0.23†
30–40 wk	83 ± 10	253 ± 41	237 ± 23	223 ± 14	199 ± 12	149 ± 5	89 ± 8	136 ± 7	1.24 ± 0.30†
	Insulin (μU/ml)								
	Basal	2 min	5 min	10 min	20 min	40 min	120 min	Int INS	
Preop	14 ± 4	52 ± 5	52 ± 5	58 ± 6	47 ± 8	21 ± 7	14 ± 3	28 ± 3	
2–4 wk	11 ± 2	61 ± 24	45 ± 15	63 ± 20	48 ± 15	27 ± 6	11 ± 3	26 ± 5	
10–20 wk	11 ± 2	41 ± 7	45 ± 13	47 ± 15	49 ± 15	39 ± 10	15 ± 3	29 ± 6	
30–40 wk	12 ± 3	41 ± 10	43 ± 10	41 ± 10	38 ± 9	33 ± 8	12 ± 2	24 ± 4	

* 0.5 g/kg min^{-1}, N = 4 in all groups.

† $p < 0.05$ (paired t-test) compared to preop.

the effects of major pancreatic resection on carbohydrate metabolism. They used 70–90% resection of the pancreas in normal dogs and reported postoperative fasting euglycemia, albeit with decrements of approximately 50% in K values.[13] Two groups of animals, "prediabetic" and "diabetic," with this resection were reported. As might be expected, the diabetic animals had higher glucose levels, depressed K values that averaged 0.41, and a severely decreased integrated insulin response. However, in the animals that tolerated the operation well with subsequent fasting euglycemia, insulin secretion was also severely altered.

We reported a 40–60% hepatic extraction of insulin over a wide range of ambient glucose and insulin values.[14] Thus, the differences seen between animals with major pancreatic resection with portal drainage and the animals that had pancreatic autotransplant show that the systemic release of insulin may result in normal systemic levels despite a decreased insulin response. This concept was supported by Gooszen and associates, who examined the

TABLE 2. *Oral Glucose Tolerance Test (OGTT)**

	Glucose (mg/dl)						
	0 min	30 min	60 min	90 min	120 min	180 min	Int G
Preop	78 ± 7	115 ± 14	114 ± 7	94 ± 6	80 ± 8	71 ± 5	87 ± 4
2–4 wks	80 ± 2	212 ± 35†	244 ± 29†	202 ± 18†	148 ± 26	103 ± 20	191 ± 19†
4–6 wks	85 ± 6	176 ± 44	324 ± 60†	291 ± 31†	225 ± 33†	124 ± 18	150 ± 7†
10–20 wks	87 ± 6	160 ± 23	208 ± 24†	227 ± 23†	174 ± 5†	136 ± 21	156 ± 3†
	Insulin (μU/ml)						
	0 min	30 min	60 min	90 min	120 min	180 min	Int INS
Preop	9 ± 2	46 ± 13	61 ± 20	51 ± 16	19 ± 3	11 ± 2	30 ± 4
2–4 wks	14 ± 4	58 ± 23	41 ± 14	39 ± 10	29 ± 13	22 ± 8	30 ± 9
4–6 wks	10 ± 2	38 ± 9	39 ± 10	46 ± 9	51 ± 16	25 ± 11	33 ± 6
10–20 wks	12 ± 1	26 ± 6	40 ± 18	54 ± 12	51 ± 18	26 ± 13	32 ± 8
	Gastric Inhibitory Polypeptide (pg/ml)						
	0 min	30 min	60 min	90 min	120 min	180 min	Int GIP
Preop	450 ± 137	1383 ± 296	1600 ± 389	1512 ± 280	999 ± 351	495 ± 224	1259 ± 182
2–4 wks	361 ± 148	2551 ± 476	2470 ± 492	1567 ± 351	1016 ± 299	779 ± 167	1015 ± 293
4–6 wks	508 ± 170	2636 ± 533	2482 ± 626	1704 ± 454	1288 ± 182	649 ± 144	1330 ± 201
10–20 wks	366 ± 67	1467 ± 392	1660 ± 315	1507 ± 235	1048 ± 188	523 ± 58	1037 ± 101

* 2 g/kg min^{-1}, N = 4 in all groups.

† $p < 0.05$ (paired t-test) compared to preop.

effects of transplantation on IVGTT performance.[15] In normal animals, a fasting insulin level of approximately 10 μU/ml rose to between 50 and 60 μU/ml during IVGTT. After pancreas autotransplantation (with a duct-obliterated segment), stimulated insulin levels reached 40–50 μU/ml, but higher values were seen after 30 minutes. These results suggest that the integrated insulin response to intravenous glucose administration is not impaired, as observed in our data. Since animals with partial pancreatectomy and portal drainage showed a decreased insulin response to less than the peak levels of 25 μU/ml, Gooszen et al. concluded that after reduction in beta cell mass, systemic drainage of insulin is important for the maintenance of peripheral levels of insulin that approach preoperative normal control values. Our data support this conclusion.

Florak and others attempted to dissect out the effects of beta cell reduction, systemic drainage, and pancreatic denervation on glucose disposal after pancreatic autotransplantation.[16] They evaluated IVGTT on normal dogs, segmentally autotransplanted dogs (in a model similar to ours), partially pancreatectomized dogs, and partially pancreatectomized dogs with *in situ* denervation. Dogs with reduction of beta cell mass had decreased fasting insulin and peak insulin responses, as well as a reduction of K values during IVGTT. Fasting glucose values were not reported, but peak glucose levels were not dramatically altered. After segmental transplantation, basal insulin values were normal but peak insulin levels were decreased. Interestingly, at 30 minutes, pancreas autotransplant animals had insulin values above normal. The authors concluded that the reduction of beta cell mass resulted in a lower peak insulin value in both the systemically drained and the portally drained transplant models. The significant reduction of K values seen in our study indicates altered glucose disposal in these animals, despite the fact that the animals were clincially well and maintaining stable body weight at 30–50 weeks after operation. Whether this alteration in glucose disposal is due to abnormal insulin action or to the disruption of other hormonal factors involved in glucose homeostasis remains uncertain.

The current study demonstrates that insulin secretion *is* altered during the hyperglycemic phase in postoperative OGTT. OGTT evaluates a more physiologic response to ingested glucose by virtue of its dependence on the enteric modulation of insulin release. It is well known that the gut affects overall response to glucose by stimulating the release of insulin via separate enteric hormonal mechanisms. In 1906, Moore and colleagues concluded that the duodenum produced a substance that affects glucose tolerance by stimulating the "internal secretion of the pancreas."[17] Perley and Kipnis demonstrated that oral glucose resulted in a greater insulin response than did the same amount of intravenous glucose[18] and concluded that the enteric mediation of the insulin response accounts for 60–70% of the insulin released after oral glucose. The principal enteric hormonal modulator of insulin release was identified in 1970 when Brown and colleagues isolated and characterized a small bowel mucosal polypeptide with 42 amino acids.[3,19] This peptide was capable of suppressing canine gastric acid secretion and was therefore named gastric inhibitory polypeptide, or GIP. Subsequently, Dupre and associates[4] and Andersen et al.[5] demonstrated that GIP augments insulin secretion in response to hyperglycemia and that the GIP-induced enhancement of insulin release correlates with the degree of hyperglycemia.[5] Because of its potent insulinotropic effect, GIP has more recently come to be known as glucose-dependent insulinotropic polypeptide.

It has been established that, after ingestion of glucose or a mixed meal, insulin and GIP levels rise rapidly.[20] In spite of the importance of GIP in postprandial insulin secretion, alterations in GIP levels after pancreas transplantation have not previously been investigated. The systemic drainage of insulin, or the disruption of the neural mediation of insulin release that results from transplantation, could be hypothesized to have direct consequences on the GIP–insulin relationship. Our data indicate the GIP response to ingested glucose is not altered after segmental transplantation, but that the insulin response to GIP may be significantly impaired. During OGTT, plasma glucose levels and the integrated glucose response were significantly elevated after operation. Therefore, the "normal" insulin levels and integrated insulin response to oral glucose are, in effect, deficient for the level of hyperglycemia achieved. Since the insulin response to hyperglycemia *per se* unaltered in the IVGTT, the relative insulin deficiency in the OGTT suggests an impairment of the beta cell response to the enteric hormonal stimulus to insulin release.

Systemic release of insulin after autotransplantation may have significant effects on glucose metabolism because of a possible lack of suppression of hepatic glucose output resulting from the loss of direct secretion of insulin into the portal venous circulation. Abumrad and associates studied the quantitative disposition of an intragastrically administered glucose load in normal animals.[21] After ingestion of an amount of glucose similar to that used in the current study, endogenous hepatic glucose production was consistently suppressed by 80%. Using an exogenous portal vein insulin infusion in awake dogs, these investigators concluded that the presence of insulin in the portal vein is important for glucose homeostasis. However, these studies used exogenous insulin infusions together with a background infusion of somatostatin to supporess endogenous hormone release.[22,23]

Alterations in hepatic glucose production rates may significantly affect overall glucose metabolism and have been implicated in glucose intolerance of chronic pancreatitis.[24] Our own previously reported preliminary studies of the relative effects of portal and systemic intravenous insulin infusion in normal dogs suggest that the intraportal delivery of insulin contributes minimally to the suppressive effect of insulin on hepatic glucose production.[25] Whether segmental pancreas transplantation alters the normal regulation of the hepatic production of glucose cannot be determined from the data in our study and awaits further investigation.

Finally, it has been hypothesized that the maintenance of normal glucose tolerance depends on the initial early insulin response to glucose, and that the denervation of the gland may be responsible for the blunted insulin elevation seen after surgical manipulation.[26] Strubbe reported the results of transplantation of the neonatal pancreas into alloxan-induced diabetic rats, using renal subcapsular transplantation of pancreatic tissue.[27] Before operation, a rapid elevation of insulin in response to oral glucose was documented; after transplantation, however, this rapid elevation was lost. In the denervated segmental grafts investigated in our study, there was no significant blunting of the early response of insulin to an intravenous glucose challenge although this early (2- and 5-minute) response appeared to decline during the 40-week postoperative period. We therefore conclude that, although denervation may alter the performance of dispersed pancreatic tissue, the effect on the insulin response of segmental grafts is minimal.

In summary, we found a number of potentially important effects of canine pancreas autotransplantation on the response to intravenous and oral glucose administration. Intravenous glucose testing to autotransplant animals reveals peripheral glucose and insulin levels that are not statistically altered from normal prospective controls. Interestingly, integrated glucose and insulin values *per se* did not identify major abnormalities. Only the K values suggest a significant alteration in glucose metabolism, which is not apparent from the basal or peak glucose levels obtained. These data agree with the preliminary findings of others[16] but, additionally and importantly, document that there is no further decline in IVGTT performance over a 30- to 40-week postoperative period.

More severe alterations in glucose metabolism are apparent in the OGTT performance seen after operation. Segmental pancreas autotransplantation resulted in an elevated integrated glucose response, and repeat oral glucose studies over 20 weeks documented no further alterations in OGTT performance. Before operation, peak insulin responses of 60 μU/ml were seen at 60 minutes. After autotransplantation, oral glucose administration resulted in rapid insulin elevations, which persisted for 120–180 minutes. This resulted in an integrated insulin response that was not different from that in preoperative animals, albeit in the face of significantly elevated glucose levels. Therefore, we consider the insulin response inappropriately low for the prevailing degree of hyperglycemia. Since the beta cell response to glucose is maintained after intravenous glucose challenge, the relative deficiency of insulin release after oral glucose suggests an alteration in the enteroinsular axis. Although pancreatic autotransplantation apparently has no influence on the GIP response to oral glucose, the ability of GIP to augment glucose-stimulated insulin release may be significantly impaired. Further studies are required to determine if the beta cell sensitivity to GIP is reduced or whether neural or hormonal factors account for the alterations seen after oral glucose administration. The clinical consequences of these findings remain unclear because the general health, body weight, and parameters of glucose metabolism remain stable in these animals over a prolonged postoperative period.

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