Insights Into Alloislets From Successful Autoislet Transplantation in Patients With Chronic Pancreatitis

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Human autoislet transplantation first began and was shown to be successful at the University of Minnesota in 1980.[1] Recipients of autoislet transplantation were people who had never had autoimmune diabetes but who had chronic, painful, unrelenting pancreatitis and normoglycemia. These were often young women with anatomical anomalies of the pancreatic duct. Each patient's pancreas was removed to relieve chronic pain and submitted to collagenase digestion to free up its islets. Then the islets were injected into a vein that emptied into the hepatic portal circulation. Wahoff et al (1995) proposed that 74% of recipients could be insulin-independent for longer than 2 years if at least 300,000 islets were autotransplanted in each patient.[2]

Extensive metabolic testing has been performed in autoislet recipients to better understand the physiologic mechanisms of their successes. An early study demonstrated that insulin and glucagon secretion in response to intravenous arginine appeared first in the hepatic vein[3] (Figure 1). The study also showed that insulin secretory responses to intravenous glucose were intact, and that the timing and the biphasic nature of insulin release was normal; however, because the number of islets autotransplanted was lower than the number of islets in a normal, healthy pancreas (≈1,000,000), the recipients' amount of insulin secretion was quantitatively less than that observed in sex, age, and body mass index–matched control subjects. A close correlation between the number of islets transplanted and the amount of insulin secreted in response to glucose and to arginine has been reported.[4]

To see whether autotransplantation of islets provides long-term control of blood glucose and whether intravenous glucose tolerance correlates with the number of islets transplanted, we analyzed data from a group of six patients who have been studied longitudinally from two to four times on an annual basis for as long as 13 years.[5] The number of islets transplanted ranged from 290,000 to 678,000. Fasting plasma glucose levels were normal in five of six patients who were up to 13 years post-transplantation. The individual with an elevated fasting plasma glucose received the fewest number of islets: 290,000. The HbA1c data indicated the same general trend; namely, that stable levels of HbA1c were established after autoislet transplantation and the highest level was obtained from the individual who received the fewest number of islets. Measurements of intravenous glucose disappearance were used to assess glucose tolerance. A statistically significant relationship existed between the glucose disappearance rate and the number of islets transplanted into the patients (Figure 2). The lower limit of normal glucose tolerance ($KG > 1.0$) was achieved with approximately 500,000 transplanted islets; greater numbers of transplanted islets provided higher levels of glucose tolerance.

An additional assessment of the number of islets required for a successful transplant was obtained from an analysis of insulin secretory reserve. This test involves giving the patient intravenous arginine pulses before and then during the third hour of a 3-hour intravenous glucose infusion. The glucose infusion is used to induce hyperglycemia, which provides beta-cell stimulation to maximize the insulin secretory response to intravenous arginine. The difference in the magnitude of the insulin response to the two intravenous injections of arginine represents the insulin secretory reserve. As with intravenous glucose tolerance, a statistically significant, linear relationship existed between the number of islets autotransplanted and insulin secretory reserve[4] (Figure 3). In both cases, that of intravenous glucose tolerance and of the insulin secretory reserve, it seems remarkable that a linear relationship existed between these measures and the number of islets autotransplanted, especially when one considers that the patients had been transplanted for varying periods of time (4–13 years) before the test was performed. The linear relationship suggests that the number of islets engrafted tends to remain constant through time, because the passage of time did not change the relationship between the numbers of islets transplanted and the variables of intravenous glucose tolerance and insulin secretory reserve. It is interesting to compare these results with those from insulin secretory reserve studies in patients who have undergone hemipancreatectomy for the purposes of providing a hemi-

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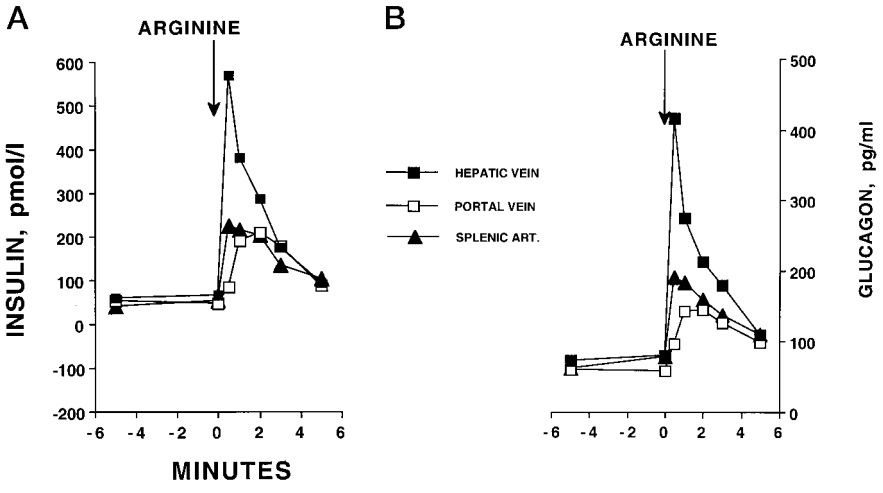

Figure 1. *Insulin and glucagon levels detected in the hepatic vein, portal vein, and splenic artery before and immediately after an injection of intravenous arginine into an antecubital vein [from Pyzdrowski et al (1992)]. Note that the hormones first appear in the hepatic vein, which reflects the presence of the autotransplanted islets in the liver.*

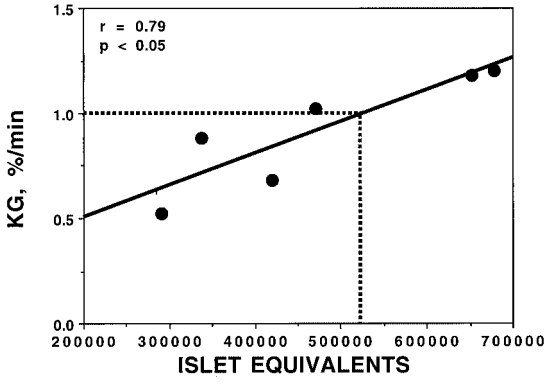

Figure 2. *Correlation between the number of islets autotransplanted in pancreatectomized non-diabetic patients [from Robertson et al (2001)] and the magnitude of the intravenous glucose disappearance rate. y axis, decline in glucose in mg/dL per minute.*

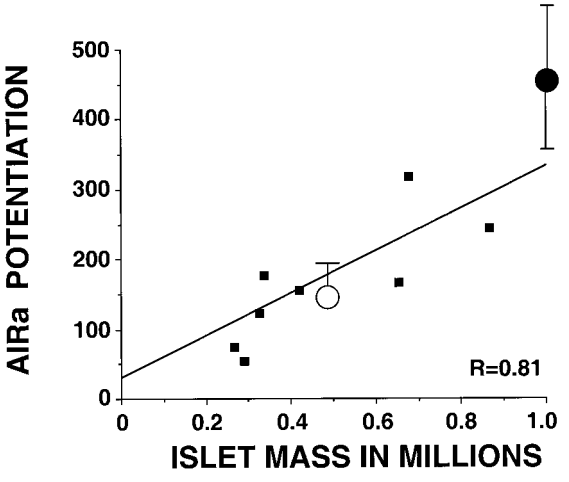

Figure 3. *Correlation between the number of islets autotransplanted in pancreatectomized non-diabetic patients and insulin secretory reserve as measured by glucose potentiation of arginine-induced insulin secretion [from Teuscher et al (1998)]. Solid squares = autotransplant recipients. Solid circles = normal control subjects. Open circles = hemi-pancreatectomized donors.*

pancreas for their siblings.[6] Hemi-pancreatectomized patients have insulin secretory values that fall on the same line that describes the linear correlation between the number of islets autotransplanted and insulin secretory reserve (Figure 3). In other words, 500,000 to 600,000 islets are predicted to remain in the donor after hemi-pancreatectomy, and their insulin secretory reserve values correspond to those of autoislet-transplanted patients who have received approximately 500,000 islets.[4]

Alpha-cell function has also been examined in recipients of intrahepatically autotransplanted islets. One study showed the puzzling result that the expected increase of glucagon secretion during hypoglycemia did not occur[7] (Figure 4). This observation led to experiments in dogs in which glucagon secretion from autoislets transplanted intrahepatically was compared with that from autoislets transplanted intraperitoneally. Intraperitoneal islets released glucagon during insulin-induced hypoglycemia, whereas the intrahepatic islets did not[8] (Figure 5). The mechanism for this failure of intrahepatic islets to release glucagon is unknown. Similar observations were made in two type 1 diabetic patients who had successfully maintained functioning allografted islets and were insulin-independent for more than 3 years. As with the autoislet recipients, the alloislet recipients failed to secrete glucagon during insulin-induced hypoglycemia. This means that even after 3 years of maintaining normal glucose levels, these two type 1 diabetic patients were not able to secrete glucagon from their native pancreatic alpha cells nor from

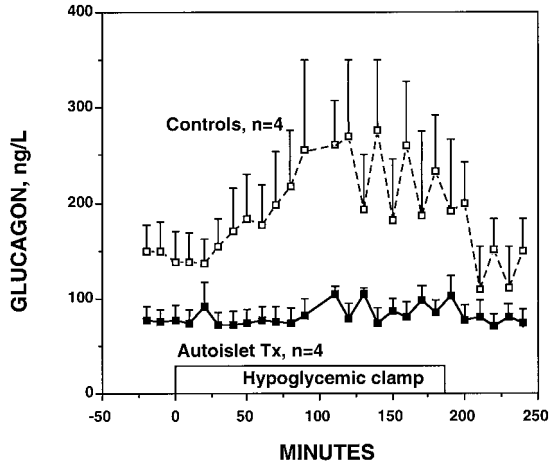

Figure 4. *Failure of glucagon release from intrahepatic autotransplanted islets in pancreatectomized patients who had been made hypoglycemic by intravenous insulin infusion [from Kendall et al (1997)].*

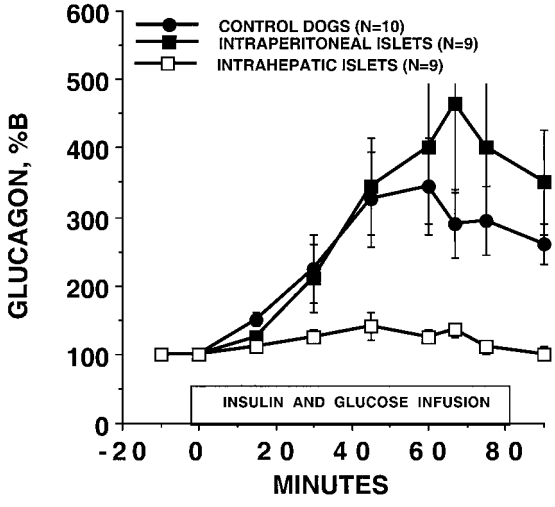

Figure 5. *Comparison of glucagon responses to insulin-induced hypoglycemia in dogs from autotransplanted islets placed either in the liver or in the peritoneal cavity. Glucagon was secreted by intraperitoneal but not intrahepatic islets [from Gupta et al (1997)].*

their donated intrahepatic alpha cells during insulin-induced hypoglycemia.

Notably, all of the alloislet and the autoislet recipients had glucagon responses to intravenous arginine. Whether or not this absence of glucagon responsiveness to hypoglycemia is clinically meaningful is not known. Nonetheless, counterregulation of hypoglycemia may become an important clinical issue for patients receiving islet transplantation, particularly should they need to return to insulin injections for management of hyperglycemia, and thereby once again become at risk for hypoglycemia. Glucagon is the primary defense against hypoglycemia because it is normally released from the islets when glucose levels fall below 55 mg/dL. This hormone then travels through the portal circulation to the liver, where it induces the rapid onset of glycogenolysis and increases glucose production, thereby returning blood glucose levels to normal. If difficulties with avoiding hypoglycemia become evident in intrahepatic islet recipients, then sites for autoislet and alloislet transplantation other than the liver should be considered in the future.

Alloislet transplantation for nondiabetic patients undergoing pancreatectomy for chronic, painful pancreatitis remains an uncommon practice in the United States and elsewhere. It seems reasonable to consider this procedure more frequently and to use it earlier in the course of the disease when it becomes obvious that the patient will eventually undergo pancreatectomy. Avoidance of certain diabetes after pancreatectomy is a very worthwhile pursuit and justifies the minimal risks of intrahepatic transplantation of islets.

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