

Islet Transplantation a Decade Later and Strategies for Filling a Half-Full Glass

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Alloislet transplantation for the treatment of type 1 diabetes enjoyed highly favorable status in the first half of the last decade but declined in favor during the second half. In this *Perspective*, I will briefly review the literature published in this area from 2000 to 2010 for the purposes of extracting lessons we have learned, considering whether the procedure should be deemed a partial success or a partial failure, and offering several strategies to improve alloislet transplantation outcomes in the future. In the end, I hope to strike a positive note about where this procedure is going, and how it will be applied to establish insulin independence in patients with type 1 diabetes. *Diabetes* 59:1285–1291, 2010

Successful pancreatic islet transplantation was established using rodents in 1972 and became a reality for humans in 1980. The application of this technology to patients with type 1 diabetes proved to be difficult and, for various reasons, lagged as a successful procedure until 2000. That year, the seminal publication by Shapiro et al. (1) from the University of Alberta, Edmonton, appeared and caused a huge wave of excitement and optimism about a cure for type 1 diabetes. A solution to insulin-induced hypoglycemia, perhaps the most vexing complication to insulin-based therapy, appeared to be at hand. Now, a decade later, a more circumspect attitude of reflection and retooling pervades the picture. This is an archetypical scenario for research findings that make a big splash in the scientific and lay press. Nonetheless, the facts remain. Seven consecutive type 1 diabetic patients were rendered insulin independent and free of hypoglycemia by islet transplantation, a remarkable accomplishment that spawned many research programs world-wide focused on curing diabetes with this procedure.

In this *Perspective* I will briefly review the recent history of successful islet transplantation and point out some of the lessons we have learned from this intensive experience. This will be followed by a consideration of whether this technology is more success or failure. The final section will look to the future, i.e., how do we apply the lessons we have learned to modify islet transplantation so that it will come closer to the expectations it elicited in 2000?

Lessons learned. The consensus father of islet transplantation is Paul Lacy. His vision, leadership, and hard work

established the procedure of using the liver as a site for successful islet transplantation. The transplants normalized glycemia in rats previously made diabetic by streptozotocin injection (2). As he and his colleagues began publishing manuscripts, it did not take long for the surgical community to apply this technique to humans (Fig. 1) (3). This proved to be a much more ambitious task than first imagined. Transporting pancreata isolated from brain-dead donors on life support, the inherent delays in islet isolation, the presence of autoimmune disease in the recipients, and the need to use powerful immunosuppressive drugs with significant side effects all presented significant barriers.

Najarian and Sutherland at the University of Minnesota transplanted islets in nondiabetic recipients who were their own donors and reported reproducible successes beginning in 1980 (4). The patients had various forms of chronic, unrelentingly painful pancreatitis and each underwent a total pancreatectomy for pain relief and nutritional rehabilitation. Rather than dispose of the patient's resected pancreas, the clinical researchers used it to make a crude extract of islets that was returned to the operating room within 2 h. The islets were infused over 30 min into the patient's liver while hepatic portal venous pressure was monitored. A summary of the results reported that if over 300,000 autoislets could be transplanted, the success rate of preventing diabetes for more than 2 years was 74% (5). Nonetheless, the first reproducible successes with allografts were not reported until 2000.

The autoislet experience was very encouraging because it proved that islet transplantation in nondiabetic humans was feasible. The stage for future successes in alloislet transplantation in patients with type 1 diabetes was set. Case reports and small patient series' revealed evidence for function of islets after transplantation and brief or partial improvement in glycemic control (6–11). One vexing variable was the irony that one of the drugs important generally for transplantation success, cyclosporine, had inhibitory effects on β -cell function (12–19). Oddly, this became the pattern for other important immunosuppressive drugs (3), especially glucocorticoids (14,18,20–22). This led to the use of a glucocorticoid-free immunosuppressive regimen developed by Shapiro et al. (1), which in turn led to their now historic series of successful islet transplants in type 1 diabetic patients. Another key aspect of the Edmonton approach was to use an average of two sequential islet transplants to establish normoglycemia.

Over time, however, the successes enjoyed by the Edmonton group began to slowly diminish. In the year 2000, the first seven patients who were insulin free had normal or nearly normal levels of glucose and A1C. Over 2 years the series had grown to 17 patients, 14 (86%) of whom were C-peptide positive and 11 of whom remained insulin free, although two were using oral hypoglycemic

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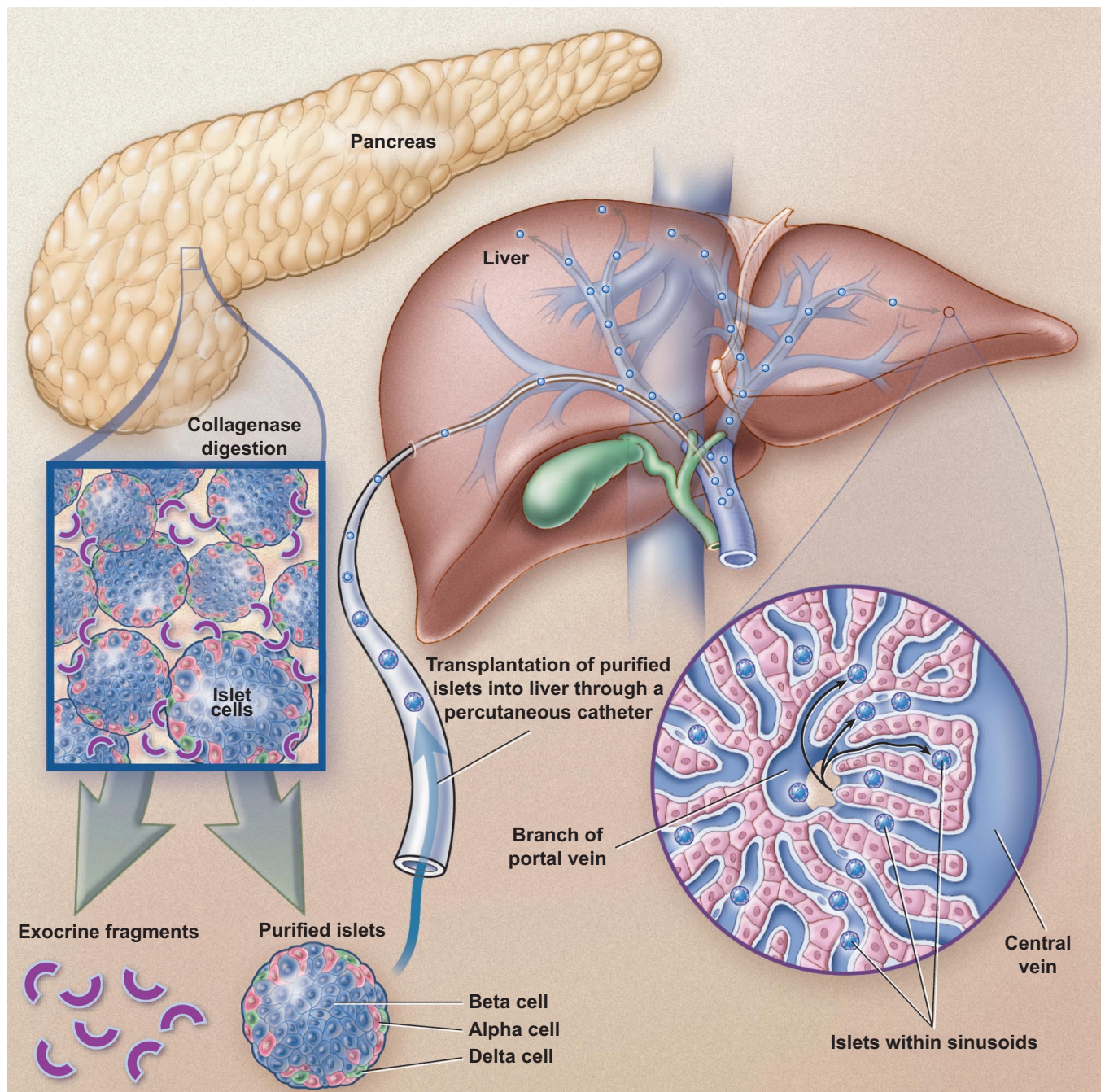


FIG. 1. General method of intrahepatic islet transplantation. Islets are removed from a donated pancreas by collagenase digestion, followed by purification to separate the islets from exocrine tissue. Islets are then infused by gravity into a catheter lodged in the hepatic portal vein. Blood flow within the vein carries the islets into the liver tributaries where they lodge within the sinusoids and establish vascular connections. Reproduced with permission from ref. 3.

agents (23). By 2005, the Edmonton series had grown to 66 patients, 85% of whom were C-peptide positive but only 15% of whom were insulin-free (24). The other 85%, who were again using insulin, were reported to be using less than they had been pretransplantation. Using these data, the median time to a return to insulin therapy was calculated to be ~15 months.

Meanwhile, the Immune Tolerance Network (ITN) had undertaken a multicenter trial of alloislet intrahepatic transplantation using the Edmonton protocol. The goal was to establish the fidelity with which nine centers in Canada, the U.S., and Europe could reproduce the initial Edmonton results. This consortium reported in 2006 (25)

that, of 36 type 1 diabetic subjects studied, 44% achieved the primary end point of insulin independence with adequate glycemic control 1 year after islet transplantation. It is noteworthy that previous experience with islet transplantation at the various research sites was strongly associated with success in achieving the primary end points. Of the 18 subjects, 12 (67%) were successful at 1 year post-transplant at sites where 4 or more patients had been transplanted in the preceding 2 years. Only 4 of 18 subjects (22%) were successful at sites where there was a history of less than four transplantations previously. This outcome clearly signaled that the procedure itself has a steep learning curve. At this time, it remains more of a

research procedure than one that is generally applicable to treating patients with type 1 diabetes.

During the past decade other groups reported results that were generally in agreement with the Edmonton and ITN outcomes. As early as 2000, Oberholzer et al. (11) reported that of 13 of 13 alloislet recipients had measurable blood C-peptide levels for at least 3 months, as did 7 of 11 recipients at 6 months and 5 of 8 recipients at 1 year post-transplant. Froud et al. (26) used the Edmonton protocol and reported success rates of 79% for insulin independence at 1 year and 43% at 18 months for 16 recipients. Toso et al. (27) used sequential kidney followed by islet transplantation and the Edmonton protocol. Of 8 patients transplanted, insulin-free status was achieved in all for at least 3 months, and 5 of 11 were insulin-free after an average of 24 months (11–34). O’Connell et al. (28) reported that of six recipients, two were insulin-free at 24 months. Cure et al. (29) reported seven patients who underwent the islet after kidney transplantation approach; two achieved insulin-independence and six had persistent graft function at 1 year. Deng et al. (30) compared islet transplantation alone (ITA) with islet after kidney (IAK) transplantation. They observed partial function (C-peptide positivity) at 24 months in four of eight and six of six recipients in the ITA and IAK groups, respectively, as well as insulin-independence at 24 months in four of eight and five of six, respectively. These reports from groups in various parts of the world using more or less the same Edmonton protocol, some with the added feature of studying islet after kidney transplantation, generally achieved similar results reported by the Edmonton and ITN groups. The overall conclusion of these studies is that islet transplantation can be considered largely successful at 1 year with a decline thereafter to an average success rate (insulin-independence and at least nearly normal glycemia) of 50% at various times during the 2nd year, and appreciably less at 5 years post-transplant.

Do persistently measurable C-peptide levels combined with either a return to less intense insulin therapy and less hypoglycemia or, alternately, a state of insulin-independence but not completely normal A1C levels both represent successes, partial successes, partial failures, or failures? These questions are still being debated.

Partial failure or partial success? The analogy of whether a glass is half full or half empty seems unavoidable in an analysis of success versus failure in alloislet transplantation. The answer to this question is in the eye of the beholder. To the skeptic’s eye, the procedure looks interesting, but is replete with problems. Given the current nearly normal life expectancy of people with type 1 diabetes who are well managed with insulin-based treatment, an invasive procedure with a 50% chance of success for only 1–2 years does not seem very useful. To the optimist’s eye, a different conclusion might be reached. Certain patients with type 1 diabetes are difficult to manage medically and have a very poor quality of life because of recurrent hypoglycemia and rapid development of chronic complications secondary to chronic hyperglycemia. The Diabetes Care and Complications Trial (31) established that maintenance of A1C levels less than or equal to 7% is mandatory for minimizing complications. A procedure, such as alloislet transplantation, which shows promise of providing C-peptide positivity, nearly normal A1C levels, and strikingly fewer episodes of hypoglycemia for as long as 5 years, cannot be easily dismissed (24,32–33). Furthermore, initial reports have appeared

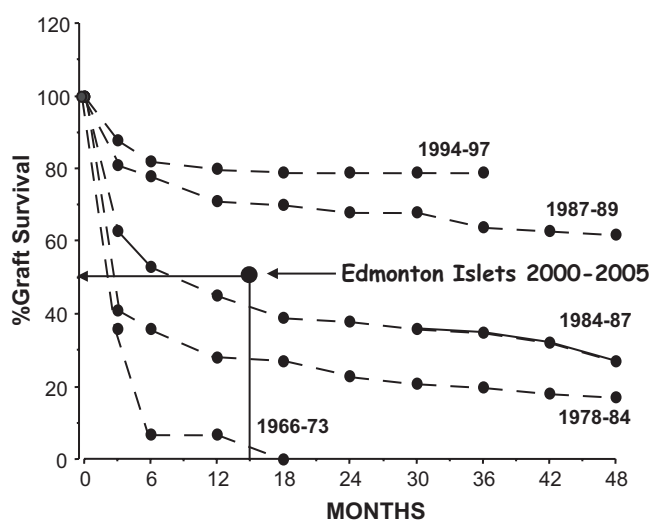


FIG. 2. Comparison of rates of progress of alloislet transplantation versus pancreas transplantation as therapy for type 1 diabetes. The first alloislet transplant to be reported as successful appeared in 1980, 20 years earlier than the Edmonton series was reported. The first pancreas transplant to be reported as successful appeared in 1966, 18 years earlier than the 1984–1987 series was reported. At 15 months post-transplant, the Edmonton series of alloislet transplants for the years 2000–2005 compared favorably with the success rate of pancreas transplants for the years 1984–1987. Data from refs. 24 and 38.

claiming that islet recipients have macro- and microvascular as well as quality of life benefits from restoration of C-peptide secretion even if A1C levels are not normalized (34–36).

An objective approach to evaluating the progress of islet transplantation is to compare its history to that of pancreas transplantation. The procedure of pancreas transplantation, originated at the University of Minnesota, struggled greatly in its early days with high patient mortality and failure of grafts by 6 months (37). However, a return to the canine lab to reshape protocols and the advent of cyclosporine changed things dramatically. In the ensuing decades, a gratifying increase in pancreas survival and decrease in patient mortality took place. At its current zenith of success, pancreas transplantation enjoys virtually no patient mortality attributable to the surgery and an average of 80% success 3 years post-transplantation (38). Plotting success rates as a function of time (Fig. 2), one sees that islet transplantation might not be doing quite as poorly as one might at first think. Pancreas allograft survival at 15 months post-transplant in the third epoch of this procedure (1984–1987) was precisely that of islet transplantation in its first successful years of 2000–2005, namely, 50%. This is an argument for patience as modifications of islet transplantation emerge.

A major deficiency of virtually all published studies of islet transplantation is the lack of a suitable control group of medically managed patients. While one might argue that islet transplantation improves the health and lives of islet recipients, this is not the central issue. Such an argument begs the question of whether the complicated and expensive procedure of islet transplantation performs better than standard insulin-based therapy. Without a randomized, nontransplanted control group, there is very likely a selection bias in transplanted groups. Patients who choose islet transplantation do so because they view their quality of life as poor, most often because of recurrent hypoglycemia. It is not always clear from published reports how

objectively the diagnosis of recurrent hypoglycemia was made or how vigorously such patients underwent a period of insulin-based management by skilled diabetologists. Consequently, one cannot be certain of the claim that partially failed islet transplantation leads to the use of less insulin and less hypoglycemia on a cause-effect basis. It could just as easily be that patients who enter transplant programs come under close clinical scrutiny by interested diabetologists who begin managing them more skillfully. The sole study that did include a medically managed control group was reported by Thompson et al. (36). In this study, 44 patients were candidates for islet transplantation; 27 became islet recipients whereas 17 continued on medical management. The group receiving transplants were reported to have less likelihood of progression of retinopathy than the medically managed patients. However, the results are confounded by two facts. First, although the two groups had comparable durations of diabetes, no randomization procedure was used to determine which patients would be transplanted, and, second, A1C levels at entry into the study were significantly lower in the transplant group. Nonetheless, this is a valuable study that illustrates the possibility for randomized studies to ascertain whether islet transplantation accrues additional benefits compared with intensive medical management.

Strategies to top off the half-full glass

Fully evaluate islet function before and after transplantation. With few exceptions, published reports of islet transplantation in type 1 diabetes have not adequately assessed the level to which endogenous insulin secretion is restored by the procedure. In most instances, basal levels and sometimes glucose-stimulated responses of C-peptide from recipients post-transplant are provided. Prior to transplant, only meager laboratory data about functionality of the islets to be transplanted are generally obtained. Typically, islets are stimulated with low and high concentrations of glucose in static incubations, and data are reported as a “secretory index” (insulin or C-peptide responses to the higher glucose concentration divided by the response to the lower glucose concentration). This practice at best relates only to whether the islets are alive or dead and imparts little about their degree of functionality. Consider, for example, that a fold response (usually 1.0 or a doubling is considered acceptable) to the higher glucose challenge will be dramatically affected by the baseline value. The lower the denominator used to divide the numerator, the more exaggeratedly high the quotient will look. What is needed is assessment of glucose-induced insulin secretion by either static or perfusion protocols. The former uses several glucose concentrations so that a half-maximal effective concentration can be calculated; the latter uses multiple samples during perfusion so that assessment of first- and second-phase responses to glucose stimulation can be obtained. These approaches would provide much more sophisticated information about the donor islets used for human transplantation and would go a long way in interpreting the clinical outcomes obtained in recipients. The usefulness of more intensive functional studies can be easily appreciated from the autoislet experience in humans. In this scenario, the number of islets transplanted correlates very well with the magnitude of insulin responses to several stimuli (39).

Improve methods of islet preparation. Reported outcomes in the current literature have come from programs that made heroic efforts to procure pancreata as quickly as

possible and then produce islet preparations that were as pure as possible. This involved exposure of islets to collagenase for variable periods of time followed by extensive centrifugation in cold temperatures. As many as 50% of islets are lost during this routine. The 50% that are recovered after purification by cold centrifugation are, not surprisingly, often damaged. The method of counting viable islets afterward may or may not include damaged islets that are not totally dead. It seems very likely that the number of healthy, transplanted islets is significantly overestimated, meaning the recipients may not have received the stated goal of 6,000 healthy islets/kg body mass. Transplanting 6,000 islets/kg body mass delivers roughly 420,000 islets per person, 40–50% the number of islets in a pancreas of a nondiabetic human. This number is similar to that contained in the remaining pancreatic segment in hemipancreatectomized donors and in the recipient of a hemipancreas, and is adequate to maintain normoglycemia for many years (40,41). Yet, the alloislet success rate is on average only 50% at 15 months. An important difference is that islets used for autoislet transplantation are not purified and undergo much less stress pretransplantation. One answer to the alloislet problem may be to eliminate the cold centrifugation step (42). Cold centrifugation minimizes the total tissue mass used to infuse islets into the liver, which is thought to lessen the likelihood of complications such as hepatic portal hypertension or lobar infarction. However, this may be a case of too much caution because autoislet transplantation, in which there is no purification, has no significant history of either complication.

Consider nonhepatic sites for transplantation.

Lacy's group originally recommended the liver, based on their rodent studies, and thereafter it was the site traditionally used for human auto- and alloislet transplantation. However, not only is the liver the site where ingested environmental toxins accumulate, but it is also where orally administered immunosuppressive drugs that are toxic to β -cells are concentrated. Drug concentrations in hepatic portal venous blood are two- to threefold greater than in systemic circulation (43,44) and reach concentrations that inhibit β -cell function in vitro (3,12–19). This and other complications of currently available immunosuppressive drugs (infection, potential cancer) demand that the search for less toxic drugs continue unabated so that the islet, as well as pancreas, transplantation approach can become more clinically acceptable.

Take full advantage of α -cell function in transplanted islets.

Intrahepatic islets do not have normal glucagon responses to hypoglycemia (Fig. 3), although they do respond normally to other stimuli, such as arginine. This has been demonstrated in human autoislet recipients (45,46), human alloislet recipients (47,48), and animals (49,50). There are numerous potential reasons for this defect (51). A likely explanation is that glucose flux within the liver comes into contact with α -cells on the periphery of transplanted islets. This is especially relevant during hypoglycemia when glycogenolysis is stimulated by catecholamines and central nervous system inputs. The intimate contact between intrahepatic glucose flux and α -cells in the islet allograft abrogates the hypoglycemic signal delivered to the transplanted α -cells from systemic blood coursing through the hepatic artery. This hypothesis was tested in animals that received alloislet transplantation in hepatic and nonhepatic sites and thereafter underwent insulin-induced hypoglycemic challenges before and

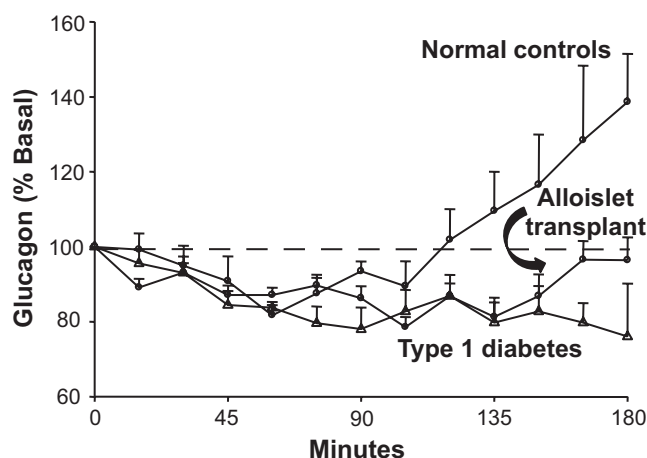


FIG. 3. Nondiabetic control subjects have plasma glucagon responses to insulin-induced hypoglycemia during a stepped hypoglycemic clamp. This response is absent in patients with type 1 diabetes as well as patients who have received successful intrahepatic alloislet or autoislet transplantation. Reproduced from ref. 47.

after prolonged fasting (50). In all sites except the liver, glucagon responses to hypoglycemia were present. When the intrahepatically transplanted animals underwent prolonged fasts and hepatic glycogen depletion, the initially absent glucagon responses to hypoglycemia were recovered (Fig. 4). Refeeding the animals to replete liver glycogen caused the glucagon response to hypoglycemia to disappear once again.

The clinical implications of these data are readily apparent. It is very important to retain α -cell responses to hypoglycemia in humans who undergo islet transplantation, return to insulin therapy, and become once again at risk for hypoglycemia. It is established that glucagon responses to hypoglycemia from the native pancreas of type 1 diabetic patients is defective because of absent signaling from neighboring β -cells. Alloislets transplanted in nonhepatic sites will respond to hypoglycemia and will protect the patient with a partially successful transplant who uses insulin to manage hyperglycemia. What alternate sites might be considered? Preclinical literature supports consideration of celiac artery, intravenous access to lung, intrapancreas, intramuscular, subcutaneous, thy-

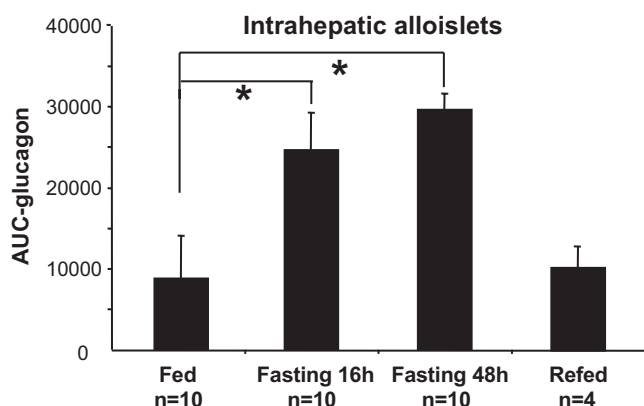


FIG. 4. Restoration of absent glucagon responses to hypoglycemia from intrahepatic islets in rats after prolonged fasting. Liver glycogen depletion caused by prolonged fasting results in restoration of the glucagon response to hypoglycemia. Absence of glucagon responses recurs after refeeding. This abnormality in α -cell function does not occur in fed animals if islets are placed into nonhepatic sites. Reproduced with permission from ref. 50. * $P < 0.05$ – 0.01 .

mus, testis, intracisterna magna, omental pouches, bowel surfaces, peritoneal cavity, spleen, bone marrow, and kidney capsule (50,52–54). I believe the use of liver should be reconsidered and a new look should be given to other sites first examined in 1972 but passed over for human use.

Bridge to the future. A valid argument against islet transplantation as a treatment for type 1 diabetes is the undeniable arithmetic that not nearly enough pancreas donors exist to treat patients with type 1 diabetes, let alone all people with type 1 and type 2 diabetes, especially in the face of the current diabetes epidemic. Does this mean we have been wasting our time and resources by studying islet transplantation? I don't believe so. There will always be diabetic patients who need β -cell replacement by transplantation of islets or the pancreas. One group of patients comprises those with rapid development of secondary complications despite optimal medical care. Another group is made up of patients with the neurological disorder of autonomic insufficiency, which is accompanied by a 50% death rate within 5 years of diagnosis. They are clearly candidates because successful pancreas transplantation converts this death rate from 50 to 10%. One must also consider what the future may bring. Our experiences with islet transplantation have taught us lessons that will be important for the use of β -cell surrogates, be they stem cell derivatives or modified cell lines. We have learned about culturing cells, isolating islets and β -cells, identifying safe and physiological sites for transplantation, avoiding immunosuppressive drugs that are toxic to β -cells, meeting environmental needs for physiological α -cell function, and selecting appropriate patients for β -cell replacement. This is important information to use as we continue to meet the challenge of creating better means of controlling hyperglycemia and avoiding its complications. We just need to continue on with new scientific work until the transplantation glass is successfully filled.

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