Islet Transplantation as a Treatment for Diabetes — A Work in Progress

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In 1993 the diabetes control and complications trial (DCCT) established the modern standard of care for the medical management of type 1 diabetes mellitus. The DCCT randomly assigned 1441 patients to conventional or intensive treatment. The latter included multiple daily determinations of blood glucose levels at home by finger stick; combinations of daily injections of long-, intermediate-, and short-acting insulin; and dietary and psychological support. The clinical outcomes in terms of secondary complication rates were much better in the intensively treated group than in the conventionally treated group; thereafter, intensive treatment became the norm. More recent improvements in home glucose and glycosylated hemoglobin monitoring and insulin preparations have further enabled patients with diabetes to attain near-normal glycemic control without frequent episodes of hypoglycemia.

In addition to improving the ability of the medical community to control glycemia in patients with diabetes, the DCCT also provided a stronger rationale for the use of pancreas transplantation. Worldwide, the three-year organ-survival rate for simultaneous kidney and pancreas transplantation is approximately 70 to 80 percent, which is similar to the rates for most other types of organ transplantation. When successful, pancreas transplantation is particularly effective in patients with type 1 diabetes and autonomic insufficiency, who struggle with glycemic control, postural hypotension, gastroparesis, and diarrhea and have a dramatically shortened life span. Pancreas transplantation is more likely to result in normal glycosylated hemoglobin levels than is the intensive insulin-based approach to management prescribed in the DCCT. Long-term studies of motor, sensory, and autonomic neuropathy have demonstrated that these complications stabilize after pancreas transplantation, and native-kidney biopsies have shown a dramatic reversal of mesangial accumulation and basement-membrane thickening 10 years after the establishment of normal glucose levels by pancreas transplantation. Macrovascular complications are also stabilized by pancreas transplantation.

Quality-of-life studies indicate that patients who undergo successful pancreas transplantation feel that the normalization of glucose levels and the freedom from daily insulin injections outweigh the problems caused by transplantation and its attendant immunosuppression.

These favorable results were obtained in a highly selected group of patients who had major difficulties related to both achieving glycemic control and the disease itself and thus do not represent outcomes from randomized trials comparing medical management with pancreas transplantation. Nonetheless, the clinical outcomes of pancreas transplantation have been impressive enough for the American Diabetes Association to recommend in 2000 and again in 2003 that simultaneous pancreas transplantation should be considered at the time of kidney transplantation, that pancreas transplantation alone should be considered for patients with unacceptably poor metabolic control and quality of life despite optimal medical treatment, and that islet transplantation should still be considered an experimental procedure.
Success with pancreatic islet transplantation in series of patients far smaller than those involved in pancreas transplantation has led to optimism that islet transplantation may ultimately replace pancreas transplantation. Islet transplantation is a less demanding method of beta-cell replacement in that it does not involve major surgery, permits a lesser degree of immunosuppression, and is potentially less expensive for the recipient. Whether the physical and emotional costs are lower remains to be established, because there have been too few procedures for the complication rates associated with percutaneous liver puncture, anticoagulation, and immunosuppressive regimens to be determined. In this review, I will sketch the history of islet transplantation, describe the procedures of islet isolation and intrahepatic transplantation, consider the limitations of transplantation technology and the immunosuppressive drugs currently in use, compare the clinical outcomes of islet transplantation with those of pancreas transplantation, examine the definition of success, suggest avenues for future studies, and address the important problem of supply and demand.

### History of Islet Transplantation from 1894 to 2000

The concept of transplanting pieces or extracts of pancreas in patients with diabetes is over a century old. The first known report appeared in 1894: Williams used minced sheep’s pancreas and extracts of pancreas in glycerine for oral and subcutaneous therapy. This approach, audacious in retrospect, used sheep xenografts without immunosuppression and was reported as an overt failure. Virtually no subsequent effort was successful until 1972, when Ballinger and Lacy reported that islet isografts from normal rats could reverse streptozocin-induced diabetes in rats. By the 1980s successful transplantation of islet autografts and, in one instance, an islet allograft was reported in humans. In the autograft approach, a patient with unremittingly painful, chronic pancreatitis and a poor quality of life undergoes complete pancreatectomy for pain relief. The removed pancreas is minced, digested with collagenase, and centrifuged to achieve a non-purified preparation of islets that is infused into the patient’s liver through the portal venous circulation within two hours after pancreatectomy. The islets lodge in the liver because they are too large to pass through the sinusoids. In 1992, Pyzdrowski et al. reported that 265,000 islets were sufficient to establish insulin independence. In 1995, Wahoff et al. reported an insulin-independence rate of 74 percent two years after autologous islet transplantation in 14 patients who had undergone total pancreatectomy and who had received a portal-vein infusion of more than 300,000 islets (the normal pancreas has roughly 1 million islets).

In the 1980s, reports of successful allogeneic islet transplantation in patients with type 1 diabetes with the use of conventional immunosuppression and purified human islets from cadaveric donors began to appear (Table 1), but internationally, the overall rates of success were reported as less than 10 percent. In 2000, Shapiro et al. reported 100 percent success in seven patients. This high rate may have been due to the many differences in their approach as compared with previous techniques — there were restrictions on recipients’ body weights, the immunosuppressive regimen was modified by the addition of sirolimus and low-dose tacrolimus together with avoidance of corticosteroids, patients received the anticytokine drug daclizumab, and multiple infusions of islets from different donors were used to attain a transplanted islet mass sufficient to achieve normal glucose levels and independence from exogenous insulin.

### Can Islet Yields Be Improved?

Paul Langerhans identified pancreatic islets in 1869, describing them as discrete islands or islets surrounded by pancreatic exocrine tissue — hence, the term “islets of Langerhans.” The islets make up approximately 2 to 3 percent of the total pancreatic volume. Islets have a portal circulation, with blood flowing from beta to alpha to delta cells, as well as afferents from the central nervous system, which regulate secretion of these cells’ hormones. The alpha, beta, delta, and PP cells secrete glucagon, insulin, somatostatin, and pancreatic polypeptide, respectively. Alpha and beta cells are exquisitely sensitive to glucose, which stimulates the beta cell and inhibits the alpha cell, thereby maintaining blood glucose levels within a narrow range. The principal actions of insulin promote the entry of glucose into tissues and decrease hepatic gluconeogenesis, whereas glucagon principally stimulates hepatic glycogenolysis when hypoglycemia threatens.

Modern islet-isolation technology involves the procurement of a healthy pancreas from a brain-dead donor whose heart is beating, although recent
success has been reported with the use of cadaveric donors. The pancreas is procured with the use of the same techniques that are used to procure a pancreas for whole-organ transplantation. The pancreatic duct is cannulated, and collagenase is infused to separate islets from exocrine and ductal tissue. Subsequently, islets are purified by density-gradient centrifugation. The final product is evaluated for purity and viability before it is transported to the angiography suite for transplantation (Fig. 1).

Although relatively simple to describe, the process of islet isolation for transplantation is complicated. The health of and the medications used by the potential donor, the care with which the surgical team removes the pancreas, and the timeliness of transportation to the laboratory are important variables. Improvements in transport of the pancreas are being attempted by advocates of the “two-layer method,” which sandwiches the pancreas between a bottom layer of perfluorodecalin saturated with oxygen and a top layer of University of Wisconsin preservation solution.

Table 1. Synopsis of Reports of Successful Islet Transplantation in Patients with Type 1 Diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of Report</th>
<th>No. of Recipients and Size of Transplant</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largiader et al.</td>
<td>1980</td>
<td>1 Recipient of pancreas microfragments containing 200,000 islets</td>
<td>Insulin-independent with normal glucose level at 9½ mo</td>
</tr>
<tr>
<td>Scharp et al.</td>
<td>1990</td>
<td>1 Recipient of 800,000 islets</td>
<td>Insulin-independent at 22 days</td>
</tr>
<tr>
<td>Tzakis et al.</td>
<td>1990</td>
<td>9 Patients with cancer and abdominal exenteration without diabetes received 205,000–746,000 islets</td>
<td>Normal glycosylated hemoglobin values in 5 patients, with some receiving insulin supplementation</td>
</tr>
<tr>
<td>Warnock et al.</td>
<td>1991</td>
<td>1 Recipient of 611,000 islets</td>
<td>Insulin-independent with normal glucose levels at 3 mo</td>
</tr>
<tr>
<td>Scharp et al.</td>
<td>1991</td>
<td>First 9 patients receiving 6161±911 to 13,916±556 islets/kg of body weight</td>
<td>3 Transplantations failed; 4 had measurable C-peptide levels for up to 10 mo but not insulin-independent; 2 with normal glucose levels and insulin-independent for 1–5 mo</td>
</tr>
<tr>
<td>Warnock et al.</td>
<td>1992</td>
<td>4 Recipients of 261,000–896,000 fresh and cryopreserved islets</td>
<td>3 Had measurable C-peptide levels for 1–8 mo, but not insulin-independent; 1 insulin-independent for 1 yr</td>
</tr>
<tr>
<td>Gores et al.</td>
<td>1993</td>
<td>2 Recipients of 502,000–528,000 islets</td>
<td>1 Had measurable C-peptide levels but not insulin-independent at 9 mo; 1 with normal glucose levels and insulin-independent at 8 mo</td>
</tr>
<tr>
<td>Soon-Shiong et al.</td>
<td>1994</td>
<td>1 Recipient of 678,000 encapsulated islets</td>
<td>Insulin-independent with normal glucose levels at 9 mo</td>
</tr>
<tr>
<td>Carroll et al.</td>
<td>1995</td>
<td>1 Patient with cancer and abdominal exenteration without diabetes</td>
<td>Insulin-independent with normal glycosylated hemoglobin values at 3 yr</td>
</tr>
<tr>
<td>Luzi et al.</td>
<td>1996</td>
<td>15 Recipients of 98,587–1,294,125 islets</td>
<td>8 Had C-peptide levels &gt;1.4 ng/liter; 4 insulin-independent with glycosylated hemoglobin values of 5.6–7.2 percent at 1–8 mo</td>
</tr>
<tr>
<td>Alejandro et al.</td>
<td>1997</td>
<td>8 Recipients of 478,000–1,271,000 islet equivalents</td>
<td>2 Insulin-independent at 1 mo and 2 insulin-independent at 6 yr with normal to near-normal glycosylated hemoglobin values</td>
</tr>
<tr>
<td>Secchi et al.</td>
<td>1997</td>
<td>20 Recipients of 3461–14,488 islet equivalents/kg</td>
<td>9 Had measurable C-peptide levels with decreased need for insulin; 6 insulin-independent at 3–11 mo; 1 insulin-independent at 48 mo; all with normal or near-normal glycosylated hemoglobin values</td>
</tr>
<tr>
<td>Keymeulen et al.</td>
<td>1998</td>
<td>7 Recipients of 2100–5300 islet equivalents/kg</td>
<td>3 Had measurable C-peptide levels for &gt;1 yr; 2 insulin-independent with normal to near-normal glycosylated hemoglobin values for 1 yr</td>
</tr>
<tr>
<td>Oberholzer et al.</td>
<td>2000</td>
<td>13 Recipients of 199,000–863,000 islets</td>
<td>All had measurable C-peptide levels for &gt;3 mo; 5 of 8 had normal C-peptide levels &gt;1 yr; 2 patients insulin-independent at 4 and 36 mo</td>
</tr>
<tr>
<td>Shapiro et al.</td>
<td>2000</td>
<td>7 Recipients of 11,546±1604 islets</td>
<td>All insulin-independent at 4–15 mo with 6-month glycosylated hemoglobin values of 5.7±0.2 percent</td>
</tr>
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* Plus–minus values are means ±SE.
required for complete processing and quality assessment of the islets.

Critics of this approach question the need for the purification step because it adds time, can cause the loss of 30 to 50 percent of islets, and traumatizes the remaining islets that are harvested. They point out that unpurified islets are used successfully in autologous transplantation and that purification removes pancreatic-duct stem cells that might give rise to new islets after transplantation.

**Figure 1. The Process of Islet Transplantation.**

A pancreas is obtained from a donor. The pancreas is digested with collagenase to free the islets from surrounding exocrine tissue. The freed islets, containing mostly beta and alpha cells, are purified by density-gradient centrifugation to remove remaining exocrine cellular debris. The purified islets are infused into a catheter that has been placed percutaneously through the liver into the portal vein, whence they travel to the liver sinusoids.
nents of purification respond by arguing that purification yields a much smaller tissue volume, which is thus less likely to cause portal hypertension. Culturing the islets after isolation would allow them to recover before transplantation and would decrease travel demands for recipients, who must currently arrive at the transplantation site within hours after notification.

**IS THE LIVER THE OPTIMAL SITE FOR ISLET INFUSION?**

The liver, spleen, kidney capsule, testes, brain, peritoneal cavity, and omentum have all been considered as potential sites of islet infusion. The liver is by far the most commonly used site because of the early successes with autologous islet transplants. However, although autologous islets are infused intraoperatively directly into the hepatic portal venous circulation under direct view, islet allografts are infused percutaneously into the portal vein. Potential complications of an infusion into the liver include bleeding, portal venous thrombosis, and portal hypertension. Although portal blood pressure is monitored during the procedure and anticoagulant agents are used to prevent clotting, anticoagulation can promote hepatic bleeding at the sites of the percutaneous needle punctures. Furthermore, intrahepatic islets may be exposed to environmental toxins and potentially toxic prescribed medications absorbed from the gastrointestinal tract and delivered into the portal vein. Ironically, all commonly used immunosuppressive drugs have been reported to have adverse effects on pancreatic beta cells (Table 2). In addition, the antiproliferative effects of sirolimus may theoretically be disadvantageous both for angiogenesis in newly transplanted islets and for islet neogenesis from ductal stem cells.

Finally, intrahepatic islets are unable to release glucagon during hypoglycemia (Fig. 2 and 3). Yet, though intrahepatic islets fail to respond to hypoglycemia, they appear to contain healthy alpha cells that process and secrete glucagon, as indicated by their response to intravenous arginine. Since not all recipients remain insulin-independent for the rest of their lives, they may become at risk for hypoglycemia and thus would benefit from having a glucagon response.

In view of these problems, it is reasonable to consider the use of nonhepatic sites. It might also be possible to infuse unpurified islet preparations into nonhepatic sites, which would eliminate the trauma to and losses of islets caused by purification. Potential alternative sites include the peritoneal cavity and omentum, both of which have been used successfully in animal models and shown to be safe for humans.

**CLINICAL OUTCOMES, 2001 TO 2003**

Since the initial report from Edmonton, Alberta, Canada, many transplantation centers throughout the world have initiated corticosteroid-free proto-

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**Table 2. Mechanisms of the Adverse Effects of Immunosuppressant Drugs on Beta Cells.**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Corticosteroids</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
<th>Mycophenolate Mofetil</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased insulin gene transcription</td>
<td>Oetjen et al.</td>
<td></td>
<td>Redmon et al.</td>
<td>Oetjen et al.</td>
<td></td>
<td></td>
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<tr>
<td>Decreased level of stability of insulin messenger RNA</td>
<td>Philippe and Missotten</td>
<td></td>
<td>Redmon et al.</td>
<td></td>
<td></td>
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<tr>
<td>Decreased insulin synthesis</td>
<td>Gold et al.</td>
<td>Chandrasekar and Mukherjee,</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Davani et al.</td>
<td>Paty et al.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Decreased insulin synthesis in vitro</td>
<td>Billaudel and Sutter</td>
<td></td>
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Although the results of other studies are beginning to appear,\textsuperscript{77,78} in most instances, success rates have not yet been published. The Immune Tolerance Network has organized a nine-center trial designed to evaluate the reproducibility of the Edmonton results in 36 recipients. Preliminary information presented at the 2003 American Transplant Congress suggests robust success rates at more experienced centers, but much lower rates at less experienced centers.\textsuperscript{79} In addition, several patients who became insulin-independent after transplantation have withdrawn from the study because of unacceptable side effects of the immunosuppressive drugs.

The largest, most recent update on the clinical outcomes of the Edmonton experience was published in 2002.\textsuperscript{80} The authors reported 54 islet infusions in 30 recipients with type 1 diabetes and provided detailed follow-up data on 17 consecutive patients, all of whom became insulin-independent, with mean (±SE) glycosylated hemoglobin values of 6.1±0.8 percent after receiving a minimum of 9000 islets per kilogram of body weight, or 630,000 islets for a 70-kg person. Typically, two separate infusions of islets from two pancreata were used an average of one month apart. Four of six patients were insulin-independent for more than two years, but two of the four had impaired glucose tolerance. Fourteen of the initial 17 recipients no longer had hypoglycemic reactions. The adverse effects of the procedure included five bleeding episodes related to percutaneous puncture of the liver in 50 procedures, three transfusions, and one partial thrombosis of the portal vein with hepatic subcapsular hemorrhage caused by anticoagulant therapy that required transfusion and surgery. Transiently elevated liver-enzyme levels, hypercholesterolemia, further increases in creatinine levels in patients with preexisting renal disease, increased proteinuria in patients with preexisting proteinuria, increases in the doses of antihypertensive drugs, and the need for retinal laser photocoagulation were among the other complications. No deaths or life-threatening infections occurred.

The interpretation of these results is complicated by the fact that the Edmonton trial design did not include a similar and concurrent control cohort. Since the observation period before transplantation was not as long or as intense as the observation period after transplantation, extensive paired analy-
ses of pretransplantation and post-transplantation clinical data are not possible. Whether two islet infusions a month apart are essential is unresolved, since recipients were not randomly assigned to receive either one infusion or two. Relevant data from studies of autologous islet transplantation suggest that islets continually regain function up to three months after infusion\(^1\) (Fig. 4). Nonetheless, one can conclude that in the hands of the Edmonton group, islet transplantation is relatively safe and efficacious in eliminating the need for exogenous insulin and in preventing recurrent hypoglycemia.

Figure 3. Glucagon Responses in Pancreatectomized Dogs That Have Received Autologous Islets during Hypoglycemia Induced by Hypoglycemic, Hyperinsulinemic Clamping (Panel A) and Intravenous (IV) Arginine (Panel B).

In Panel A, glucagon responses remain intact when autologous islets are placed in the peritoneal cavity but not when they are placed in the liver. During the study, insulin is infused at a steady rate and glucose at a decreasing rate so that glucose levels gradually reach 40 mg per deciliter. In Panel B, glucagon responses remain intact after the intravenous infusion of arginine whether autologous islets are placed in the peritoneal cavity or in the liver. Reprinted from Gupta et al.,\(^{72}\) with the permission of the publisher.
albeit at a cost of a roughly 10 percent incidence of liver bleeding related to the procedure. The initial graft survival rate of 80 percent with the use of islets from multiple donors compares favorably with that of successful pancreas transplantation and successful autologous islet transplantation. Whether or not the long-term survival of allografts will equal that of autologous grafts is unknown. Autologous grafts can function successfully for many years after transplantation. A recipient of one such autologous graft was reported to have normal fasting glucose and glycosylated hemoglobin levels 13 years after transplantation and remains insulin-independent 16 years later. However, recipients of islet allografts face the additional risk of recurrent autoimmune diabetes, as well as of side effects from treatment with immunosuppressive drugs that are potentially lethal to beta cells.

DEFINING SUCCESS

A major problem in judging the success of islet transplantation lies in the definition of success. The typical candidate has recurrent hypoglycemia with poor recognition of the resulting symptoms and abnormal glycosylated hemoglobin values. Although the first two issues can be resolved by lessening the intensity of insulin management, this approach increases glycosylated hemoglobin values. The use of a rigorous definition of success means recipients no longer use insulin, do not have hypoglycemia and poor recognition of symptoms, and have normal preprandial and postprandial glucose levels and glycosylated hemoglobin values for prolonged periods. The use of a more flexible definition means that the main problems that resulted in transplantation in the first place — frequent hypoglycemia with poor symptom recognition, a poor quality of life, and abnormal glycosylated hemoglobin values — have been solved. The more flexible view allows the use of oral hypoglycemic drugs and residual impaired glucose tolerance and is supported by some experts in the field, but not all.

Putting aside definitions of success, an equally important consideration is the cost–benefit ratio of islet transplantation, in both personal and financial terms. In addition to the clinical complications of the procedure, patients pay a personal price for using immunosuppressive drugs because of their adverse effects. In defense of islet transplantation, all types of allogeneic transplantation carry a risk of adverse effects related to immunosuppressive drugs and the financial cost of islet transplantation is less than that of pancreas transplantation. On the other hand, pancreas transplantation is more efficient, since it typically involves only a single procedure and quickly results in normal glucose and glycosylated hemoglobin values. A comparison of these two procedures illustrates another important difference. Whole pancreata are most often used for patients with renal failure who simultaneously receive kidney transplants. The increase in the quality of life, satisfaction with the procedure, and tolerance of adverse drug effects are likely to be greater among recipients of combined pancreas and kidney transplants than recipients of an islet transplant alone, because the former group of patients is typically more ill to begin with. This outcome leads many clinicians to conclude that simultaneous kidney and islet transplantation or islet transplantation after kidney transplantation is the preferred approach, rather than the transplantation of islets, in patients without renal failure. The combined procedures are used for the sicker patients, and the issue regarding the burden of immunosuppressive drugs can be finessed because patients scheduled for kidney transplantation know that they must receive these drugs.
THE NEXT GENERATION OF RESEARCH STUDIES

Although the prospect of islet transplantation as a treatment for diabetes is exciting, there are no data that allow firm conclusions to be drawn about who should receive this therapy. Continuing improvements in the medical management of diabetes invalidate the use of data from historical controls, even those obtained in the DCCT. Controlled studies are needed to evaluate the efficacy and complications of islet transplantation. If randomization is not possible, a case–control approach that includes patients who qualify for but decline to undergo the procedure could be used. Subgroups should be stratified according to the secondary complications of diabetes and to whether islets are transplanted alone or in conjunction with a kidney. Allowances must also be made for the further development of procurement and laboratory techniques for the isolation of islets, as well as the development of new immunosuppressive drugs that are less toxic to beta cells.

PROBLEMS OF SUPPLY AND DEMAND

Demand for islet transplantation far exceeds the number of islets available. Even if the procedure is limited to adults with type 1 diabetes who have recurrent hypoglycemia and poor symptom recognition, there are not enough pancreata to meet the need. The relatives of patients with diabetes often ask whether they can donate part of the pancreas, a practice performed successfully, primarily at the University of Minnesota, for the purposes of segmental pancreas transplantation.\(^\text{89}\) However, postoperative complications of pancreatitis and pancreatic pseudocyst, although infrequent, represent major risks to the donors. The most frequent issue for donors is the potential for diabetes. Donors are excluded if they are obese or have abnormal glucose tolerance or islet-cell antibodies, or if less than 10 years has lapsed since the onset of diabetes in the potential recipient. By the first year after hemipancreatectomy, almost all donors still have normal fasting glucose levels but 25 percent have oral glucose-tolerance results that are diagnostic of diabetes.\(^\text{90}\) Long-term follow-up for one to two decades indicates that fasting hyperglycemia is more likely to develop in donors who become obese and insulin-resistant.\(^\text{91}\)

The pressure to create an adequate supply of islets has led to extensive basic-science research into the potential use of islet surrogates. These include islet expansion, encapsulated islet xenografts, human islet-cell lines, and embryonic stem cells. The concept that expanding islets is feasible was strengthened by a report that digested pancreatic tissue from which islets had been removed could be expanded as a monolayer of epithelial cells that formed ductal cysts from which islet-like clusters of endocrine cells budded.\(^\text{47}\) However, these results cannot be taken entirely at face value, because the pancreatic tissue was positive for insulin messenger RNA and insulin. Many investigators have advocated the use of xenografts, usually pig islets. Although there have been reports of success,\(^\text{92,93}\) none have reported consistent success with the use of this approach to transplant islets across species.

The establishment of human beta-cell lines has been a goal, because this method might provide unlimited quantities of cells for transplantation. De la Tour et al. reported that transformed, differentiated human beta cells were capable of secreting insulin in response to glucose in vivo.\(^\text{94}\) The reproducibility of these results and the demonstration that such cell lines are stable await confirmation by other investigators. Pluripotent embryonic stem cells have reportedly been converted into insulin-secreting cells,\(^\text{95–99}\) but the reproducibility of these results has been questioned.\(^\text{100}\) Very promising results have been reported with the use of monoclonal antibodies to induce tolerance and antitoxins directed against components of the allogeneic response system in primates,\(^\text{101–104}\) but no successful experiment has yet been reported in recipients of human islets.

CONCLUSIONS

The dream that began in 1972 of transplanting islets to patients with diabetes to restore normoglycemia and to eliminate the need for insulin injections remains a work in progress. Many important problems must be solved before islet transplantation can take its place as a conventional therapeutic option. The worldwide success rate of pancreas transplantation renders it the more effective procedure, especially since it uses only one donated organ. Practical issues, such as the huge losses of islets during isolation and purification, the clinical complications associated with the use of the hepatic site, adverse reactions to immunosuppressive drugs, and insufficient supply, require resolution. Until then, only specialized centers should carry out islet
transplantation. Information about the long-term benefits of transplantation with respect to the secondary complications of diabetes has only recently begun to emerge.105 Nonetheless, it is clear the remaining problems should be resolvable through the use of currently available scientific methods. The good news is that the rates of successful islet transplantation are increasing, and each such success is teaching us valuable lessons about improving beta-cell replacement in patients with diabetes.

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