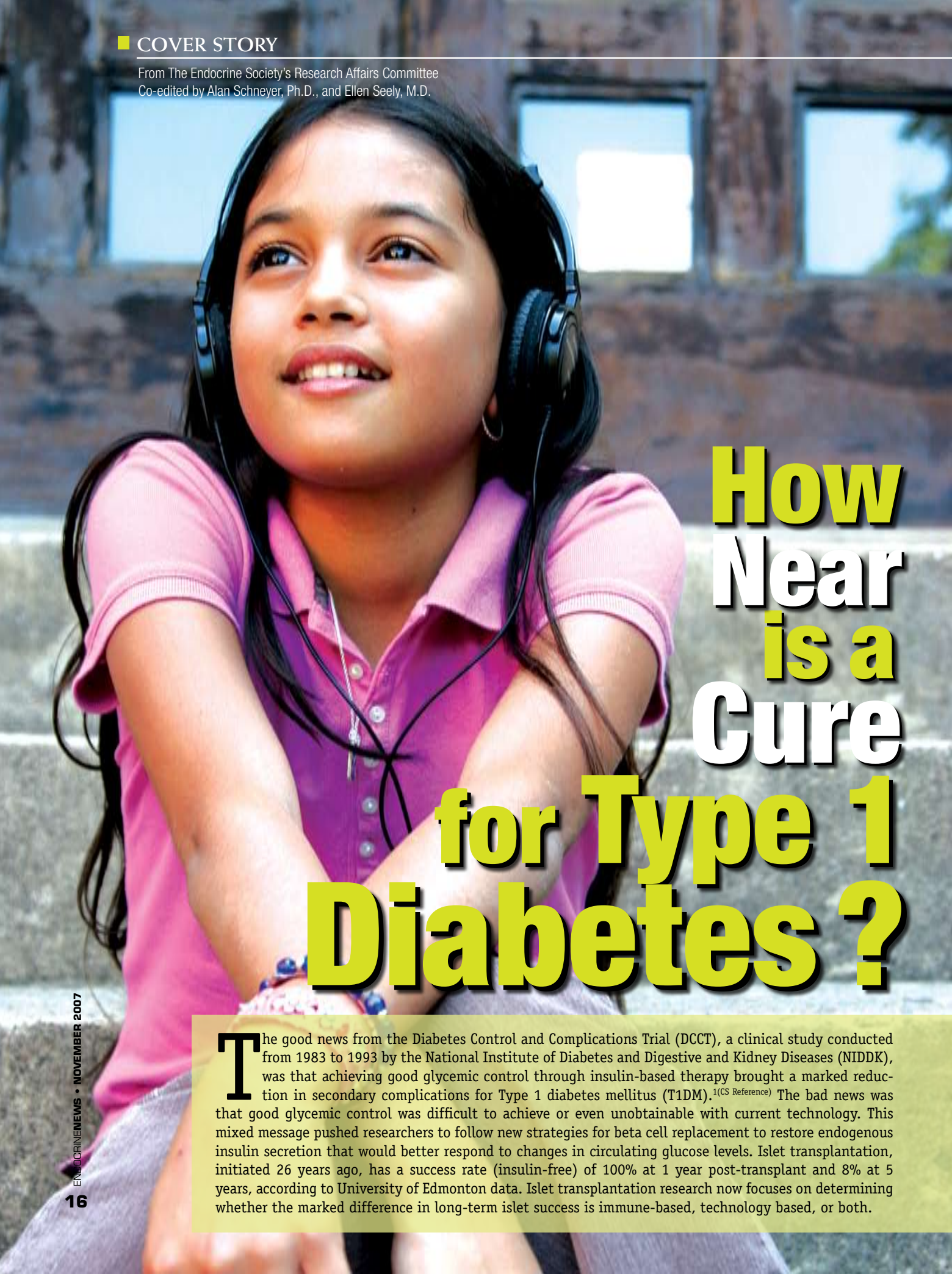


From The Endocrine Society's Research Affairs Committee  
Co-edited by Alan Schneyer, Ph.D., and Ellen Seely, M.D.



# How Near is a Cure for Type 1 Diabetes?

**T**he good news from the Diabetes Control and Complications Trial (DCCT), a clinical study conducted from 1983 to 1993 by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), was that achieving good glycemic control through insulin-based therapy brought a marked reduction in secondary complications for Type 1 diabetes mellitus (T1DM).<sup>1(CS Reference)</sup> The bad news was that good glycemic control was difficult to achieve or even unobtainable with current technology. This mixed message pushed researchers to follow new strategies for beta cell replacement to restore endogenous insulin secretion that would better respond to changes in circulating glucose levels. Islet transplantation, initiated 26 years ago, has a success rate (insulin-free) of 100% at 1 year post-transplant and 8% at 5 years, according to University of Edmonton data. Islet transplantation research now focuses on determining whether the marked difference in long-term islet success is immune-based, technology based, or both.

## From the Basic Scientist Perspective

- Insulin replacement regimens for T1DM do not fully mimic beta cell function.
- Shortages of organ donor tissue limit islet transplantation efforts.
- Insulin production can be induced from multiple cell types in culture, including embryonic stem cells and cells derived from pancreas, liver, and bone marrow.
- Pancreatic beta cell mass can adaptively increase in response to environmental stimuli.
- Future treatment strategies might include cell replacement therapy and/or agents that stimulate endogenous increases in beta cell mass.

### Pancreatic Beta Cell Replacement Therapy

Despite advances in therapeutic approaches to remedying the absolute insulin deficiency of T1DM, affected individuals encounter substantial morbidity and life-threatening complications from the disease. The best available insulin replacement strategies do not replicate the nutrient-responsive, dynamic, and precisely regulated production of insulin from the beta cells of the endocrine pancreas, and patients often tolerate mild hyperglycemia to avert hypoglycemia. Although the initial success of pancreatic islet transplantation using the Edmonton Protocol is a significant therapeutic advance, attempts to cure T1DM by islet transplantation are limited by low supplies of organ donor tissue and the requirement for continued insulin therapy in most transplanted patients.<sup>1</sup> Widespread T1DM research efforts are directed toward generating a renewable source of insulin-producing beta cells for cell replacement therapy. Investigators aim to identify candidate stem/progenitor cells, amplify beta cell progenitors in vitro, and develop differentiation protocols to generate insulin-producing cells from pancreatic or extrapancreatic cells.

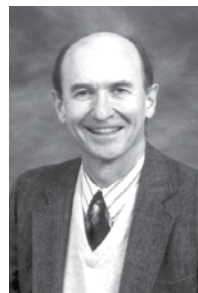
### Experimental Sources of Progenitors for Insulin-Producing Cells

Several experimental possibilities for candidate beta cell progenitors are under active investigation.<sup>2</sup> Embryonic stem (ES) cells of mouse or human origin can be expanded, selected, and induced to differentiate and produce insulin. Genetic engineering, gene-trapping, or pharmacologic selection techniques have been used to enrich for subpopulations of ES cells that synthesize and secrete insulin. Some differentiated ES cells secrete insulin in response to glucose. Transplanting differentiated ES cells into insulin-deficient diabetic mice can reduce hyperglycemia in selected instances.<sup>3</sup> One promising experimental strategy for generating insulin-producing cells mimics extracellular signaling events essential for the embryonic development of pancreatic beta cells by sequentially administering growth factors and morphogens to ES cells at distinct stages of their differentiation in culture.<sup>4</sup>

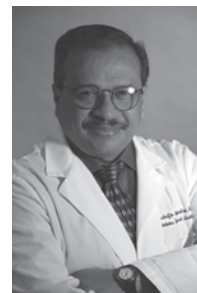
Putative intrapancreatic adult progenitor cells have been isolated from adult human or mouse pancreatic islets,



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Giving the clinical scientist perspective is R. Paul Robertson, M.D., president and scientific director of Pacific Northwest Research Institute in Seattle, Washington.



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ducts, or acinar tissue, and expanded in culture.<sup>5, 6</sup> Several differentiation protocols successfully induce insulin expression and secretion from candidate pancreatic progenitor cells in culture or after transplantation into mouse models of diabetes. Extrapancreatic cells from liver, spleen, bone marrow, and umbilical cord blood represent additional candidate sources for beta cell progenitors or for transdifferentiation into insulin-producing cells.<sup>2</sup> Multiple cell types have some capacity for de-differentiation and amplification when cultured *ex vivo*; modifying cell culture conditions induces variable levels of insulin production.

Recent advances in generating pancreatic beta cells *ex vivo* are highly promising. However, experimental attempts to generate and expand beta cells in culture, regardless of the cellular origin, have encountered limitations in levels of insulin production and in the degree of cellular responsiveness to glucose and other secretagogues. The functional properties of beta cells generated *ex vivo* often resemble those of partially differentiated neonatal more than of fully functional mature beta cells. More extensive *in vivo* demonstrations of efficacy and safety of cellular candidates for beta cell replacement are needed for clinical translational efforts to proceed. The capability of cultured cell models to differentiate into different cell types with extended proliferative capacity highlights the importance of identifying cellular sources for transplantation with no—or only minimal—potential for tumor formation.

### Stimulation of Adaptive Increases in Pancreatic Beta Cell Mass

An alternative to developing renewable sources of beta cells for transplantation is to generate pharmacologic approaches to stimulate mechanisms that increase endogenous pancreatic beta cell mass. Beta cells are dynamic and capable of proliferating in response to insulin resistance, obesity, pregnancy, aging, and injury. In mouse models of T1DM, reducing autoimmune-mediated beta cell injury unmasks an endogenous capacity for restoration of beta cell mass and in-

sulin production.<sup>7</sup> Relative increases in beta cell mass occur in obese individuals who do not develop diabetes and deficits are seen in those with type 2 diabetes.<sup>8</sup> Thus, approaches to restore insulin production by stimulating the endogenous generation of new beta cells could have potential therapeutic relevance for both type 1 and type 2 diabetes. The relative contributions of pancreatic beta cell proliferation, apoptosis, and/or differentiation from a yet unidentified pool of progenitor cells to the adaptive expansion of postnatal pancreatic beta cells are under active investigation.

The question of whether stem/progenitor cells exist in the adult pancreas is controversial. Lineage tracing studies in a genetically modified mouse model suggest that new pancreatic beta cells in adult mice arise from replication rather than from stem cells.<sup>9</sup> Additional mouse models are in development to study the possible existence of other intrapancreatic sources of beta cell progenitors. An intriguing theory proposes that differentiated beta cells may have latent plasticity with the capacity to de-differentiate and acquire a more “stem-like” phenotype, undergo replication and migration, and then re-differentiate to become functional beta cells.<sup>10, 11</sup> Molecular mechanisms by which new pancreatic beta cells are formed during embryonic pancreatic development are being compared with experimental models of postnatal expansion of beta cell mass to identify common molecular signatures or themes of regulation required to generate new beta cells.

New diabetes drugs may focus on molecular targets that govern the expansion of pancreatic beta cell mass. From this perspective, it is interesting to note that glucagon-like peptide-1 receptor agonists increase the mass and decrease the apoptosis of beta cells in animal models.<sup>12</sup> Future development of reliable noninvasive techniques to image functional beta cell mass in humans should accelerate the design and clinical assessment of therapeutic agents with these capabilities.

## From the Clinical Scientist Perspective

- Historically, transplanted pancreases succeed long-term, but islets do not.
- In 2000, the Edmonton group reported 100% success with islets.
- By 2005, the Edmonton success rate with islets fell below 10%.
- Is islet failure immune-based?
- Is islet failure technology-based?

### Pre-Edmonton Era—the Past

Successful clinical pancreas transplantation for T1DM was first reported from the University of Minnesota in 1966.<sup>2</sup> During the years since, operative techniques and immunosuppressive drug regimens have improved significantly. Three general transplantation approaches are most common, namely, simultaneous pancreas and kidney (SPK), pancreas after kidney (PAK), and pancreas transplant alone (PTA).<sup>3</sup> The 1-year post-transplant pancreas survival rates for these

procedures are 79%, 69%, and 69%, respectively, whereas the 5-year organ survival rates are 70%, 45%, and 45%, respectively.<sup>4</sup> The 1-year patient survival rates are 95%, 96%, and 97%, respectively, and the 5-year survival rates are 90%, 89%, and 91% respectively.<sup>4</sup> Because patient deaths usually do not occur within 3 months of the procedures and are usually cardiovascular in etiology, it seems likely the mortality is more related to chronic diabetes than to the surgery.

Successful islet transplantation was first reported in 1980.<sup>5</sup> Although numerous reports of single successes appeared thereafter up to 2000,<sup>6</sup> 1-year post-transplant success rates were less than 10%. No uniformly successful series was reported until 2000, when the Edmonton group reported 100% of islet transplant recipients were insulin-free for an average of 1 year post-transplant.<sup>7</sup>

During the years since, operative techniques and immunosuppressive drug regimens have improved significantly.

### The Edmonton Era—the Present

The distinguishing features of the Edmonton approach were to redesign the immunosuppressive regimen (avoid glucocorticoids, include daclizumab) and to infuse intrahepatically multiple preparations of islets. Although all 7 recipients were insulin free, with normal HbA1c levels, at an average of 1 year post-transplant, as a group they still had impaired glucose tolerance. They also had clinical complications such as abnormal liver function, serum creatinine, and hepatic bleeding secondary to the liver puncture required for infusing islets via the hepatic portal vein. After this series was published, the Edmonton group reported that successful islet transplantation (insulin-free) 2 years post-transplant had decreased to 65%<sup>8</sup> and by 5 years to 8%.<sup>9</sup> Five years after transplantation, 82% of recipients still had evidence of c-peptide production, allowing for ameliorating glycemic lability and hypoglycemia.

### Post-Edmonton—the Future

Future efforts in islet transplantation will focus on what went wrong with the initially impressive clinical outcomes reported by the Edmonton group. Although two obvious explanations are immunorejection of the engrafted islets and return of autoimmune-based beta cell destruction, no convincing evidence to support either of these possibilities has been reported. However, and more optimistically, there is ample room to suspect technology-based difficulties. Possibilities include use of islet isolation procedures that damage

islets and islet-toxic immunosuppressive drugs that highly concentrate in the hepatic portal vein and hence liver tissue.<sup>6,10</sup> These considerations have prompted research focused on non-hepatic sites, avoiding both the need for purification and consequent islet damage, and for toxic concentrations of immunosuppressive drugs. This focus will also obviate the problem of liver bleeding caused by liver puncture.

## From the Clinician Perspective

- Transplantation of allogeneic pancreatic islets for the treatment of patients with T1DM is now a reality.
- Close follow-up of patients who have received islet cell transplantation, including immunosuppressive trough levels, complete blood counts, basic metabolic parameters, and toxicity assessment should be frequent to identify and monitor side effects.
- The majority of adverse events have been mild, self-limiting, and easily treated. However, some have required urgent medical attention.
- A multidisciplinary team approach is necessary to offer optimal care to islet transplant recipients.

### Clinical Success of Islet Cell Transplantation

Transplantation of allogeneic islets is mainly performed in patients with type 1 diabetes mellitus (T1DM). Allogeneic islets have been transplanted in patients with end-stage renal disease (ESRD) together with the kidney, and in patients with a stable kidney allograft. In recent years, transplantation of allogeneic islets alone has also been performed in patients with brittle diabetes characterized by hypoglycemia unawareness and progressive diabetes complications for which the risk of life-threatening hypoglycemia outweighed those of the transplantation procedure and chronic immunosuppression. Transplantation of allogeneic pancreatic islets for the treatment of patients with T1DM is now a reality.

In addition to the goal of increasing the number of patients who achieve insulin independence, decreasing the number of severe hypoglycemic events that have occurred subsequent to the islet infusion procedure is another important goal. More than 85% of participants experienced one or more severe hypoglycemic events prior to their first infusion. This decreased to 4% in months 1–12 after the last infusion. All participants who experienced a severe hypoglycemic event during follow-up were on insulin at the time of the event.<sup>4</sup>

### Immunosuppressive Regimens

Current immunosuppressive protocols for islet transplantation alone are based on a glucocorticoid-free regimen that includes induction therapy with monoclonal antibody against interleukin-2 receptor (daclizumab) and maintenance immunosuppression with sirolimus and tacrolimus, known as the “Edmonton Protocol.”

The levels of sirolimus are higher than those used in solid organ transplantation in order to prevent allograft rejection,

because no sensitive methods exist to predict immunologic islet graft loss. These higher immunosuppressive levels could account for some of the adverse events that are more frequent in islet recipients compared with solid organ transplants.<sup>6</sup> In some instances, due to drug toxicity, mofetil or mycophenolate sodium may be introduced as maintenance therapy instead of tacrolimus or sirolimus.<sup>2,3</sup>

Management of maintenance immunosuppressive drugs is one of the most important factors in the prevention of graft rejection and the minimization of side effects and drug toxicity. Follow-up, including immunosuppressive trough levels, complete blood counts, and basic metabolic parameters (electrolytes, liver function tests, magnesium, calcium, and phosphorus) should be done frequently. Toxicity should also be assessed monthly to identify more subjective side effects (i.e., memory loss, tremor) that can interfere with the patients' normal daily functions and affect their quality of life.

Upon starting immunosuppressive therapy, both the patient and the transplant team are faced with risks such as the worsening of pre-existing medical diseases and the presentation of new complications such as hyperlipidemia, hypertension, opportunistic infections, cancer, and other systemic diseases secondary to immunosuppression. The full extent of immunosuppressive-related complications in the field of islet transplantation is not fully known, given that the field and its success are relatively young.<sup>6</sup>

**To date, no post-transplant lymphoproliferative disorder or graft-versus-host disease has been reported.**

Worsening kidney function has been reported after islet transplantation, most probably secondary to the combination of sirolimus and tacrolimus, particularly in those with significant renal dysfunction before transplant.<sup>2,3</sup> The development of sensitization to islet donor HLA antigens has been observed in patients who required discontinuation of immunosuppression.<sup>10,11</sup> The significance of this observation in a future kidney transplant (or any transplant), if needed, remains to be defined. However in our cohort of 35 islet transplantation-alone recipients, no one has developed sustained macroalbuminuria or severe kidney dysfunction in a 4-year mean follow-up, maybe due to aggressive treatment of associated risk factors such as hypertension and dyslipidemia.

The majority of adverse events have been mild, self-limiting, and easily treated. However, some have required urgent medical attention. Patient education and frequent monitoring have been extremely important in timely detection and treatment of these events. To date, no post-transplant lymphoproliferative disorder or graft-versus-host disease has been reported.<sup>4</sup> Four deaths (methadone toxicity,

stroke, West Nile Virus 3 years after last islet infusion, and unknown cause) have been reported to the registry.<sup>4,12</sup> Their relationship to the islet transplant procedure or immunosuppression is unlikely. Newer immunosuppressive agents with more specific and limited mechanisms of action will help to decrease the widespread range of side effects and to minimize complications and organ toxicity.

### The role of a multidisciplinary team

A multidisciplinary team approach, expert in the management of immunosuppression and related complications, including the complex medical and psychosocial needs of transplant patients, is necessary to offer optimal care to islet transplant recipients. In conclusion, islet transplantation in the short term can consistently and reliably reverse insulin dependency in subjects with "severe" T1DM, with normalization of all diabetic parameters and prevention of severe hypoglycemia, even in subjects who require reintroduction of exogenous insulin. Long-term graft dysfunction may be immunologically mediated with chronic drug toxicity and/or beta-cell exhaustion contributing. The lack of more sensitive methods to predict graft loss, the need to elucidate its mechanisms to preserve islet mass over time, the need for less toxic immunosuppressive regimens, and the possibility of reducing the number of islets required to reverse diabetes, leave room for improvement to realize the full potential of this treatment. Pancreas or islet transplantations should be performed in tertiary care centers that have an active kidney transplant program and are equipped to adequately handle the complex medical and psychosocial needs of transplant patients over the long term.

As the ADA position statement says,<sup>8</sup> "Pancreatic islet transplants hold significant potential advantages over whole gland transplants. Recent strides have been made in improving the success rates of this procedure. However, at this time, islet transplantation is a rapidly evolving technology that also requires systemic immunosuppression and should be performed only within the setting of controlled research studies." ■

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## About this Series

This is the fifteenth appearance of the tri-point perspective articles in *Endocrine News*, on a wide range of endocrinology subjects. The topics, authors, and outside reviewers are selected by The Endocrine Society's Research Affairs Committee (RAC) to explore subject areas from different angles. The authors write their articles independently, then the drafts are reviewed by contributing co-editors and by independent experts in the specific topic area.

*Endocrine News* staff would like to thank Drs. Ellen Seely and Alan Schneyer, co-chairs of the RAC and co-editors of the tri-points, for their dedication in developing this series for our readers.

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