Evidence Report

Chapter 1. Introduction

Scope and Objectives

Whole-organ pancreas transplant was initially performed in uremic type 1 diabetic patients who were undergoing kidney transplant, with the pancreas transplanted either simultaneously with the kidney or in a subsequent operation. Over the past decade, pancreas transplant alone (PTA) has been used selectively in type 1 diabetic patients in whom the potential benefit is judged sufficient to offset the adverse consequences of lifelong immunosuppression. PTA is, therefore, recommended only for patients with a history of frequent and severe metabolic complications, severe and incapacitating clinical and emotional problems with exogenous insulin therapy, or consistent failure of insulin-based management to prevent acute complications. The number of transplants is limited by availability of donated organs; in 2002, 1,870 pancreas organs were recovered for use in any pancreas transplant procedures (Organ Procurement and Transplantation Network, 2003).

Islet transplantation is an attractive alternative to whole-organ transplantation. Pancreatic islets are small clusters of endocrine cells that include insulin-producing beta cells; the beta cells alone are immunologically destroyed in type 1 diabetes, resulting in a loss of insulin production. Transplanted islets are infused into the portal vein via catheter and lodge in the liver, avoiding the morbidity of a complex surgery. However, until recently, islet transplantation had very poor results, with only approximately 10 percent of patients achieving insulin independence at 1 year after the procedure. Much improved results have been achieved using the Edmonton protocol and subsequently developed protocols. These contemporary transplant protocols use a glucocorticoid-sparing, low-dose immunosuppressive regimen, improved islet preparation, and infuse a minimum islet mass of 9,000 islet equivalents per kilogram (IEq/kg) of body weight. A limitation of islet transplantation is that two or more donor organs are usually required for a successful transplant. In the U.S., organs used are typically those rejected for use in whole-organ transplant.

This evidence report is a systematic review and synthesis of available evidence on the outcomes of islet transplantation in patients with type 1 diabetes. The report's scope is limited to transplantation of unaltered human allogeneic islets harvested from donor organs. Thus, cultured islets are included, but the following are excluded: autologous islets, porcine islets, genetically altered islets, and islets prepared from stem cells. Only studies that used the Edmonton protocol or subsequently developed protocols are relevant to this review.

This Introduction chapter describes the burden of type 1 diabetes; the characteristics of patients who are potential candidates for islet transplantation; the development of islet transplantation; the Edmonton protocol and subsequent research; regulation of islet transplantation; outcome measures of the success of islet transplantation; and the role of the Collaborative Islet Transplant Registry (CITR).

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus represents 5 to 10 percent of the estimated 13 million people in the U.S. who have been diagnosed with diabetes (Centers for Disease Control and Prevention, 2003). About 206,000 individuals under age 20 have diabetes, mostly type 1 diabetes. Among children

and adolescents, an estimated one in 400 to 500 has type 1 diabetes. Incidence of type 1 diabetes in the U.S. is about 30,000 new cases each year (LaPorte, Matsushima, and Chang, 1995). The mortality rate among type 1 diabetes patients is high. Life-table analysis of individuals in Allegheny County, PA (site of a population-based registry) diagnosed at age younger than 18 years with type 1 diabetes from 1975–1979 indicated survival of 90 percent after 25 years' duration of disease (Nishimura, LaPorte, Dorman, et al., 2001). The standardized mortality ratio, or the ratio of observed to expected deaths, was 281 for this cohort. Patient cohorts diagnosed in 1965–1974 had poorer survival, suggesting that better management has improved prognosis for this disease (Centers for Disease Control and Prevention, 2003).

Type 1 diabetes mellitus is characterized by severe insulin insufficiency and lack of circulating endogenous insulin, which is required for normal glucose metabolism. Aberrant glucose metabolism can cause acute health problems such as diabetic coma or ketoacidosis, or long-term consequences such as end-organ damage (e.g., neuropathy, renal failure, blindness). Experimental evidence strongly suggests that autoimmune mechanisms play a role in the pathogenesis of type 1 diabetes. If tested shortly after diagnosis, most patients have detectable autoantibodies to a variety of molecules expressed on the different endocrine cells that make up the pancreatic islets. Although none of the autoantibody targets is beta-cell specific, only the beta cells, which produce insulin, are selectively destroyed.

Medical management of type 1 diabetes includes exogenous insulin administration, either by multiple daily injections or use of a programmable insulin-infusion pump, rigorous dietary management, and exercise. Ideally, insulin should be delivered in a physiologic manner, that is, responsive to changing glucose concentrations, as occurs with a normally functioning pancreas. Because this level of control is not possible with exogenously administered insulin, glucose levels are not consistently normal and tissue-damaging complications may occur. These may be microvascular, resulting in retinopathy, nephropathy, and neuropathy; or macrovascular, resulting in atherosclerosis. Microvascular and macrovascular complications of inadequate glucose control are the cause of increased morbidity and mortality in type 1 diabetic patients.

Death in the early years after diagnosis is most often due to acute coma, whereas renal disease predominates in the middle years, and cardiovascular disease is more common after 30 years of type 1 diabetes (Portuese and Orchard, 1995). The proportion of type 1 diabetic patients reporting disability is 2–3 times higher than reported by persons without diabetes. Approximately 50 percent of patients with type 1 diabetes may experience work limitations by age 45 (Harris, 1995).

The Diabetes Control and Complications Trial (DCCT), a 10-year prospective, randomized, controlled study, showed that tight control of glucose metabolism through intensive insulin treatment over a 7-year period was associated with a 60 percent reduction in risk of secondary complications, delay in onset of complications, and less progression of nephropathy, neuropathy, and retinopathy, compared with standard treatment (The Diabetes Control and Complications Trial Research Group, 1993). However, tight control was associated with a threefold greater risk of severe hypoglycemia, a condition that can be life threatening (Robertson, 1999). Additionally, many patients cannot readily control blood glucose with insulin therapy.

The DCCT cohort has been followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, during which all participants were encouraged to switch to (control arm) or continue (experimental arm) intensive insulin therapy. At 5 years' followup, there was no longer a significant difference between the tight-control group and the conventional group in glycosylated hemoglobin (HbA_{1c}) levels, a measure of glycemic control. Nevertheless, at 7

years, progression of retinopathy was significantly less in the tight-control group (Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2002) and at 8 years, there were significantly fewer cases of clinical albuminuria and hypertension (Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2003). Intensive therapy also resulted in less progression of intima-media thickness 6 years after the end of the trial (Nathan, Lachin, Cleary, et al., 2003).

Although strictly controlling blood glucose concentration decreases long-term consequences of diabetes, it may also increase the likelihood of hypoglycemic episodes (Fanelli, Epifano, Rambotti, et al., 1993; Bolli, 1997). While some patients with labile type 1 diabetes may improve with medical efforts, others remain severely affected despite optimal medical management. These few patients have difficulty maintaining glucose control with exogenous insulin administration; some develop profound hypoglycemia without the usual associated warning signs. These include autonomic nervous system responses such as anxiety, palpitations, hunger, sweating, irritability, and tremors (Bolli, 1997). Symptoms of hypoglycemia include neuroglycopenic responses such as dizziness, tingling, blurred vision, difficulty in thinking, faintness, and unconsciousness (Bolli, 1997). Hypoglycemia-unaware patients may develop life-threatening episodes that require assistance and emergency medical intervention. Untreated, severe hypoglycemic episodes may result in coma, seizures, and death. Such patients may require constant family or caretaker supervision.

Combining fast- and slow-acting insulin analogs helps address normal variation in insulin requirements. Insulin infusion pump technology offers a closer approximation of physiologic insulin secretion and improved quality of glycemic control by delivering insulin according to programmed, variable infusion rates (Renard, 2002). Advantages include better insulin absorption with the use of fast-acting insulin preparations and facilitated manual dosing before meals and for correction of high glucose readings between meals. Another delivery technology, interstitial continuous glucose monitoring, is hypothesized to improve timing of exogenous insulin delivery, and thereby improve diabetes control. However, published evidence consists primarily of uncontrolled, observational studies that make it difficult to draw conclusions regarding effect on diabetic health outcomes (BCBSA Technology Evaluation Center, 2002).

Implantable devices are being developed to function as an artificial pancreas by continuously monitoring glucose and adjusting insulin delivery. In a study presented at the 2003 American Diabetes Association Annual Meeting, Renard, Shah, Miller, and co-workers tested an implantable sensor in a fully automated closed loop system with an insulin pump in 10 patients for 48 hours and reported that glucose levels were maintained in a near-normal range (70–240 mg/dL) more often (92 percent of the time) than during the previous week using capillary blood glucose measurements to determine insulin need (65 percent) (Renard, Shah, Miller, et al., 2003). However, it will be 5 years or more of development and testing before this device is marketed.

Thus, a purified islet or a pancreas organ transplant is the only treatment now available that promises physiologic insulin delivery, independence from insulin injections, and avoidance of diabetic complications and severe hypoglycemia associated with tight glucose control. However, these benefits may be offset by the risks of surgery and the potentially serious adverse effects of immunosuppression. Candidates are those patients with history of frequent and severe metabolic or acute complications uncontrolled by insulin-based management who do not have co-morbidities that preclude surgery.

Whole-Organ Pancreas Transplantation

Whole-organ pancreas transplantation to treat type 1 diabetes mellitus was introduced in 1966 at the University of Minnesota. Since then, more than 19,600 organ transplants have been reported to the International Pancreas Transplant Registry (IPTR; International Pancreas Transplant Registry, 2003; Gruessner and Sutherland, 2002); over 14,300 of these were performed in the U.S. Most transplants have been performed since 1994, after the introduction of tacrolimus and mycophenolate mofetil (MMF) immunosuppression.

The availability of pancreas organs limits the number of transplants that can be performed. For 2002, the Organ Procurement and Transplantation Network (OPTN) reported 6,187 total deceased organ donors, 1,870 pancreas organs recovered, and 1,461 pancreas organs transplanted (Organ Procurement and Transplantation Network, 2003). From the same deceased organ donors, a total of 9,691 individual kidneys were transplanted, indicating much higher organ recovery and use than for pancreas organs. However, the OPTN data do not reflect additional pancreas organs harvested specifically for islet transplantation; for example, 582 were harvested for this purpose in 2000–2002 per a report for the OPTN/United Network for Organ Sharing (UNOS) Kidney and Pancreas Transplantation Committee meeting in May, 2003 (Organ Procurement and Transplantation Network/United Network for Organ Sharing Kidney and Pancreas Transplantation Committee, 2003).

Patients and Procedures

Pancreas transplant candidates include: 1) type 1 diabetic patients with renal failure who may receive a cadaveric simultaneous pancreas/kidney transplant (SPK); 2) type 1 diabetic patients who may receive a cadaveric pancreas transplant after kidney (PAK) transplantation from either a cadaveric or a living-related donor; and 3) nonuremic type 1 diabetic patients with severely disabling and potentially life-threatening acute diabetic complications who may be offered a pancreas transplant alone (PTA) (American Diabetes Association, 2003; Steinman, Becker, Frost, et al., 2001).

In all cases, patients are usually excluded for evidence of prohibitive cardiovascular risk, active infection, recent malignancy, or other contraindications to major surgery. Evidence also suggests that graft loss is lower when patients are transplanted prior to extensive dialysis (Papalois, Troppmann, Gruessner, et al., 1996). In successful transplants, blood glucose normalizes immediately; glycosylated hemoglobin concentration (i.e., hemoglobin A_{1c}, HbA_{1c}) normalizes and remains normal while the graft is functional (Larsen and Stratta, 1996; Robertson, Sutherland, Kendall, et al., 1996).

Immunosuppressive Therapy

Rejection is the most common cause of graft loss, and lifelong immunosuppressive therapy is required to prevent graft loss. Current strategies attempt to prevent rejection while minimizing injury to the allograft and overall risk to the patient from immunosuppressive agents. Tacrolimus, favored over cyclosporine A since about 1994, is administered with prednisone and mycophenolate mofetil (MMF) for long-term maintenance immunosuppression. With this

regimen, 1-year graft survival rates for all types of pancreas transplants are 82 to 86 percent (Gruessner and Sutherland, 2002). Some centers have successfully tapered or discontinued post-transplantation glucocorticoids over time to avoid exacerbating peripheral vascular disease and other organ damage (Jordan, Chakrabarti, Luke, et al., 2000).

Tacrolimus inhibits insulin secretion and can cause post-transplant diabetes mellitus. However, this complication is reversed in more than 80 percent of cases by decreasing tacrolimus dose (Jordan, Chakrabarti, Luke, et al., 2000). In a multicenter trial of tacrolimus primarily for SPK transplantation, 3 percent of patients had their immunosuppression changed from tacrolimus to cyclosporine A due to post-transplant diabetes (Gruessner, 1997). Another center reports at least 2-year outcomes without evidence of tacrolimus toxicity (Jordan, Shapiro, Gritsch, et al., 1999). Tacrolimus also affects kidney function in a dose-dependent manner (Wagner, Herget, and Heemann, 1996; Goral and Helderman, 1997).

Replacing azathioprine with MMF, combined with either cyclosporine A or tacrolimus, significantly lowered risks of acute rejection and graft loss (International Pancreas Transplant Registry, 2001). MMF inhibits the cellular and humoral immune response via a different mechanism and is associated with neither nephrotoxicity nor diabetes (Goral and Helderman, 1997). However, approximately 25 percent of renal transplant patients have discontinued MMF due to gastrointestinal upset, leukopenia, and infections (Jindal, Sidner, and Milgrom, 1997).

Indefinite immunosuppression may also be necessary to prevent recurrent autoimmune organ damage. When an identical twin receives a syngeneic pancreatic segmental organ graft without immunosuppression, selective autoimmune destruction of the beta cells in the transplanted organ occurs rapidly (Sutherland, Goetz, and Sibley, 1989). At least one publication has documented selective loss of beta cells in allogeneic pancreas transplants that were ultimately rejected (Tyden, Reinholt, Sundkvist, et al., 1996). If anti-islet autoimmunity persists long after diabetes onset, it could contribute to pancreas transplant rejection.

Outcomes of Whole-Organ Pancreas Transplantation

This overview of the outcomes of whole-organ pancreas transplant procedures addresses patient survival, graft survival and diabetic complications.

Patient Survival. Several studies comparing long-term survival after SPK versus kidney-alone transplants (KTA) report that pancreas transplantation confers a survival advantage (Smets, Westendorp, van der Pijl, et al., 1999; Tyden, Bolinder, and Solders, 1999; Becker, Brazy, and Becker, 2000; La Rocca, Fiorina, Astorri, et al., 2000; Fiorina, Folli, Maffi, et al., 2003). However, short-term, mortality and morbidity are substantially higher with SPK.

Recently three multivariate analyses of longitudinal registry data have attempted to assess the short- and long-term trade-offs of SPK versus cadaveric KTA and to quantify, if possible, the projected survival advantage.[1] Overall, these analyses show that survival after SPK is better than KTA in the long term, but during the early post-transplant period, survival is worse with SPK. Ojo, Meier-Kriesche, Hanson, and colleagues (2001) analyzed 13,467 uremic adults with type 1 diabetes who were wait-listed for transplant between 1988 and 1997. Operative and early infectious deaths were approximately twice as high for SPK compared to KTA. Time to equal

[1] The studies cited in this paragraph performed various analyses and no studies overlapped as to sample and methodology. This summary focuses on analysis of SPK versus cadaveric KTA, adjusted for donor and recipient factors, reporting risk ratios with confidence interval, and robust number of patients at follow up (not necessarily longest follow-up). In the study by Reddy, Stablein, Taranto, and colleagues (2003), the risk ratio and confidence interval were not available for cadaveric KTA.

mortality as wait-listed patients was 95 and 170 days after cadaveric KTA and SPK transplantation, respectively. By 5 years, however, the mortality risk relative to wait-listed patients was 0.40 for 4,718 SPK patients (95 percent confidence interval [CI] = 0.33–0.49) and 0.75 for 4,127 KTA patients (95 percent CI = 0.63–0.89).

Bunnapradist, Cho, Cecka, and co-workers (2003) analyzed survival of 3,642 SPK and 2,374 KTA patients with type 1 diabetes reported to UNOS during 1994–1997 and followed through 2000. After controlling for favorable donor and recipient factors in the SPK group, risk of death in the KTA group relative to the SPK group was 1.06 (95 percent CI: 0.88–1.28), suggesting SPK had neither a favorable nor adverse effect on patient survival at 3–6 years. Reddy, Stablein, Taranto, and colleagues (2003) analyzed 18,549 kidney recipients with type 1 diabetes transplanted 1987 to 1996. At 8 years, unadjusted survival was 72 percent for SPK (n = 4,602) and 55 percent for cadaveric donor KTA (n = 9,956).

Survival after PTA has been reported to be comparable to that after SPK (Sutherland, Gruessner, Dunn, et al., 2001). However, Venstrom, McBride, Rother, and colleagues (2003) found that from "1995-2000, survival for those with diabetes and preserved kidney function and receiving solitary pancreas transplant was significantly worse compared with the survival of waiting list patients receiving conventional therapy." Of the 11,572 patients enrolled on the UNOS waiting list for pancreas transplants during this period, 5,379 received SPK, 838 received PAK, and 378 received PTA. The authors make the case for the comparability of transplant and wait-listed recipients on the grounds that solitary organ allocation is prioritized not by diabetes severity, but by time on the wait-list, for which the analysis was adjusted so that the groups were comparable. Compared to patients wait-listed for the same procedure, PTA and PAK recipients had a higher relative risk for overall mortality at followup of over 4 years. The relative risk for PTA was 1.57 (95 percent CI = 0.98–2.53; $p = 0.06$) and for PAK 1.42 (95 percent CI =1.03–1.94, $p = 0.03$). Survival of SPK recipients was far superior to wait-listed patients, but this analysis did not compare SPK to KTA.

Graft Survival. SPK cadaveric transplantation in patients with diabetic renal disease results in kidney graft survival that is at least equivalent to KTA. A followup study of SPK versus KTA observing patients over a 1- to 8-year period indicated that a pancreas transplant had no detrimental influence on long-term renal function (Hricik, Phinney, Weigel, et al., 1997). The longitudinal analysis by Bunnapradist, Cho, Cecka, and co-workers (2003) found no protective or detrimental effect on renal graft survival at approximately 5 years. Pancreas graft survival is slightly poorer than kidney graft survival (84.7 percent and 92 percent at 1 year, respectively (International Pancreas Transplant Registry, 2003). Aggregating all pancreas transplant procedures, at 3 years, pancreas graft survival is approximately 78 percent (International Pancreas Transplant Registry, 2003).

PAK transplants allow patients the benefits of a living-related donor kidney graft, if available, or a cadaveric kidney graft that is not associated with a simultaneously available pancreas graft. At 1 and 3 years after transplant, 78.5 and 63 percent of PAK transplant patients, respectively, have a functioning pancreas (International Pancreas Transplant Registry, 2003).

As noted, pancreas transplants alone are performed in highly selected patients. Graft survival data suggest that 78.2 and 62 percent of grafts are functioning at 1 and 3 years after transplant, respectively (International Pancreas Transplant Registry, 2003). Adverse outcomes and technical failure rates appear to be increased compared to SPK. Hospital admissions are higher at 73 percent versus 52 percent, respectively, for rejection; 53 percent versus 33 percent for infection,

respectively; and 45 percent versus 13 percent for repeat laparotomy, respectively (Stratta, Weide, Sindhi, et al., 1997; Stratta, Taylor, Sindhi, et al., 1996).

The rate of technical failure (nonimmunologic graft loss) is higher for pancreas transplantation of any type than for other routine solid-organ transplants. However, the International Pancreas Transplant Registry reports improvement in technical failure rates comparing 1988–1989 cases to 2000–2001 cases: from 16 to 8 percent, respectively, for SPK; from 16 to 9 percent, respectively, for PAK; and from 19 to 13 percent for PTA, respectively (Gruessner and Sutherland, 2002). Immunologic failure rates have also improved significantly; those reported for SPK, PAK, and PTA transplants were 2 percent, 6 percent, and 9 percent, respectively, for 2000–2001 cases. Improvement in pancreas graft survival is largely due to improvements in immunosuppressive regimens.

Diabetic Complications and Quality of Life. Whole-organ transplantation has clear and positive effects on hypoglycemic and renal complications. Patients with hypoglycemia unawareness despite optimal medical management before transplant no longer have hypoglycemia following successful PTA (Kendall, Rooney, Smets, et al., 1997; Robertson, 1999). Pancreas grafts prevent nephropathy (Wilczek, Jaremko, Tyden, et al., 1995) and established renal lesions may be reversed in nonuremic patients after more than 5 years of normoglycemia (Fioretto, Steffes, Sutherland, et al., 1998). In contrast, histologic changes of diabetic nephropathy commonly recur in diabetic KTA patients within 2 years of transplantation, and progress to endstage disease after 10 years (Najarian, Kaufman, Fryd, et al., 1989).

Polyneuropathy is a common complication of diabetes; whether or not pancreas transplantation alleviates this complication is unclear. For example, Navarro, Sutherland, and Kennedy (1997) reported that progression was significantly delayed and motor and sensory nerve conduction improved in pancreas transplant patients with prior evidence of polyneuropathy compared to type 1 diabetic patients managed medically or with KTA. The effect was greatest 5 to 8 years post-transplantation. In another report, however, not all patients improved, nor did any patient characteristics predict response (Recasens, Ricart, Valls-Sole, et al., 2002).

Although available evidence is inconclusive, some studies suggest that retinopathy may stabilize or improve (Chow, Pai, Chapman, et al.; 1999; Koznarova, Saudek, Sosna, et al., 2000). Pancreas transplantation appears to have a beneficial effect on hypertension (Elliott, Kapoor, Parker, et al., 2001) and may improve cardiac function, but there is no discernable recovery from existing peripheral vascular disease in studies to date (Morrissey, Shaffer, Madras, et al., 1997; Knight, Schanzer, Guy, et al., 1998; Nakache, Merhav, and Klausner, 1999). Effects on progression of early asymptomatic vascular disease are uncertain.

Several studies assessed quality of life, primarily in patients successfully transplanted by SPK, comparing them to patients given SPK transplants who subsequently lost pancreas function, to patients receiving KTA, and to eligible patients not transplanted. Results for several measures generally support significantly improved quality of life after successful transplants (Adang, Engel, van Hooff, et al., 1996; Zehrer and Gross, 1994; Piehlmeier, Bullinger, Kirchberger, et al., 1994; Nakache, Tyden, and Groth, 1994; Kiebert, van Oosterhout, van Bronswijk, et al., 1994; Hathaway, Hartwig, Milstead, et al., 1994). In one study, PTA patients reported better quality of life with insulin independence and immunosuppression than with labile diabetes (Zehrer and Gross, 1991). However, it should be noted that available quality of life studies have serious shortcomings including: lack of comparable control groups; use of different

quality of life instruments; use of instruments not validated in transplant patients; and potential selection bias (Holohan, 1995; Robertson, Holohan, and Genuth, 1998).

Table 1 arrays outcomes reported in the literature for whole-organ pancreas transplants contrasted with kidney transplant only or medical management in patients with type 1 diabetes. Where available, data from direct comparison studies were summarized; however, in some cases, summarized data represent indirect comparisons. In some cases, pancreas transplant results are from one type of transplant (e.g., PTA), in other cases from different types of pancreas transplants combined. Note that although registry data are from large numbers of patients, outcomes reported in individual papers typically include fewer patients and, thus, have greater uncertainty.

Islet Transplantation

Although whole-organ pancreas transplants are relatively successful, the surgery is complicated and associated with serious morbidity. Islet transplantation avoids the complications of open abdominal surgery. Islet transplantation is a procedure in which pancreatic islets from whole organs are prepared in vitro, and then infused via a catheter into the liver, where they lodge. Successfully transplanted islets produce and release insulin in response to physiologic glucose concentrations and may normalize glucose concentration without exogenous insulin.

Until recently, the proportion of patients remaining insulin independent after islet transplantation had been disappointingly low. The major reasons for failure included graft rejection, local inflammatory response, and possibly greater sensitivity of the grafted islets to immunosuppressive drug toxicity. Additionally, several cadaveric pancreas organs had to be processed in order for each patient to obtain sufficient functional islets; organ quality may have been poor. More recently, researchers in Edmonton, Canada using an improved islet preparation protocol harvested sufficient islets for one patient from two organs, and reported maintenance of islet function for over a year with a glucocorticoid-sparing, reduced-dose immunosuppressive protocol (Shapiro, Lakey, Ryan, et al., 2000). The “Edmonton protocol” and subsequently developed protocols are being tested in clinical trials.

History of Islet Transplantation

In 1972, Ballinger and Lacy reported the first successful implant of purified rat islets into inbred (autograft) and non-inbred (allograft) diabetic rats (Ballinger and Lacy, 1972). All diabetic immunosuppressed controls died within a few weeks. Longer survival and normalization of blood glucose was observed in both the autografted and allografted rats, although the autografted animals had better results. Successful human islet autotransplantation was reported early (Najarian, Sutherland, Baumgartner, et al., 1980), but only in a small proportion of patients. Successful allotransplantation remained rare for several years.

Table 1. Outcomes reported in the literature for whole-organ pancreas transplantation contrasted with kidney transplant only or medical management in patients with type 1 diabetes.

	Pancreas Transplant (+/- Kidney Transplant)	Kidney Transplant Alone	Medical Management
Hypoglycemia unawareness[a]	Return to normoglycemia avoids hypoglycemia; symptom awareness returned to near normal in hypoglycemic clamp studies	Strict glycemic control increases episodes of hypoglycemia unawareness and decreases symptom recognition	Strict glycemic control increases episodes of hypoglycemia unawareness and decreases symptom recognition
Nephropathy 5 years	No significant change[b]	Significant changes in 45.8% over 2.5 years[c]	Total mesangial volume increased significantly over 5 years[c]
10 years	Indicators returned to normal or baseline[b]		
Neuropathy Motor nerve conduction[d]			(Progression at usual rate)
% improved, 7 years	65	6	
% stable, 7 years	23	25	
Sensory nerve conduction[d]			
% improved, 7 years	41	0	
% stable, 7 years	24	37	
Cardiorespiratory reflex[d]			
% improved, 7 years	47	20	
% stable, 7 years	47	20	
% patients normotensive, 18 months[e]	34	0	0
Retinopathy[f]			
% improved, 3 years	21	6	(Progression at usual rate)
% stable, 3 years	62	49	
Tacrolimus toxicity[g]			N/A
% nephrotoxicity	20		
% neurotoxicity	19		
% gastrointestinal toxicity	12		
% diabetogenicity	12		
Mycophenolate mofetil toxicity	25 (total)[h]		
% CMV infection	7[i]		
% myelosuppression			
% gastrointestinal toxicity			

[a]Robertson, 1999
[b]Fioretto, Steffes, Sutherland, et al., 1998
[c]Fioretto, Mauer, Bilous, et al., 1993; Wilczek, Jaremko, Tyden, et al., 1995
[d]Navarro, Sutherland, and Kennedy, 1997
[e]Elliott, Kapoor, Parker, et al., 2001
[f]Koznarova, Saudek, Sosna, et al., 2000
[g]Stratta, 1999
[h]Stratta, Shokouh-Amiri, Egidi, et al., 2003
[i]Gruessner and Sutherland, 1998

An automated method for human islet isolation significantly improved yield (Ricordi, Lacy, Finke, et al., 1988) and allowed large scale isolation for clinical studies. Later, a standardized mixture of highly purified enzymes (Liberase) was developed and replaced the variable activities of collagenase lots for separating human islets, improving islet yield and integrity (Linetsky, Bottino, Lehmann, et al., 1997). These advances led to greater standardization of islet processing protocols, allowing clinical trials to proceed at multiple centers. Research continues in order to improve islet yield from autologous and cadaveric pancreata, investigate other islet sources, and develop better methods of immunosuppression and/or tolerance induction for long-term maintenance of transplanted islets.

The last summary of the International Islet Transplant Registry (ITR) reported on 240 islet autografts (140 well documented) between 1990 and 2000 performed at 15 institutions (International Islet Transplant Registry, 2001). These autografts were performed to preserve and restore islets to patients undergoing pancreatectomy, who would otherwise be left diabetic by the surgery. Of these cases, 47 percent were insulin independent at 1 year. However, among patients who received at least 300,000 islet equivalents (IE), 71 percent were insulin independent at 1 year and the rest had better diabetic control than patients undergoing total pancreatectomy without islet transplant (Wahoff, Papalois, Najarian, et al., 1995; Panaro, Testa, Bogetti, et al., 2003). Stable beta-cell function and normal levels of blood glucose after autotransplantation have been reported for up to 13 years (Robertson, Lanz, Sutherland, et al., 2001). Registry data show that increasing the yield of islets is an important success factor (Morrison, Wemyss-Holden, Dennison, et al., 2002).

After the introduction of the Ricordi isolation method, well-documented cases of insulin independence after human islet allotransplantation began to appear (Scharp, Lacy, Santiago, et al., 1990; Warnock, Kneteman, Ryan, et al., 1992; Ricordi, Tzakis, Carroll, et al., 1992; Gores, Najarian, Stephanian, et al., 1993; Bretzel, Brandhorst, Brandhorst, et al., 1999). In some cases, patients maintained insulin independence or graft function for several years (Alejandro, Lehmann, Ricordi, et al., 1997; Davalli, Maffi, Socci, et al., 2000; Cretin, Caulfield, Fournier, et al., 2001). Overall rates of insulin independence at and beyond 1 year, however, remained disappointingly low (11 percent overall, Table 2) until the advent of the Edmonton protocol.

Reports from the Islet Transplant Registry provide the largest dataset on outcomes of patients with type 1 diabetes who received islet allografts in the pre-Edmonton protocol era. Between 1990 and December, 2000, 355 such transplants had been reported to the Registry, of which 237 had at least 1 year of followup (Islet Transplant Registry, 2001). This includes nearly 90 percent of worldwide transplants completed in the same time period. A subsequent meeting presentation reported on a total of 466 well-documented patients transplanted between 1990 and August, 2002 (Brendel, Hering, Schultz, et al., 2002), with 1 year of followup for 270 of these cases. Table 2 summarizes outcomes reported in 2001 for all patients receiving islet transplants under pre-Edmonton protocols (up to 1999) followed for at least 1 year, and for various subgroups of these patients.

Although most patients (73 percent; not shown) demonstrated evidence of insulin production 1 month or more after an islet allograft, only 41 percent of patients had functional islets at 1 year. Furthermore, only 11 percent of all patients remained insulin independent at 1 year. Thus, for the overwhelming majority (89 percent) of patients treated in the pre-Edmonton era, islet allotransplants did not achieve the intended outcome. Little, if any, mortality was associated with the procedure, since 96 percent of transplanted patients remained alive for at least 1 year. The Registry also reported that of 200 patients followed for at least 3 years after an islet

allotransplant, 94 percent were alive and 19 percent retained some evidence of islet function (not shown; Islet Transplant Registry, 2001). However, the proportion remaining insulin independent at 3 years was not reported. In a later update (Brendel, Hering, Schultz, et al., 2002), the Registry reported functional graft survival in 24 percent, insulin independence in 4 percent, and overall survival in 95 percent of 235 patients followed for at least 3 years.

Table 2. Outcomes of Islet Allografts Transplanted 1990-1999[a]

Patient Group	n included	n (%) with C-peptide ≥0.5 ng/mL at 1 year	n (%) insulin independent at 1 year	n (%) patients alive at 1 year
all reported	237	98 (41)	25 (11)	227 (96)
SIK	131	61 (47)	12 (9)	126 (96)
IAK	87	34 (39)	13 (15)	85 (98)
ITA	9			
SIL	7			
≥ 6000 IEq/kg	146	63 (43)	25 (17)	
< 6000 IEq/kg	78	30 (38)	0 (0)	
≤8 hrs. cold ischemia	162	73 (45)	21 (13)	
>8 hrs. cold ischemia	62	18 (29)	3 (5)	
no T-cell AB	40	9 (23)	1 (3)	
ATG/ALG/IL-2R	162	80 (49)	23 (14)	
OKT3	30	9 (30)	1 (3)	
yes, all 4 criteria	67	35 (52)	16 (24)	
no, ≥1 criterion	170	63 (37)	9 (5)	
1990–93 transplants	82	31 (38)	7 (9)	
1994–97 transplants	118	43 (36)	9 (8)	
1998–99 transplants	37	25 (68)	5 (14)	

[a]Note: Data presented here are from pre-Edmonton protocol transplants

The overwhelming majority of patients given islet allotransplants in the pre-Edmonton era were treated either simultaneously with (simultaneous islet/kidney, SIK, 55 percent) or after (islet after kidney, IAK, 37 percent) a kidney transplant (Islet Transplant Registry, 2001). Only nine patients (4 percent) received an islet transplant alone (ITA). Immunosuppression regimens for most patients transplanted using pre-Edmonton protocols likely were primarily based on those used to manage kidney transplant recipients. The subsequent update (Brendel, Hering, Schultz, et al., 2002) included 138 SIK patients and 90 IAK patients. Among these, functional graft survival at 1 year was 51 percent and 40 percent, respectively, while insulin independence at 1 year was 9 percent and 15 percent, respectively.

Registry analyses identified several factors that influence outcomes of islet transplants (Islet Transplant Registry, 2001). These include the site of the transplant (data not tabulated; liver [n = 220] versus others [n = 17]); the number of islet equivalents transplanted per kilogram of body weight (≥6000 versus <6000); the duration of cold ischemia from cross-clamping to islet isolation (≤8 hours versus >8 hours); and the regimen used to induce immunosuppression (no anti-T cell antibody versus ATG, ALG, or antibody to IL-2R versus OKT3). A substantially greater proportion of transplants that were favorable on all four of these predictive criteria than of those that failed on one criterion or more remained functional (31 percent versus 9 percent, respectively) and maintained insulin independence (24 percent versus 5 percent, respectively) at 1 year after treatment (Table 2). Note also that success was more frequent among those patients transplanted in years 1998 and 1999 than among those transplanted earlier.

The Registry reports did not include any data on effects of insulin independence following islet allotransplantation on diabetic complications. Fiorina, Folli, Maffi, and co-workers (2003) followed 37 islet allotransplanted type 1 diabetic kidney transplant patients, of whom, 24 maintained islet function (C-peptide >0.5 ng/mL) for longer than 1 year and 13 lost or never achieved islet function during the first year, for an average of 63 months. Patients with successful islet transplants had significantly reduced: cardiovascular and all-cause mortality; microvascular-endothelial injury; atherothrombotic risk factors; and renal damage (as measured by urine albumin excretion) compared to those whose transplants were not successful (Table 3). Additionally, the cardiovascular death rate for successful islet transplant patients was similar to that of a control group of whole-organ pancreas transplant patients, and better than that of kidney-alone transplant patients. Patients with successful islet transplants had significantly lower exogenous insulin requirements than those with unsuccessful transplants at all timepoints.

Table 3. Long-term outcomes of kidney-islet, kidney-pancreas organ, kidney alone transplantation and uremic type 1 diabetes with no transplantation (Fiorina, Folli, Maffi, et al., 2003).

	Kidney-Islet Transplant (All)	Kidney-Islet Transplant, Successful	Kidney-Islet Transplant, Unsuccessful	Kidney-Pancreas Transplant	Kidney Alone Transplant	Uremic Type 1 Diabetic
Patient survival (%)						
1 year	95	100	84	93	92	94
4 years	86	100	75	86	74	67
7 years	68	90	45	74	56	37
Cardiovascular death (%)	18	5	46	8	19	16
Exogenous insulin required (units/day)						
1 year		19	46			
4 years		23	52			
7 years		18	36			
Patients with increased urine albumin excretion (%)		4	46			

An earlier small study (n = 8) reported that stable islet function after an allograft (n = 6) significantly reduced HbA_{1c} concentrations and insulin requirements (Alejandro, Lehmann, Ricordi, et al., 1997). Over 6 years of followup, these patients also remained free of the severe hypoglycemic episodes observed in the Diabetes Control and Complications Trial, even though they were not insulin independent. Other investigators also have reported that functional islets after allotransplants decrease hypoglycemia unawareness and improve hormonal counter-regulation in response to hypoglycemia (Meyer, Hering, Grosmann, et al., 1998).

Edmonton Protocol and Subsequent Research

In 2000, Shapiro, Lakey, Ryan, and co-workers at the University of Alberta in Edmonton, Canada, published the results of a patient series of islet transplants using a modified protocol, thereafter known as the Edmonton protocol. The key elements of this protocol were the minimization of cold ischemia time after pancreas removal; the preparation of islets in medium free of animal protein; the transplantation of at least 9,000 IEq/kg (which usually entails islet transplants from two donor organs**)**; and an immunosuppressive regimen that replaced

glucocorticoids with a post-transplant course of daclizumab (anti-IL-2 receptor monoclonal antibody) and used low-dose tacrolimus in combination with sirolimus. Such combination immunosuppressive therapy had been shown in animal models and later in human organ transplantation to enhance therapeutic efficacy and minimize individual drug toxicity (Vu, Qi, Xu, et al., 1997; McAlister, Gao, Peltekian, et al., 2000). Avoiding glucocorticoids and reducing the tacrolimus dose lessens the risk of dyslipidemia and nephrotoxicity.

Eligibility criteria for this protocol included the following:

- diagnosis of type 1 diabetes based on a stimulated serum C-peptide concentration of less than 0.48 ng per milliliter;
- diabetes for more than 5 years;
- uncontrolled glucose concentration despite exogenous insulin therapy;
- severe hypoglycemia requiring outside help to treat or labile diabetes, with evidence of daily lifestyle disruption;
- no or stable coronary artery disease;
- no prior transplants.

In general, eligible patients were judged to be at greater risk from uncontrolled diabetes than they would be from the global risk of transplantation and immunosuppression.

Seven consecutive patients received islet transplantation using the Edmonton protocol; all seven maintained insulin independence for a median of nearly 1 year without further episodes of hypoglycemic coma (Shapiro, Lakey, Ryan, et al., 2000). This series was extended and in an update, Ryan, Lakey, Paty, and co-workers (2002) reported that of 15 consecutive patients with at least 1 year of followup, 12 (80 percent) remained insulin independent. A number of centers around the world are now performing islet transplantation based on the Edmonton protocol to expand efficacy data, determine the duration of the effect, evaluate the potential for reducing or preventing the long-term complications of diabetes, and assess the effect of lifelong immunosuppressive therapy, particularly in younger patients. For example, the National Institutes of Health (NIH) and the Juvenile Diabetes Research Foundation International (JDRFI) are funding the Immune Tolerance Network (ITN) Multicenter trial, testing the Edmonton protocol in nine centers: University of Alberta, Edmonton, Alberta, Canada; University of Minnesota, Minneapolis; University of Miami, Miami; Pacific Northwest Research Institute, Seattle; Washington University, St. Louis; Harvard Medical School, Boston; Justis-Liebig University, Giessen, Germany; University of Milan, Milan, Italy; and University Hospital, Geneva, Switzerland (Immune Tolerance Network Clinical Trial Research Summary, 2003).

In addition, a number of centers are studying new glucocorticoid-free protocols that address other aspects of the procedure:

- The initial patient series was limited to patients with highly labile and potentially life-threatening diabetes but no uremia. Since diabetes is a major risk factor for kidney failure, studies of islet transplantation in conjunction with kidney transplantation are in progress to assess efficacy (e.g., Berney, Bucher, Mathe, et al., 2002). Because simultaneous kidney/islet transplants are difficult to coordinate, most transplants are likely to be islet after kidney, in which case, kidney transplant patients must be

weaned from chronic glucocorticoid treatment and converted to low-dose tacrolimus plus sirolimus.

- Various methods are under study to improve islet yield and extend the interval of in vitro islet viability. Demonstrated improvements are quickly translated into clinical practice. These include improved methods of organ preservation prior to islet harvest (Matsumoto, Kandaswamy, Sutherland, et al., 2000; Hering, Matsumoto, Sawada, et al., 2002; Matsumoto and Kuroda, 2002; Lakey, Kneteman, Rajotte, et al., 2002; Fraker, Alejandro, and Ricordi, 2002) and islet culture (Hering, Bretzel, Hopt, et al., 1994; Gaber, Fraga, Callicutt, et al., 2001; Fraga, Sabek, Hathaway, et al., 1998). Use of islet culture allows for transport of purified islet preparations to distant clinical centers without loss of functional viability; islet culture and other procedural optimization has allowed some patients to achieve insulin independence with transplanted islets from a single organ (Alejandro, 2002; Hering, Kandaswamy, Ansite, et al., 2003).

  Animal models suggest that up to two-thirds of transplanted islets may be lost within the first 30 days of transplantation (Davalli, Ogawa, Ricordi, et al., 1995). Islets from two and sometimes three organs are required for most individuals (Ryan, Lakey, Paty, et al., 2002; Markmann, Deng, Huang, et al., 2003). Marked improvements in pre- and post-transplant viability could increase the number of patients that can be transplanted from available organ donations, and potentially allow new islet sources such as segmental pancreata from live donors. Thus, there is incentive to modify and improve current protocols. For example, enzymatic dissociation of islets from pancreatic tissue relies on the use of Liberase HI, a crude enzyme mixture of proteases with lot-to-lot variability.

  Recently it has been shown that a recombinant collagenase may have similar activity with less variability (Brandhorst, Brandhorst, Hesse, et al., 2003). The use of perfluorocarbons extends the organ cold ischemia time post-procurement and may enhance islet function; combination with marginal donor sources that would be rejected for whole-organ transplantation may increase the available organ pool (Ricordi, Fraker, Szust, et al., 2003; Markmann, Deng, Desai, et al., 2003).

- Various methods are being investigated to reduce the number of harvested islet equivalents required for a successful transplant (currently most patients require islets from at least two whole pancreas organs). The addition of infliximab (a tumor necrosis factor inhibitor) to reduce insulin use and promote success with single-donor transplants has met with mixed success (Geiger, Caulfield, Froud, et al., 2002; Shapiro, 2002). Other methods include replacing tacrolimus with nondiabetogenic agents synergistic with sirolimus (Hering, 2002; Vu, Qi, Xu, et al., 1998) and inhibiting autologous and allogeneic immune reactions with agents such as the anti-CD3 antibody hOKT3gamma1 (Ala-Ala), both of which have been used successfully in single transplants (Hering, 2002; Herold, Hagopian, Auger, et al., 2002).

- In the U.S., islets are currently obtained from the small number of donor organs that have not been utilized for whole organ transplantation. Alternative sources of islets, such as pancreata obtained from marginal donors and rejected for whole-organ transplant (Ricordi, Fraker, Szust, et al., 2002) or nonheart beating donors (Markmann, Deng, Desai, et al., 2003), have been tried with some success. The study of xenotransplants in humans remains controversial (Valdes-Gonzalez, Elliot, Dorantes, et al., 2002), but is proceeding in animal models. Ongoing basic and clinical research is examining the potential of genetic engineering of nonpancreatic cells to produce insulin (Shen, Qin, Xiao, et al., 2002); and of transforming stem cells or pancreatic ductal cells into islets (Campbell, 2002; Lumelsky, Blondel, Laeng, et al., 2001).

- Various methods that may reduce or eliminate the need for lifelong immunosuppression are currently under study. These include costimulatory blockade of T-cell activation to induce tolerance (Parker, Greiner, Phillips, et al., 1995; Kawai, Sogawa, Koulmanda, et al., 2001; Adams, Shirasugi, Durham, et al., 2002) and immune isolation by islet encapsulation (de Vos, Hamel, Tatarkiewicz, et al., 2002; Sharp, 2002).

Trials testing various protocols are currently underway; examples are summarized in Table 4.

Table 4. Examples of ongoing clinical trials of islet transplant protocols.

Study ID Number	Phase	Location	Purpose
NCRR-M01RR00400-0672	I/II, recruiting	U Minnesota	Determine the safety, tolerability, immune activity, and pharmacokinetics of hOKT3 gamma1 (Ala-Ala) administration for the prevention of autoimmune destruction and rejection of allogeneic islet transplants
(Sponsored by NIDDK)	II	U Miami	Determine the efficacy of nonglucocorticoid, low-dose tacrolimus plus sirolimus immunosuppression with vs. without the administration of infliximab in islet-alone transplantation in type 1 diabetic patients.
NIH # DK 56953-03	II	U Miami	Determine the efficacy of islet transplantation alone and with CD34+ enriched donor bone marrow cell infusion in patients with type 1 diabetes mellitus; glucocorticoid-free regimen.
JDFI-Penn Comprehensive Islet Transplantation Program		U Pennsylvania	Application of the Edmonton protocol in patients who have already received a renal allograft. "Edmonton" immunosuppression is modified to include patients receiving low doses of glucocorticoids and other combinations of maintenance immunosuppression.
Northwestern U General Clinical Research Center #715	?	Northwestern U	Test induction with 15-deoxyspergualin (DSG) with the Edmonton protocol to determine efficacy of islet transplantation from a single donor. 15-DSG is hypothesized to inhibit factors responsible for the generation of primary islet nonfunction.
NCRR-M01RR00036-0775	I	Washington U	Determine the efficacy of oral antidiabetic drugs in conjunction with the Edmonton islet transplant protocol to allow for successful transplantation of islets from a single donor pancreas; and expand the Edmonton protocol to diabetic patients who are also receiving kidney transplantation and determine the effect on kidney function and blood glucose control.
NCRR-M01RR00036-0779	I	Washington U	Determine how immunosuppressive regimens affect glucose metabolism and insulin utilization in diabetic patients who have received both kidney and islet transplants and compare to nondiabetic patients who have received only kidney transplants

The NIH National Center for Research Resources, Division of Clinical Research supports 10 Islet Cell Resource (ICR) centers in the U.S. These centers isolate, purify, characterize, and distribute human pancreatic islets for subsequent transplantation in approved clinical protocols. These centers also study improvements in islet isolation and purification techniques, and methods of storage and shipping (www.ncrr.nih.gov/clinical/cr_icr.asp).

Regulatory Issues

Because the use of cells derived from whole organs meets criteria for biologic product regulation under the Public Health Service Act, the U.S. Food and Drug Administration (FDA) considers allogeneic islet transplantation to be somatic cell therapy, thus, requiring premarket approval (Weber, McFarland, and Irony, 2002). Islets also meet the definition of a drug under the Federal Food, Drug, and Cosmetic Act. Because allogeneic islet transplantation is considered experimental therapy, clinical studies to determine safety and effectiveness outcomes must be conducted under FDA investigational new drug (IND) regulation (Weber, McFarland, and Irony, 2002).

Applications for marketing approval will require information that demonstrates manufacturing control and product consistency as characterized by composition, size distribution, potency, and purity/impurity profiles across multiple islet preparations. Consistency in the dissociation method will be important for licensing. Source organ procurement, transport, and donor screening and testing issues must also be addressed in the manufacturing process. Thus, for licensing it has been recommended that a well-defined islet preparation method be chosen and supported by data (Weber, 2002). Adoption of a standard protocol will be necessary to allow for data collection and submission in support of FDA approval; subsequent protocol improvements must be incorporated later with regulatory review. It is unclear what impact protocol evolution will have on the FDA approval process, in terms of the need for additional data collection or reapplication for approval.

A biologics license application (BLA) approval will also require supportive data demonstrating safety and effectiveness. To this end, clinical trials of islet transplantation must be conducted according to good clinical practices and should be done within the context of an adequate clinical trial safety monitoring program. Trial protocols should include well-defined eligibility criteria; prespecified endpoints; and a statistical plan for endpoint analysis. As of this writing, no center has as yet submitted a biologics license application.

In order to develop specific guidance for marketing approval, on October 9–10, 2003, the FDA held a public meeting of the Biological Response Modifiers Advisory Committee (U.S. Food and Drug Administration, 2003). As introduced by the FDA, the goal of the meeting was for the FDA to get "advice and perspectives from … the committee in terms of discussing the data that … should be provided in a BLA" for marketing approval of allogeneic islet transplantation. Topics discussed included acceptance criteria for donor organs; islet isolation procedure standardization; pretransplant assessment of islet function; key criteria for demonstrating allogeneic islet product comparability including clinical studies, and endpoints.

Immunosuppressive drugs used in post-transplantation islet maintenance that are already FDA approved for other related indications do not need separate approval. However, use of unapproved drugs may require approval as combination therapy with islet transplants (Weber, McFarland, and Irony, 2002).

At least 35 IND applications for the use of allogeneic islets to treat type 1 diabetes have been submitted to the FDA, more than 75 percent since 2000 (Weber, McFarland, and Irony, 2002). Current INDs are "in early phase clinical studies." Charging for an investigational product that is subject to clinical trials under an IND is permitted only with prior FDA approval and may be limited to certain aspects of the procedure. An amendment to the recently approved Medicare Prescription Drug, Improvement, and Modernization Act of 2003 mandates that National Institute of Diabetes and Digestive and Kidney Diseases conduct a clinical investigation of pancreatic islet transplantation to include Medicare beneficiaries, and that routine costs, transplantation and appropriate related items and services be paid by Medicare for beneficiaries who are participating in the clinical trial (Office of Legislative Policy and Analysis, 2003).

Currently, human islets prepared for the purpose of clinical transplantation are produced by only a few established and experienced centers. Because startup costs are high, legal and regulatory issues are demanding, and a substantial learning curve is necessary for consistent success, not all transplant centers are likely to have associated islet preparation centers. Rather, institutional collaborations with transportation of whole organs to distant preparation centers and return of islet preparations meeting regulatory requirements will play a large role in islet transplantation (Goss, Schock, Brunicardi, et al., 2002).

Measuring the Success of Pancreas or Islet Transplantation

Outcomes of interest to this evidence report include clinical outcomes, long-term diabetic outcomes, biologic outcomes that are indicators of graft function and glycemic control, and adverse outcomes. In the future, the Collaborative Islet Transplant Registry will be the most comprehensive source of data on the outcomes of islet transplant. Reports from individual transplant centers will supplement the registry data with greater detail and with center-specific outcomes.

Outcomes of Interest

Based on the Biological Response Modifiers Advisory Committee meeting (U.S. Food and Drug Administration, 2003), a consensus definition of success for islet transplantation is: Restoration of sustained euglycemia (i.e., absence of hyper- and hypoglycemia) with no or a reduced exogenous insulin requirement. Clinical outcome parameters that can be used together to measure success are insulin independence or percent of prior insulin use, hypoglycemic episodes, and quality of life.

- Insulin independence: Islet transplantation attempts to restore normal glucose metabolism by in vivo production of insulin regulated by changing glucose concentrations without the need for exogenous insulin supplementation. The percentage of patients who do not require exogenous insulin at yearly post-transplant intervals is a direct measure of success.

- Percent prior insulin use: failing absolute insulin independence, successfully transplanted patients may attain good control without glycemic excursions accompanied by a marked decrease in the need for exogenous insulin.

- Hypoglycemic episodes: Hypoglycemia unawareness and life-threatening hypoglycemic episodes can be a consequence of strict glucose control with exogenous insulin, and are indications for pancreas whole-organ or islet transplantation. Elimination of hypoglycemic episodes in conjunction with glycemic control is also a direct measure of transplant success.

- Quality of life: Islet transplantation can improve quality of life for patients by eliminating hypoglycemic and hyperglycemic episodes, the need for insulin injections, frequent self-monitoring of blood glucose levels, and dietary restrictions. General and specific standardized measures of quality of life may include the Health Utilities Index, SF-36, Immunosuppressant Quality of Life (QOL) Survey, and Hypoglycemia Fear Survey (Johnson, 2002). Characteristics of these instruments are briefly summarized in Table 5.

Although sustained euglycemia may be of highest clinical interest, in the absence of well-controlled studies, insulin independence may be the most persuasive measure available to establish the success of the procedure.

Table 5. Measures for evaluation of transplantation and quality of life.

Survey	Description	Reference
36-item Short Form health survey (SF-36)	Evaluates general quality of life. Survey addresses 8 areas of health status, summarized in 2 component scores: *Physical component:* physical functioning; physical limitations; pain; general health perception *Mental component:* vitality; social functioning; emotional limitations; mental health	Terada and Hyde, 2002; Ware and Sherbourne, 1992
Health Utilities Index Mark 2 (HUI2)	Comprehensive description of health status in 8 core domains: Vision; hearing; speech; ambulation; dexterity; emotion; cognition; pain.	Furlong, Geeny, Torrance, et al., 2001
Hypoglycemia Fear Survey (HFS)	Addresses behaviors and worries related to potential hypoglycemic episodes. Increased awareness of hypoglycemia correlates with decreased HFS scores in validation studies.	Cox, Irvine, Gonder-Frederick, et al., 1987
Immunosuppressant QOL Survey (Memphis Survey)	Evaluates side effects of immunosuppressive therapy for organ transplantation. Employs 4 subscales: emotional burden, life/role responsibilities, mobility, gastrointestinal distress.	Winsett, Stratta, Alloway, et al., 2001

Improvement in long-term diabetic outcomes is the measure of ultimate success of islet transplantation in type 1 diabetes. The objective is to reduce or eliminate long-term diabetic outcomes such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Transplantation after complications have already become apparent may not be able to reverse or even stabilize the process. Transplantation prior to complications is more likely to delay or preclude their occurrence, but studies will require a minimum of 5–10 years in order to collect robust data on clinical outcomes.

Potential adverse events of islet transplant may be direct consequences of the procedure (e.g., hemorrhage or thrombosis from percutaneous access of the portal vein) or the continued immunosuppression needed to maintain viability and function of the transplanted islets. Adverse effects of immunosuppression may be near-term (e.g., mouth ulceration, diarrhea, anemia) or long-term (e.g., renal insufficiency, post-transplant lymphoproliferative disorders, other malignancies, cytomegalovirus or other infections).

Measurement of C-peptide and HbA_{1c} (glycated hemoglobin) are biological outcomes that are indicators of graft function and glycemic control, respectively.

- C-peptide: C-peptide is an inactive cleavage product of insulin production. Because C-peptide is metabolized minimally by the liver, has a longer half-life than insulin, and measurement is not affected by the presence of exogenous insulin, serum C-peptide levels are better indicators of beta-cell function than the peripheral insulin concentration (Sacks, 1999), and thus, the preferred measure for monitoring post-transplant islet function.

- HbA_{1c}: Measurement of glycated hemoglobin is the standard method for assessing glycemic history over 2–3 months. HbA_{1c} is the standard assay for measurement of glycated hemoglobin and, thus, of post-transplant glycemic control.

A variety of metabolic measures are available to estimate pancreatic beta cell functional reserve. These include intravenous glucose tolerance tests (IVGTT), from which can be calculated the acute insulin response to glucose (AIR_g), glucose disposal (K_G), and areas under the curve for insulin and C-peptide (AUC_i and $AUC_{C\text{-}p}$, respectively); intravenous arginine stimulation, from which are derived the acute insulin response to arginine (AIR_{arg}) and the acute C-peptide response to arginine (ACPR); oral glucose tolerance testing (OGTT); and mixed meal stimulation. Several of these measures have been reported as near normal and stable over at least 5 years in pancreas organ transplant recipients (Robertson, Sutherland, Kendall, et al., 1996; Robertson, 2003). Islet transplant recipients have demonstrated results that are similar to those of segmental pancreas graft recipients, but lower than those of whole-organ transplant patients, despite exogenous insulin independence (Secchi, Taglietti, Socci, et al., 1999).

Various metabolic measures have been reported in conjunction with islet transplant outcomes by a few centers (Baidal, Froud, Ferreira, et al., 2003; Hering, Kandaswamy, Harmon, et al., 2004 [In press]; Ryan, Lakey, Paty, et al., 2002). However, there does not yet appear to be consensus on the measures most predictive of continuing beta-cell function, on the clinical significance of impaired glucose tolerance in islet transplantation (Baidal, Froud, Ferreira, et al., 2003), nor is there consistent reporting among the majority of transplant centers.

Collaborative Islet Transplant Registry (CITR)

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) initiated and funded the Collaborative Islet Transplant Registry (CITR) in September, 2001. As stated on the CITR website (http://spitfire.emmes.com/study/isl/index.html), the goals of the Registry are:

- "To develop and implement standards for reporting islet/beta cell transplants and their outcome.

- To collect and compile data on all islet/beta cell transplants in human recipients performed in the United States and Canada. [European transplant data will also be included under a funding arrangement with the Juvenile Diabetes Research Foundation]

- To increase the safety of islet/beta cell transplantation by distributing electronically the pertinent information of submitted serious adverse event reports to all participating clinical centers in a timely fashion.

- To perform scientific analysis on islet/beta cell transplant data, with particular emphasis on:
  - safety of islet/beta cell transplant product and procedure and protocol-regulated treatment products;
  - number of islet/beta cell transplants and retransplants performed, categorized by transplant institution, donor tissue source and handling, recipient category, transplant technique and site, and recipient treatment protocols;
  - efficacy of islet/beta cell transplants as defined by standardized outcome measures and as determined by donor factors, recipient demographics, donor-recipient matching, islet/beta cell processing and product characteristics, transplant technique and site, recipient treatment, and post-transplant events.

- To communicate comprehensive and current information on islet/beta cell transplantation to transplant institutions, the diabetes and general health care community, and the interested general public via the CITR website (http://www.citregistry.org), publications, and presentations.

- To stimulate prospective and retrospective studies on emerging issues of importance."

The Registry is now completing collection of data from participating institutions. Unfortunately, data from the first CITR report were not yet available at the time this evidence report was being prepared.