Evidence Report/Technology Assessment
Number 98

Islet Transplantation in Patients with Type 1 Diabetes Mellitus

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Preface

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To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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Acknowledgments

Structured Abstract

Context. Pancreas transplantation is used selectively for labile type 1 diabetes to achieve physiologic insulin regulation. Infusing pancreatic islets into the liver via catheter ("islet transplant") may offer similar benefit with less surgical risk.

Objectives. Systematic evidence review on the outcomes of islet transplantation, particularly using the Edmonton or a subsequently developed islet transplant protocol.

Data Sources. MEDLINE® searched through October 2003. Primary evidence from published papers and registries, supplemented with evidence from recent meeting abstracts and presentations.

Study Selection. Selected studies were prospective trials of allogeneic islet transplant for treatment of type 1 diabetes that reported glycemic outcomes and/or adverse events at least 3 months post-procedure, and used the Edmonton or a subsequently developed islet transplant protocol.

Data Extraction. A single reviewer selected studies and abstracted data. A second reviewer fact-checked the evidence tables.

Data Synthesis. Twelve published articles reporting efficacy and adverse outcomes, and two others reporting only adverse outcomes, constituted the available primary evidence. Supplemental sources provided preliminary results of studies in progress. Outcomes of interest were summarized in tables and synthesized across studies.

Conclusions. Evidence on outcomes of islet transplant is limited by small patient numbers, short followup, and lack of standardized reporting. (These issues are being addressed by the NIH-funded Collaborative Islet Transplant Registry.) Of 37 patients from three centers, 28 (76 percent) maintained insulin independence at 1 year (published evidence); similarly, 50 to 90 percent of 104 patients from four centers were insulin independent (supplemental evidence). Serious adverse events, including portal vein thrombosis and hemorrhage, occur infrequently. Data are lacking on long-term durability of the procedure, effects on diabetic complications, or long-term consequences of immunosuppression. Evidence is insufficient for comparison with whole-organ pancreas transplant.

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Islet Transplantation in Patients with Type 1 Diabetes Mellitus
Summary

Introduction

Pancreatic islets are small clusters of endocrine cells in the pancreas that include insulin-producing beta cells. In type 1 diabetes—also known as juvenile or insulin-dependent diabetes—the body's immune system specifically destroys the beta cells, resulting in a loss of insulin production. Pancreas transplants have been used as a way to restore insulin production, but require long-term treatment to prevent immune rejection of the transplanted organ. Islet transplantation offers a potential alternative to whole-organ pancreas transplantation, but early attempts rarely succeeded. Following the introduction of the Edmonton transplant protocol in 1999, developed at the University of Alberta in Canada, major islet transplant centers have developed and refined new procedures, are enlisting patients into clinical studies and following their progress, and are reporting detailed data to a new transplant registry. This report represents the current state of the evidence in a field where clinical research is actively progressing.

Whole-organ pancreas transplants were initially performed in patients with type 1 diabetes who were undergoing kidney transplants (for kidney failure), with the pancreas transplanted either at the same time as the kidney or in a later operation. Compared with patients receiving only a cadaver kidney transplant, patients receiving a simultaneous pancreas–kidney transplant have improved long term survival—although immediately after surgery, during the early post-transplant period, survival is worse.[1–3] Transplant of a pancreas together with a kidney also has positive effects on low blood sugar/hypoglycemia,[4,5] kidney complications,[6,7] and high blood pressure/hypertension.[8]

Over the past decade, pancreas transplant alone (PTA) has been used selectively in some type 1 diabetes patients. Patients considered for this approach are those for whom the potential benefit of the procedure is expected to offset the adverse consequences of lifelong immunosuppressive therapy, which keeps their immune system from rejecting the transplanted organ. PTA is recommended only for patients with a history of frequent and severe metabolic complications, severe and incapacitating clinical and emotional problems with receiving insulin shots, or consistent failure of insulin-based management to prevent acute complications.[9] The results of the Diabetes Control and Complications Trial (DCCT) demonstrate that intensive insulin therapy significantly improves control of blood sugar (glucose) levels and reduces the risk of secondary complications, such as eye problems, nerve damage, kidney damage, and cardiovascular disease.[10] However, there is a small population of patients with unstable type 1 diabetes who, nevertheless, have difficulty maintaining glucose control with administration of insulin injections. Some of these patients develop severe hypoglycemia without the usual associated warning signs.[11] Untreated, severe hypoglycemic episodes may result in coma, seizures, and death. Such patients may require constant supervision by a family member or caretaker. Following the introduction of the Edmonton protocol, islet transplantation has largely been used in patients who are candidates for PTA; most have been selected due to their severe and frequent hypoglycemic episodes.

Transplanted islets are infused into the portal vein through a catheter and lodge in the liver. Because islet transplantation does not require a large abdominal incision, it is a less-invasive alternative to whole-organ transplantation and avoids the unhealthy side-effects of complex surgery. However, early protocols resulted in only around 10 percent of patients achieving insulin independence at 1 year after the procedure. Nevertheless, interest in this approach remained

high due to improvement in long-term diabetic consequences in studies of islet-transplanted animals and in those patients undergoing islet transplant who were able to maintain insulin independence. For example, in the pre-Edmonton era, one center reported reduced cardiovascular mortality and kidney damage in their few patients with long-term, successfully transplanted islets.[12]

Improved results for insulin independence and maintenance of normal blood glucose levels have been achieved with newer protocols that use a low-dose immunosuppressive therapy without glucocorticoid drugs, improved islet preparation, and infuse a minimum islet mass of 9,000 islet-equivalents per kilogram (IEq/kg) of body weight. The first of these protocols was the Edmonton protocol;[13] subsequent protocols have been developed at other centers (e.g., Universities of Minnesota and Miami).[14,15] As interest in establishing new islet transplant centers increases, institutional collaborations with established preparation centers will play a large role due to the startup costs for an islet preparation facility, regulatory issues, and complexity of the isolation procedure.[16] Currently, the Division of Clinical Research at the National Institutes of Health's National Center for Research Resources, supports 10 Islet Cell Resource Centers in the U.S. These centers isolate, purify, characterize, and distribute human pancreatic islets for subsequent transplantation in approved clinical protocols (for additional information see http://www.ncrr.nih.gov/clinical/cr_icr.asp)

Currently, a limitation on transplanting islets is that two or more donor organs are usually required for successful transplantation. The low availability of donor pancreas organs limits the number of pancreas or islet transplants that can be performed. For 2002, the Organ Procurement and Transplantation Network reported 6,187 total deceased organ donors, 1,870 pancreas organs recovered, and 1,461 pancreas organs transplanted.[17] A smaller, unreported number of pancreas organs are also collected and preserved (harvested) specifically for islet transplantation research.[18] In contrast, a total of 9,691 individual kidneys were harvested and transplanted from the same group of organ donors.

Islet preparations are subject to regulation by the U.S. Food and Drug Administration (FDA) as biological products and as drugs. Because the use of cells derived from whole organs meets the criteria for a biologic product to be regulated under the Public Health Service Act, the FDA classifies transplantation of allogeneic (not genetically identical to the recipient) islets as somatic cell therapy, which requires premarket approval.[19] Islets also meet the definition of a drug under the Federal Food, Drug, and Cosmetic Act. Clinical studies to determine the safety and effectiveness outcomes of allogeneic islet transplantation must be conducted under FDA's investigational new drug (IND) regulations. At least 35 IND applications have been submitted to the FDA,[19] but, as of this writing, no center has as yet submitted a biologics license application.

Outcomes of interest to the authors of this evidence report are early and long-term clinical diabetic outcomes, biologic outcomes that are indicators of graft function and glycemic (blood-sugar) control, and adverse outcomes. Early clinical outcome measures are insulin independence, percent of prior insulin use, hypoglycemic episodes, and quality of life. For patients with type I diabetes, improvement in long-term diabetic outcomes is the measure of ultimate success of islet transplantation. The objective is to reduce or eliminate long-term diabetic complications such as eye disease, nerve damage, kidney damage, and cardiovascular disease. Measurement of C-peptide and HbA1c (glycated hemoglobin) are biological outcomes that are indicators of graft function and glycemic control, respectively. Potential adverse events of islet transplant may be direct consequences of the procedure (for example, hemorrhage or thrombosis from through-the-skin access to 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 (such as mouth ulceration, diarrhea, or anemia) or long-term (including kidney disease, post-transplant cancers of the immune system, other cancers, and cytomegalovirus or other infections).

A consensus definition of successful islet transplantation was proposed at a recent meeting of the FDA Biological Response Modifiers Advisory Committee: restoration of sustained euglycemia with no or a reduced exogenous insulin requirement.[20] Clinical outcome parameters that can be used to measure success are insulin independence or percent of prior insulin use, frequency and severity of hypoglycemic episodes, and quality of life. However, in the absence of well-controlled and well-reported studies, insulin independence is the most persuasive measure available to establish the success of the procedure.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) initiated and funded the Collaborative Islet Transplant Registry (CITR) in September 2001. The CITR will develop and implement reporting standards, compile data on islet transplants in the U.S. and Canada, and perform and communicate analyses of outcomes (http://spitfire.emmes.com/study/isl/index.html). Unfortunately, the first CITR report was not yet available at the time this evidence report was prepared. In the future, the Registry will be the most comprehensive source of data on the outcomes of islet transplant. While the CITR will provide aggregated data on outcomes, published studies from individual centers still remains the best source of detailed results and of data on center-specific outcomes.

Methods

As much as possible, the protocol for this review was designed prospectively to define: study objectives; search strategy; patient populations of interest; study selection criteria; outcomes of interest; data elements to be abstracted and

methods for abstraction; and methods for study quality assessment.

The report addresses the following four key questions:

1. *What are the outcomes for selected diabetes patients treated with islet transplantation compared with similar patients who receive whole-organ pancreas transplants or medical (nontransplant) management of their disease? Are similar outcomes achievable outside of the investigational setting?*

2. *What criteria should be used to select patients for islet transplantation and what are the outcomes for relevant patient subgroups?*

3. *What are the incidence and severity of adverse effects associated with the islet transplantation procedure and with the immunosuppressive regimens? How do these compare with the adverse effects associated with whole-organ pancreas transplantation or medical management?*

4. *What is the evidence that the insulin independence or significantly reduced insulin dependence achieved with islet transplantation can be maintained long-term after the initial transplant, or with additional transplants in the event of failure of the original procedure? How often must successive transplants be performed?*

This report is limited to transplantation of unaltered human allogeneic islets harvested from donor organs. Thus, cultured islets from donor organs are included, but the following are excluded: autologous islets (from the patient's own pancreas), islets from pig pancreas, genetically altered islets, and islets prepared from stem cells.

The MEDLINE database was searched through October 2003 for recently published research articles and for relevant background information. Search was limited to articles with an English-language abstract. Bibliographies of relevant articles were also searched and the project's Technical Expert Panel was queried for additional relevant articles. Registry data, recent meeting abstracts, and presentations by investigators from key research centers were also sought.

For all of the key questions, studies were included if they:

- reported prospective trials of islet transplantation; AND
- reported on outcomes of interest with at least 3 months of followup; AND
- used a transplant protocol based on the Edmonton protocol or a subsequently developed protocol designed to improve upon aspects of the procedure; AND
- provided sufficient details on trial design, methods, and outcomes to assess study quality; AND
- were available as a full-length publication, abstract, or poster/slide presentation provided by the original presenter.

All abstracts initially retrieved by the search strategy were reviewed by one researcher who also reviewed the full-text articles to determine whether study selection criteria were met. Selected papers were abstracted by a single reviewer and

evidence tables were fact-checked by a second reviewer. After initial review of the evidence on islet transplantation, the decision was made that it was premature to compare this technique with whole-organ pancreas transplants; hence, a systematic review of the evidence on pancreas transplant outcomes was not undertaken for this report.

Results

Although more than 2,000 abstracts were reviewed, almost all indexed clinical studies were completed prior to the adoption of the Edmonton protocol. As a result, few articles were retrieved and included in this review. Of the studies relevant to the Edmonton protocol, only 12 published articles[13,14,16,21–29] reported efficacy and adverse outcomes, and two additional articles[30,31] reported only adverse outcomes.

Due to the scarcity of published articles, abstracts and presentations from five scientific conferences were reviewed, and those meeting the selection criteria were summarized as supplementary sources that provide preliminary results of studies anticipated to be fully reported in the next 2 years. Because summary data from the CITR is not yet available, a summary of results from transplant groups attending the 2002 Second Annual Annenberg Symposium, in Rancho Mirage, CA, represents the only available effort to collate islet transplant data from active centers and is also included in this report.

It was not possible to summarize and pool together the most recent outcomes from each reporting center for several reasons. First, some centers reported different outcomes on different numbers of patients in more than one publication, precluding an accurate synthesis. Second, different centers reported the same type of outcome in different ways. Thus, a standardized data collection, such as that in progress by the CITR, will be needed for an accurate and complete data summary. For these reasons, data in this report are generally presented by center. Moreover, reports on the outcomes of islet transplantation from a single center often combine results from patients treated on different protocols. Protocol characteristics are noted in the evidence tables for published reports, but this review makes no attempt to compare the outcomes of different protocols.

Published data on the clinical outcomes of islet-only transplantation are limited by small patient numbers, few transplant centers, short duration of followup, and by lack of standardized methods of reporting outcomes. Data are also lacking on quality-of-life outcomes. Meeting abstracts and presentations supplemented published reports with larger numbers of patients and reporting transplant centers. Efforts are ongoing to update and expand long-term transplant results and quality-of-life data, disseminate protocols to additional centers, and standardize reporting of outcomes. The available evidence is summarized below:

- Islet-alone transplantation has been used in a highly selected population of type 1 diabetic patients who have been selected for transplantation based on 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.

- There are sufficient data to conclude that there is a high rate of technical success for islet-alone transplantation. Five centers published reports[14,16,21,25,29] on 47 patients who completed a transplant protocol. Of these, patients 44 (94 percent) achieved insulin independence over the 3-month post-transplant period.

- Clinical outcomes from presently available data can be summarized as follows:

  - Published data from three centers[14,21,29] report that 28 of 37 patients (76 percent of those completing a transplant protocol) maintained insulin independence for 1 year. Four centers that followed 104 patients for at least 12 months report insulin independence in 50 to 90 percent of patients in recent abstracts.

  - Only one published study (from the Edmonton group)[22] reported four of six patients remained insulin independent after 2 years of followup. In one abstract from Edmonton, 48 patients underwent transplantation and 15 were followed for 2 or more years. Statistical analysis estimated that the probability of remaining insulin-independent at 2 years was 64 percent.

  - Two institutions published[14,22] detailed information on 23 transplant patients who had at least 1 year of followup. Of these, 19 (83 percent) had normal blood-sugar levels without hypoglycemic episodes (were euglycemic), and needed no or reduced amounts of additional insulin.

  - All published series report that hypoglycemic episodes were less frequent or intense in insulin-independent transplant patients. In three series[14,22,29] reporting on 26 patients who completed the transplant protocol, hypoglycemic episodes were also reduced in nine patients who exhibited continued C-peptide secretion, but who were not insulin independent at 1 year. Abstracts report this outcome less consistently but, where reported, hypoglycemic episodes were eliminated in insulin-independent patients.

  - In each published series[14,16,22,25,26,29] and for all insulin-independent patients, mean HbA1c decreased from greater than 7 percent to less than 6.5 percent; 7 percent or less is recommended to avoid or delay progression of diabetic complications. Where reported in meeting abstracts, in most cases the mean HbA1c level after transplantation was less than 6.5 percent; this level, was maintained for up to 3 years post-transplant in two series (13 patients reported on, total).

- Data are scant on the effects of islet transplantation on long-term diabetic consequences. In one publication,[22] the Edmonton group reported on 17 subjects who completed the transplant protocol. Damage to the retina progressed in three patients and required laser photocoagulation treatment. Nine patients either started or increased treatment for high blood pressure. Cholesterol rose in 15 patients, of whom 11 required statin therapy. There were no major changes in nerve damage. Serum creatinine and urine protein levels only showed significant changes in two patients with pre-existing kidney disease.

- Infrequent but serious adverse events (such as portal vein thrombosis or hemorrhage) have occurred in patients given islet transplants, but it is not possible from present data to estimate their frequency.[14,21,29] Recent changes in the transplant procedure reportedly minimize the risks of these adverse events. No procedure-related deaths have been reported among patients who received islets alone. Notably, no publication or abstracts reported cytomegalovirus infection in any patients given islet-only transplants. Post-transplant immune system cancers also have not been reported so far, but this may reflect the small number of subjects studied.

- The available evidence is insufficient to evaluate the long-term consequences of immune system suppression, any long-term effects of the islet graft, and the potential need for and consequences of supplemental islet transplants.

- The majority of transplants using the newer protocols have been of islets alone. However, it has been reported (mainly in meeting abstracts and presentations) that 30 islet transplants after or simultaneous with kidney transplants have been attempted; in most cases, followup is less than 1 year. The present evidence is insufficient to permit conclusions for this type of transplant.

Discussion

The available evidence demonstrates the technical feasibility and superior procedural success of islet transplantation using the Edmonton and more recent protocols. Where 1-year followup has been reported, most patients are insulin independent and free of severe hypoglycemic episodes. At present, 100 or more patients have been followed for 1 year after transplantation, and the Edmonton group recently reported on 15 patients followed for 2 years or more. Evidence on longer-term outcomes or durability of the procedure is not yet available. Therefore, it is not yet possible to assess the effects on diabetic complications or the consequences of lifelong immunosuppression.

Reports from the CITR are expected in the near future. These will provide systematic data on outcomes of patients treated at the major islet transplant centers, and will eventually accumulate data on long-term outcomes. The CITR plans to collect data on patient characteristics at transplantation (for post-Edmonton protocols only, and including retrospective data) as well as long-term followup data on the secondary complications of diabetes. The addition of data on the presence and severity of retinopathy, nerve damage, and other diabetic complications in the patients prior to transplantation

would aid the interpretation of long-term results. Randomized, controlled trials of islet transplantation (in direct comparison to no treatment or whole-organ transplantation) do not exist and are unlikely to be conducted. Thus, pre- and post-procedure evaluations, which are likely to be the only source of evidence to evaluate this procedure, should proceed with the utmost rigor.

As is the case with many medical or surgical procedures, outcomes may vary by center due to the transplant team's experience or specifics of the treatment. Moreover, such variation can be difficult to discover when the number of procedures is too small to reach firm statistical conclusions. Center-specific data will complement aggregate data in evaluating the outcomes of islet transplants, setting standards for performance, and improving outcomes.

Long-term followup will outline the durability of islet graft function and the need for repeat procedures. Uncertainties remain: Should patients who fail to maintain insulin independence be administered additional islet transplants? Does reactivation of autoimmune reactions against beta cells affect the success of subsequent transplants? Do the risks of the procedure increase with successive transplants?

At present, the supply of donor pancreases stringently limits the availability of islet transplants. However, refining the islet isolation and transplant procedures could promote more vigorous efforts at organ collection, and perhaps make islet transplantation more available. Simultaneous transplant of islets and kidneys is being attempted and may represent another population of patients using islet transplantation. Ongoing research on innovations in immunosuppression regimens, and in techniques to prevent rejection or induce tolerance of transplants, may eventually improve the benefit-to-risk ratio of the procedure; methods of *in vitro* production may also increase the availability of islets for transplantation. While pancreas and islet transplantation are now the only means of achieving physiologic insulin regulation, continuous glucose monitoring and **insulin** infusion technologies are being developed in hope of someday developing an artificial pancreas. As innovations in the management of type I diabetes emerge, risks and benefits, relative-effectiveness, and cost-effectiveness for various patient populations should be carefully evaluated.

Availability of the Full Report

The full evidence report used to create this summary was taken was prepared for the Agency for Healthcare Research and Quality, by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, under Contract No. 290-02-0026. It is expected to be available late in the summer of 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling (800)-358-9295. Inquiries should include a request for Evidence Report/Technology Assessment No. 98, Islet *Transplantation in Patients with Type 1 Diabetes Mellitus*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Website at www.ahrq.gov

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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

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[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-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.

Chapter 2. Methods

This report is the product of a systematic review of the evidence on the outcomes of islet transplantation for type 1 diabetes mellitus.

The protocol for this review was designed prospectively as much as possible to define: study objectives; search strategy; patient populations of interest; study selection criteria; outcomes of interest; data elements to be abstracted and methods for abstraction; and methods for study quality assessment.

This chapter of the report describes the objectives, key questions, and search strategies used to find articles; the criteria and methods for selecting eligible articles; the methods for data abstraction; the methods for quality assessment; and finally, the peer review and technical assistance received during the project.

Objective and Key Questions

The overall objective of this report is to systematically review and synthesize available evidence on the outcomes of islet transplantation in patients with type 1 diabetes who lack functioning islets. 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.

Relevant evidence for this review only includes studies that used the Edmonton protocol or subsequently developed protocols. Outcomes of islet transplants using earlier procedures than the Edmonton protocol were summarized briefly in the Introduction chapter of this review. They are considered relevant evidence only insofar as they may contribute to a causal chain that can be linked to outcomes of islet transplants using the Edmonton or subsequently developed transplant protocols.

To achieve these objectives, the report addresses the following key questions:

1. What are the outcomes of managing selected diabetes patients with islet transplantation compared with similar patients receiving whole-organ pancreas transplant or medical management? Are similar outcomes achievable outside of the investigational setting?
2. What criteria should be used to select patients for islet transplantation and what are the outcomes for relevant patient subgroups? Relevant subgroups include:

   - patients with severe or uncontrolled diabetes symptoms such as hypoglycemia unawareness despite (or due to) intensive medical management;

   - patients with prior, failed, whole-organ pancreas transplant (i.e., have already met eligibility criteria for pancreas transplant alone [PTA]);

   - patients with existing, functioning kidney transplants or who are candidates for kidney transplant and will thus be on immunosuppressive therapy;

   - special patient populations, including women, racial and ethnic minorities, pediatric and elderly populations, and those of low socioeconomic status.

3. What are the incidence and severity of adverse effects associated with the islet transplantation procedure and with the immunosuppressive regimens? How do these compare with the adverse effects associated with whole-organ pancreas transplantation or medical management?

4. What is the evidence that insulin independence or significantly reduced insulin dependence achieved with islet transplantation can be maintained long-term after the initial transplant or with additional transplants in the event of failure? How often must successive transplants be performed?

An initial review of the islet transplant literature revealed the following limitations: small patient sample sizes from a small number of islet transplant centers; relatively short followup times; and, variably reported outcomes. These limitations precluded a comparison of islet transplant outcomes with those for whole organ pancreas transplantation. Thus, a formal literature search and data abstraction on the clinical outcomes of whole-organ transplantation was not attempted and whole-organ transplantation was instead summarized in the Introduction chapter.

Search Strategy

Available registry data, recent meeting abstracts and presentations by investigators from key research centers are the primary sources of evidence for Key Questions 1–4. The MEDLINE database was searched for recently published research articles and for relevant background information. The database was searched initially from 1966 through October, 2002; subsequent search updates were performed through October, 2003. Additionally, bibliographies of relevant articles were also searched and the project's Technical Expert Panel was queried for any relevant articles omitted from the search results. During the peer review process, reviewers informed the Evidence-based Practice Center (EPC) staff of articles recently published or accepted for publication and in the case of certain imminent publications, provided prepublication manuscripts.

The search strategy selected for review all citations that included any of the following terms:

"Islets of Langerhans Transplantation"[Medical Subject Heading® (MeSH®)];
"Islets of Langerhans"[MeSH®] AND "transplantation"[MeSH®];
islet*[tw] AND transplant*[tw]; or
beta cell*[tw] AND transplant*[tw].

The search was limited to studies on human subjects with English-language abstracts. Papers published in foreign languages were reviewed if the English abstract appeared to meet inclusion criteria. No studies relevant to the evidence review were published in a language other than English.

Study Selection Criteria

For all key questions in this report, studies were included if they:

1. reported prospective series of islet transplantation; AND

2. reported on outcomes of interest with at least 3 months of followup (1 year preferred); AND

3. used a transplant protocol based on the Edmonton protocol or a subsequently developed protocol; AND

4. provided sufficient details on study design, methods, and outcomes to assess study quality (see below); AND

5. were available as a full-length publication, abstract, or poster/slide presentation provided by the original presenter.

Patients

Patients of interest for this review were those with long-standing type 1 diabetes mellitus based on a stimulated serum C-peptide concentration of less than 0.48 ng per milliliter; whose glucose concentration remained uncontrolled despite exogenous insulin therapy; who had episodes of severe hypoglycemia requiring assistance or labile diabetes with evidence of daily lifestyle disruption; and had no comorbidities precluding transplantation or immunosuppression therapy. In general, eligible patients were judged by the treating centers to be at greater risk from uncontrolled diabetes than they would be from the global risk of transplantation and immunosuppression.

Outcomes of Interest

The outcomes of interest are grouped into near-term and long-term efficacy outcomes and adverse events. Near-term efficacy outcomes include clinical outcomes:
- proportion of patients remaining insulin independent at yearly intervals after transplantation;
- percentage of baseline insulin use at yearly intervals after transplantation; and
- severe episodes of hypoglycemia.

Biological outcomes include:
- C-peptide levels;
- hemoglobin A1c.

Long-term efficacy outcomes include effects on complications of diabetes, such as:
- nephropathy;
- retinopathy;
- atherosclerosis, etc.

Adverse outcomes include those related to the islet infusion procedure, such as:
- mortality;
- bleeding;
- thrombosis;
- pain;

and those related to the immunosuppressive regimen:
- mortality;
- nephrotoxicity;
- hypertension;
- hypercholesterolemia;
- thrombocytopenia;
- leukopenia;
- infection;
- post-transplant lymphoproliferative disease.

Additional adverse outcomes of interest are:
- possible long-term effects of islets; and
- need for additional transplants.

Methods of the Review

Article Selection

All abstracts initially retrieved by the search strategy were reviewed by one researcher who also reviewed the fulltext articles to determine whether study selection criteria were met (MP). Selected papers were abstracted by a single reviewer (MP or JS) and evidence tables were fact-checked by a second reviewer (MP or JS).

Although a total of 2,052 abstracts were initially reviewed, very few articles were retrieved as almost all indexed clinical studies were completed prior to the adoption of the Edmonton protocol. Of the studies relevant to the Edmonton protocol, the vast majority were reviews, animal studies, or technical reports. Including articles published and retrieved during the preparation of this review, only 12 published studies (Owen, Ryan, O'Kelly, et al., 2003; Ryan, Lakey, Paty, et al., 2002; Paty, Ryan, Shapiro, et al., 2002; Johnson, Kotovych, Ryan, et al., [In press]; Markmann, Deng, Huang, et al., 2003; Goss, Schock, Brunicardi, et al., 2002; Kaufman, Baker, Chen, et al., 2002; Shapiro, Lakey, Ryan, et al., 2000; Ryan, Lakey, Rajotte, et al., 2001; Markmann, Deng, Desai, et al., 2003; Hering, Kandaswamy, Harmon, et al., 2004 [In press]; Hirshberg, Rother, Digon, et al., 2003) reported efficacy and adverse outcomes, and 2 additional (Casey, Lakey, Ryan, et al., 2002; Goss, Soltes, Goodpastor, et al., 2003) reported only adverse outcomes.

Additional sources of evidence. Due to the scarcity of published articles, additional sources of evidence were sought. Abstracts and presentations from scientific conferences were reviewed, and those meeting study selection criteria are summarized in this review as supplementary

sources that provide preliminary results of studies anticipated to be fully reported in the next 2 years. The scientific conferences reviewed were:

- XIX International Congress of the Transplantation Society; 2002 August 25-30; Miami, FL (abstracts searched)

- City of Hope Rachmiel Levine Symposium; 2002 October 9-12; Anaheim, CA (attended)

- Islet Transplantation 2002 and Beyond: 2nd Annual Annenberg Symposium; 2002 December 5-7; Rancho Mirage, CA (attended)

- American Transplant Congress 2003: The Fourth Joint American Transplant Meeting, May 30, 2003 - June 4, 2003, Washington, DC (abstracts searched)

- 9th Congress of the International Pancreas and Islet Transplant Association. 8-11 July 2003, Dublin, Ireland (abstracts searched)

- 1st Islet Transplant Congress; 2003 November 13-16; Miami Beach, FL (attended)

In the future, the most comprehensive source of data will be the Collaborative Islet Transplant Registry (CITR), which is initiated and funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The registry is coordinated by the EMMES Corporation of Rockville, Maryland; Dr. Bernhard Hering of the University of Minnesota is the Medical Director.

CITR was initiated in September 2001. CITR is collecting extensive, retrospective data on all patients who have received islet transplants using Edmonton or subsequently developed transplant protocols, and will maintain an ongoing data collection process for new patients. The data elements are more comprehensive than those collected by the previous International Islet Transplant Registry, and require original data entry (i.e., data from the International Islet Transplant Registry has not been downloaded into the CITR database).

As of November 2003, CITR was still collecting data from the participating institutions. Thus, data and analyses from CITR were not available for this evidence report.

Technical Expert Panel and Peer Review

The development of this evidence report was subject to extensive expert review including ongoing guidance from a Technical Expert Panel (TEP) and document review by the TEP and by a panel of designated peer reviewers (Appendix B lists the members of the Technical Expert Panel and external peer reviewers).

TEP members provided ongoing guidance and review on all phases of this project including review of the draft report.

The draft report was also reviewed by a panel of external peer reviewers that included experts in endocrinology, pancreas transplantation, and islet transplantation, as well as a patient advocacy representative. Reviews were also solicited from the Immune Tolerance Network (ITN; currently overseeing multicenter studies of the Edmonton protocol), the Juvenile Diabetes

Research Foundation (currently funding, along with the National Institutes of Health, ITN studies of the Edmonton protocol), and the American Diabetes Association. Comments were elicited from external peer reviewers using a structured comment form, compiled, and submitted with a description of comment disposition to the Agency for Healthcare Research and Quality.

Chapter 3. Results

Published Journal Articles

Overview

Clinical and biological outcomes of islet transplantation from peer-reviewed, published studies constitute the main evidence for this systematic review. Only studies of protocols incorporating new preparation methods, sufficient islet mass, and glucocorticoid-sparing, reduced-dose immunosuppressive regimens were considered. The first of these protocols was developed at the University of Alberta at Edmonton and has since been called the Edmonton protocol. Subsequent protocols have varied different aspects of islet preparation, transplant procedure and/or immunosuppressive regimen seeking to improve outcomes. Reports on the outcomes of islet transplantation often combine results from patients treated using different protocols. This review makes no attempt to compare the outcomes of different protocols; however, the reader should note where indicated, that different protocols are being used.

Evidence Tables 1 and 2 summarize six patient series, reporting on 64 patients[2] in the 10 most recent publications from these series (Ryan, Lakey, Paty, et al., 2002; Owen, Ryan, O'Kelly, et al., 2003; Paty, Ryan, Shapiro, et al., 2002; Johnson, Kotovych, Ryan, et al., [In press]; Hering, Kandaswamy, Harmon, et al., 2004 [In press]; Goss, Schock, Brunicardi, et al., 2002; Goss, Soltes, Goodpastor, et al., 2003; Markmann, Deng, Huang, et al., 2003; Hirshberg, Rother, Digon, et al., 2003; Kaufman, Baker, Chen, et al., 2002) Older publications superceded by later updates of similar information are not summarized, but the corresponding citations are indicated in footnotes (Shapiro, Lakey, Ryan, et al., 2000; Ryan, Lakey, Rajotte, et al., 2001). Later publications detailing information already summarized in earlier publications are also indicated in footnotes (Casey, Lakey, Ryan, et al., 2002; Markmann, Deng, Desai, et al., 2003).

Although an attempt was made to summarize the most recent outcomes for each reporting center and pool results for an overall summary, this was not possible. First, some centers reported different outcomes on different numbers of patients in more than one publication, precluding an accurate synthesis. Second, different centers reported the same type of outcome in different ways. For example, HbA_{1c} was reported for either all patients, or for only those who remained insulin independent. Thus, a standardized data collection, such as that in progress by the Collaborative Islet Transplant Registry (CITR), will be needed for an accurate and complete data summary. For these reasons, data are generally presented here by center.

No attempt was made to compare islet transplant outcomes with those for whole-organ pancreas transplantation. Initial review of the islet transplant literature revealed the following limitations: small patient sample sizes from a small number of islet transplant centers; relatively short followup times; and, as noted, variably reported outcomes. In particular, success in islet transplantation is dependent on the use of protocols that have been only recently introduced, and for which there are minimal data beyond 1–2 years of follow-up. In contrast, outcomes of whole-organ pancreas transplantation are available for 5 to 8 years' post-transplant.

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[2] The maximum number of patients was counted from each center for which diabetic clinical outcomes were reported. In the case of the University of Alberta, 34 rather than 35 patients were counted.

Evidence Table 1. Clinical islet transplantation: Patient and transplant characteristics reported in journal articles. All transplants are islet alone unless otherwise indicated.

Transplant Center; Citation(s)	N	N completed protocol	Follow-up (mos.)	Patient description	Donor organs/pt	Infusions/pt	IEq/kg, average of all infusions/pt
University of Alberta	*Protocol: Edmonton immunosuppression[a]; Ricordi chamber islet isolation; +/- 2-layer perfluorocarbon organ storage; +/- islet culture*						
Owen, Ryan, O'Kelly, et al., 2003	34	26		Labile type 1 diabetes, hypoglycemia unawareness resulting in frequent or severe hypoglycemic reactions, or progressive complications (few)			~13,000 required for insulin independence
Ryan, Lakey, Paty, et al., 2002[b]	30	17	≤34	As above	1.8	1.8	
	17		Median 20	As above; 17 who completed transplant protocol, of 30	2.4	2.2	12,330
Paty, Ryan, Shapiro, et al., 2002	7			Subset of patients tested for hypoglycemic counterregulation and symptom recognition			
Johnson, Kotovych, Ryan, et al. (In press)	35			As for Owen, Ryan, O'Kelly, et al., 2003			

[a]Edmonton immunosuppression: Daclizumab; sirolimus; reduced-dose tacrolimus
[b]Includes patients reported by Shapiro, Lakey, Ryan, et al., 2000, and Ryan, Lakey, Rajotte, et al., 2001. Also includes information reported by Casey, Lakey, Ryan, et al., 2002.

Evidence Table 1. Clinical islet transplantation: Patient and transplant characteristics reported in journal articles. All transplants are islet alone unless otherwise indicated. (continued)

Transplant Center; Citation(s)	N	N completed protocol	Follow-up (mos.)	Patient description	Donor organs/pt	Infusions/pt	IEq/kg, average of all infusions/pt
University of Minnesota	*Protocol: Immunosuppression with hOKT3gamma1 (Ala-Ala)/sirolimus/reduced-dose tacrolimus; 2-layer perfluorocarbon organ storage; Ricordi chamber islet isolation; islet culture; single-donor transplantation*						
Hering, Kandaswamy, Harmon, et al., 2004 (In press)	6	6	12	Type 1 diabetes ≥13 years; 5-100 severe episodes per year pretransplant of hypoglycemia unawareness associated with blood glucose <50 mg/dL and requiring the assistance of another person	1	1	10,302
University of Pennsylvania	*Protocol: Edmonton immunosuppression; Ricordi chamber islet isolation; islet culture*						
Markmann, Deng, Huang 2003[c]	9	7	≤13	Type 1 diabetes ≥5 years; multiple episodes of dangerously severe hypoglycemic unawareness requiring hospitalization despite optimal medical management; C-peptide <0.5 ng/mL	1.7	1.4 (4 of 7 patients, 1 infusion)	8,204 (9,282 for successful single infusions)

[c]Includes results from 1 patient transplanted with islets isolated from a non-heart-beating donor pancreas, as reported by Markmann, Deng, Desai, et al., 2003.

Evidence Table 1. Clinical islet transplantation: Patient and transplant characteristics reported in journal articles. All transplants are islet alone unless otherwise indicated. (continued)

Transplant Center; Citation(s)	N	N completed protocol	Follow-up (mos.)	Patient description	Donor organs/pt	Infusions/pt	IEq/kg, average of all infusions/pt
Baylor College of Medicine and University of Miami	*Protocol: Edmonton immunosuppression; Ricordi chamber islet isolation*						
Goss, Schock, Brunicardi, et al., 2002	3	2	≤ 4	Severe recurrent hypoglycemia, coma, or metabolic instability and uncontrolled serum glucose despite maximal exogenous insulin therapy for at least 5 years	1.7	1.7	14,439
Goss, Soltes, Goodpastor, et al., 2003	8	7		As above		2.1	
NIH/NIDDK	*Protocol: Edmonton immunosuppression; Ricordi chamber islet isolation*						
Hirshberg, Rother, Digon, et al., 2003	6	5	17-22	Type 1 diabetes of 13-50 years; severe, recurrent hypoglycemia events secondary to unawareness and requiring the assistance of others	1.7	1.7	$\geq 10,000$
Northwestern University	*Protocol: Edmonton immunosuppression*						
Kaufman, Baker, Chen, et al., 2002	1	1	4	Type 1 diabetes of 40 years with severe recurrent hypoglycemia resulting in multiple visits to the ER or resuscitation by others; successful kidney allograft		1	4,100

Evidence Table 2. Clinical islet transplantation: Outcomes reported in journal articles. All transplants are islet alone unless otherwise indicated.

Transplant Center; Citation(s)	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	Change in Mean HbA1c (SD)		Hypoglycemic reactions	Comment	Complications
					Baseline, %	Current, %			
University of Alberta	**Protocol: Edmonton immunosuppression; Ricordi chamber islet isolation; +/- 2-layer perfluorocarbon organ storage; +/- islet culture**								
Owen, Ryan, O'Kelly, et al., 2003	34	26		**26/__** **21 at 1 year** post-initial transplant					Serious in 6 of 68 (9%) procedures 2-portal vein thrombosis (hepatic hematoma requiring surgery in 1) 4-hemorrhage (3 transfused)
Ryan, Lakey, Paty, et al., 2002[a]	30	17	≤34	17/11	8.5 (0.49) patients who remained insulin independent	5.8 (0.13) insulin-independent patients	None in patients with C-peptide secretion		Acute: 2-transient bradycardia 5-hemorrhage 2-portal vein thrombosis No deaths, CMV, or PTLD
	17		Median 20	17/11 (**12 of 15 at 1 year** post-initial transplant; **4 of 6 at 2 years**)	8.2 (0.36) all 17 patients	6.08 (0.77) all 17 patients	None in patients with C-peptide secretion	6 pts required insulin at median 10.1 months: 3 are C-peptide-positive and on daily insulin dose 57% of pretransplant dose; 3 are C-peptide negative; urine protein unchanged in 15	From immunosuppression: 15-mouth ulcers 2-recurrent nausea/vomiting requiring rehydration 1-arthralgias 1-rheumatoid arthritis 10-diarrhea 8-anemia From diabetes: 3-retinopathy progression 2-increased serum creatinine 4-increased urine protein 10-increased BP 15-increased cholesterol

Note: Bolded outcomes are of key importance.
[a]Includes patients reported by Shapiro, Lakey, Ryan, et al., 2000, and Ryan, Lakey, Rajotte, et al., 2001. Also includes information reported by Casey, Lakey, Ryan, et al., 2002.

Evidence Table 2. Clinical islet transplantation: Outcomes reported in journal articles. All transplants are islet alone unless otherwise indicated (continued)

Transplant Center; Citation(s)	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	Change in Mean HbA1c (SD)		Hypoglycemic reactions	Comment	Complications
					Baseline, %	Current, %			
University of Alberta (continued)	*Protocol: Edmonton immunosuppression; Ricordi chamber islet isolation; +/- 2-layer perfluorocarbon organ storage; +/- islet culture*								
Paty, Ryan, Shapiro, et al., 2002	7						No improvement in hypoglycemic symptom recognition	Subset of patients tested for hypoglycemic counterregulation and symptom recognition	(not reported)
Johnson, Kotovych, Ryan, et al. (In press)	35							Fear of hypoglycemia significantly lower in transplant patients compared to transplant-eligible patients (n=46)	
University of Minnesota	*Protocol: Immunosuppression with hOKT3g1 (Ala-Ala)/sirolimus/reduced-dose tacrolimus; 2-layer perfluorocarbon organ storage; Ricordi chamber islet isolation; islet culture; single-donor transplantation*								
Hering, Kandaswamy, Harmon, et al., 2004 (In press)	6	6	12	**4/4 at 1 year post-transplant**	7.2 (1.0) patients who became insulin independent	5.4 (0.6) insulin-independent patients	None (all patients)	1 patient requires 60% of pretransplant insulin; 1 patient early transient reduction in insulin requirement	1 serious: nystatin-related generalized rash; Transient increased liver enzymes, 1 severe, 3 mild to moderate; Transient neutropenia, 3; OKT3-related: low-grade fever, chills, nausea, transient rash. Other, mild to moderate: mouth ulcers, weight loss. No PTLD or increased infections

Note: Bolded outcomes are of key importance.

Evidence Table 2. Clinical islet transplantation: Outcomes reported in journal articles. All transplants are islet alone unless otherwise indicated. (continued)

Transplant Center; Citation(s)	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	Change in Mean HbA1c (SD)		Hypoglycemic reactions	Comment	Complications
					Baseline, %	Current, %			
University of Pennsylvania	*Protocol: Edmonton immunosuppression; Ricordi chamber islet isolation; islet culture*								
Markmann, Deng, Huang, et al. 2003[b]	9	7	≤13	7/6 1 patient lost function at 8 mos.	7.6 patients who became insulin independent	6.3 insulin-independent patients at 6 mos.	None in insulin-independent patients	At 8 mos. 1 patient requires 50% of original insulin dose; C-peptide 0.5-1.0 ng/mL	None serious
Baylor College of Medicine and University of Miami	*Protocol: Edmonton immunosuppression; Ricordi chamber islet isolation*								
Goss, Schock, Brunicardi, et al., 2002	3	3	≤4	3/3	9.0 (0.2)	5.8 (mean of 2 patients)	None (all patients)	Islets prepared at distant processing center (U. Miami) and transplanted at Baylor	No complications observed
Goss, Soltes, Goodpastor, et al., 2003	8	7							No sustained portal vein hypertension; no transfusions; no intraparenchymal or intra-abdominal hemorrhage; 71%-moderate abdominal pain 59%-nausea

Note: Bolded outcomes are of key importance.
[b]Includes results from 1 patient transplanted with islets isolated from a non-heart-beating donor pancreas, as reported by Markmann, Deng, Desai, et al., 2003.

Evidence Table 2. Clinical islet transplantation: Outcomes reported in journal articles. All transplants are islet alone unless otherwise indicated. (continued)

Transplant Center; Citation(s)	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	Change in Mean HbA1c (SD)		Hypoglycemic reactions	Comment	Complications
					Baseline, %	Current, %			
NIH/NIDDK	*Protocol: Edmonton immunosuppression; Ricordi chamber islet isolation*								
Hirshberg, Rother, Digon, et al., 2003	6	5	17-22	4/2 **3 of 5 at 1 year after second transplant**	8.2 (1.2)	6.0 (0.6) at 1 year	None (all patients)	2 patients who stopped immunosuppression due to adverse events have residual C-peptide production; 3rd patient discontinued when all islet function lost	*Transplantation-related:* 1-portal vein thrombosis, precluded 2nd transplant; 1-intra-abdominal bleeding requiring 4 units *Immunosuppression-related:* All-oral ulcers, diarrhea, leg edema, fatigue, declining over time; 2-transient severe neutropenia treated with G-CSF; 0-CMV 1-Pitisporidium skin infection; 1-recurrent UTI 1-interstitial pneumonitis requiring discontinuation of immunosuppression 1-intolerable fatigue, and renal dysfunction, patient elected to discontinue immunosuppression
Northwestern University	*Protocol: Edmonton immunosuppression*								
Kaufman, Baker, Chen, et al., 2002	1	1	4	1/1	6.9	5.3	No clinically relevant hypoglycemia episodes	Renal allograft function unchanged	(not reported)

Note: Bolded outcomes are of key importance.

Because islet transplant studies report pre- versus post-transplantation outcomes, the implicit comparison in these studies is to pretransplantation medical management. This is based on the assumption that, without intervention, patients would continue medical management and would require exogenous insulin, maintain higher HbA_{1c}, and experience hypoglycemic episodes at constant doses, levels, and numbers, respectively.

Patients

Sixty-four patients in all series combined had type 1 diabetes of 5 or more years' duration, stimulated serum C-peptide less than 0.5 ng/mL (0.16 nmol/L), and severe metabolic instability or recurrent hypoglycemia unawareness despite optimal medical management. Although a few patients with progressive complications of diabetes were initially enrolled in the University of Alberta series (Ryan, Lakey, Paty, et al., 2002), this indication was discontinued. Study patients meeting eligibility criteria may also have had retinopathy or neuropathy, but except for the patient reported by Kaufman, Baker, Chen, and co-workers (2002), patients neither had received nor needed a renal transplant.

Study protocols either called for 2 islet transplant procedures (generally the equivalent of islets prepared from two whole organs) or a second transplant within a few months if the first did not achieve insulin independence. Of the 64 enrolled patients, 52 had completed the islet transplant protocol at the time of the report; the rest were awaiting an additional transplant or, in the cases of two patients, had withdrawn from the protocol (Markmann, Deng, Huang, et al., 2003; Hirshberg, Rother, Digon, et al., 2003). In some cases, patients who had completed the protocol were given a supplemental islet transplant to achieve or maintain insulin independence. Patients were followed for up to 3 years in the University of Alberta, Edmonton series (Owen, Ryan, O'Kelly, et al., 2003; Ryan, Lakey, Paty, et al., 2002; Paty, Ryan, Shapiro, et al., 2002; Johnson, Kotovych, Ryan, et al., [In press]), up to 22 months at the National Institutes of Health (Hirshberg, Rother, Digon, et al., 2003), up to 1 year at the University of Minnesota (Hering, Kandaswamy, Harmon, et al., 2004 [In press]) and the University of Pennsylvania (Markmann, Deng, Huang, et al., 2003), and for no more than 4 months at Baylor (Goss, Schock, Brunicardi, et al., 2002; Goss, Soltes, Goodpastor, et al., 2003), and Northwestern University (Kaufman, Baker, Chen, et al., 2002).

Clinical Outcomes

Five centers published diabetic clinical outcomes on 47 patients[3] who completed an islet-alone transplant protocol (Owen, Ryan, O'Kelly, et al., 2003; Hering, Kandaswamy, Harmon, et al., 2004 [In press]; Markmann, Deng, Huang, et al., 2003; Goss, Schock, Brunicardi, et al., 2002; Hirshberg, Rother, Digon, et al., 2003). Of these, 44 patients (94 percent) achieved insulin independence over the 3-month, post-transplant period.

In the largest series, Owen, Ryan, O'Kelly, and co-workers (2003) reported all 26 patients who completed the Edmonton transplant protocol were initially insulin independent, and that 21 patients remained independent 1 year after their first transplant. In an earlier report on the same series, Ryan, Lakey, Paty, and co-workers (2002) reported 11 of 17 fully transplanted patients were insulin independent at a median of 20 months' followup. Because only 5,000 islet

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[3] This total excludes four patients for whom only adverse events were reported in Goss, Soltes, Goodpastor, and co-workers (2003) and excludes the islet after kidney transplant reported by Kaufman, Baker, Chen, and co-workers (2002).

equivalents per kilogram (IEq/kg) on average were isolated from a single donor organ, and approximately 13,000 IEq/kg were required for insulin independence, a third, supplemental transplantation was required in seven cases (Owen, Ryan, O'Kelly, et al., 2003). During the course of this patient series, the original Edmonton protocol was modified with techniques such as islet culture and 2-layer perfluorocarbon organ storage to improve islet viability.

Hering, Kandaswamy, Harmon, and colleagues (2004 [In press]) reported on six patients, each transplanted with cultured islets prepared from a single donor after 2-layer perfluorocarbon organ storage. All patients received immunosuppression with humanized OKT3 anti-T cell monoclonal antibody (Ala-Ala), sirolimus, and reduced-dose tacrolimus. Four of six patients initially achieved insulin independence and remained independent at 12 months, while one patient required 60% of the pretransplant insulin requirement. The last patient was lost to followup.

Of seven patients receiving cultured islets and Edmonton immunosuppression (daclizumab; sirolimus; reduced-dose tacrolimus), Markmann, Deng, Huang, and co-workers (2003) reported that all patients were initially insulin independent. Five achieved independence after only one islet infusion, although in two of these cases the single infusion delivered pooled islets from two donor organs. In this series, six of seven patients followed for 13 months or less remained insulin independent, including one who received a supplemental transplant at 13 months.

Goss, Schock, Brunicardi, and co-workers (2002) reported on three patients, who remained insulin independent after 4 months or less followup. Hirshberg, Rother, Digon, and co-workers (2003) transplanted six patients, of whom, four initially achieved and two remained insulin independent at 17 to 22 months post-transplant. Kaufman, Baker, Chen, and co-workers (2002), reported on the only published transplant that was not islet alone. They transplanted islets into a patient with a functional renal allograft and achieved insulin independence after only one infusion of 4,100 IEq/kg. However, followup was only 4 months.

Three centers reported that 28 of 37 patients (76 percent of those completing a transplant protocol) maintained insulin independence for 1 year (Owen, Ryan, O'Kelly, et al., 2003; Hering, Kandaswamy, Harmon, et al., 2004 [In press]; Hirshberg, Rother, Digon, et al., 2003). Only one published study (from the Edmonton group) reported on patients with 2 years of followup: four of six patients remained insulin independent (Ryan, Lakey, Paty, et al., 2002). Patients who did not achieve or who lost insulin independence tended to use far less insulin than before transplantation. Ryan, Lakey, Paty, and co-workers (2002) reported daily insulin doses were 57 percent of pretransplant doses for six patients who resumed insulin use at a median of 10 months; three of these patients continued to produce C-peptide. Markmann, Deng, Desai, and co-workers (2003) described one patient who lost insulin independence but continued to produce detectable C-peptide and required only 50 percent of the pretransplant insulin dose.

All series reported abatement of hypoglycemic episodes in insulin-independent transplant patients. In three series reporting on 26 patients completing the transplant protocol, hypoglycemic episodes were also abated in nine patients with continuing C-peptide secretion who required some exogenous insulin at 1 year (Ryan, Lakey, Paty, et al., 2002; Hering, Kandaswamy, Harmon, et al., 2004 [In press]; Hirshberg, Rother, Digon, et al., 2003). All series described severe, recurrent hypoglycemic episodes (usually requiring the assistance of others and despite intensive medical management; see Evidence Table 1) as the most common indication for islet transplantation. However, only one report quantified the number of such episodes in the year pre- (5–100 episodes in each of six patients) and post-transplant (0 episodes, all patients; Hering, Kandaswamy, Harmon, et al., 2004 [In press]).

Although not mentioned in published reports, the Edmonton group has provided greater detail on patient indications for their center in subsequent meeting presentations: reduced hypoglycemia awareness as defined by the absence of adequate autonomic symptoms at plasma glucose levels less than 54 mg/dL; metabolic lability/instability characterized by two or more episodes of severe hypoglycemia associated with blood glucose less than 54 mg/dL and requiring assistance of another person within 12 months; or two or more hospital visits for diabetic ketoacidosis over the previous 12 months (Shapiro, 2003). Standard, quantifiable eligibility criteria for islet transplant alone are being developed and evaluated (Ryan, Shandro, Vantyghem, et al., 2003).

While insulin independence is the gold standard for clinical outcomes, analogous to a functioning whole pancreas transplant, the consensus recommendation of the U.S. Food and Drug Administration (FDA) Biological Response Modifiers Advisory Committee was that restoration of sustained euglycemia (i.e., absence of hyper- and hypoglycemia) with no or a reduced exogenous insulin requirement should be the primary definition of success for islet transplantation (U.S. Food and Drug Administration, 2003). Clear information on this outcome was available from two publications with at least 1 year of followup (Ryan, Lakey, Paty, et al., 2002; Hering, Kandaswamy, Harmon, et al., 2004 [In press]). Of 23 patients completing a transplant protocol, 19 (83 percent) were euglycemic.

Biological Outcomes

In each series and for all insulin-independent patients, mean HbA_{1c} decreased to levels recommended to avoid or delay progression of diabetic complications (i.e., <7 percent at a minimum, American Diabetes Association, 2003; recommended <6.5 percent, U.S. Food and Drug Administration, 2003); mean pretransplant baseline levels were all greater than 7 percent except for one case report (6.9 percent; Kaufman, Baker, Chen, et al., 2002). Patients with measurable graft function, but requiring some exogenous insulin, were seldom reported separately. However, in one study, two patients who did not achieve complete insulin independence but produced measurable C-peptide for several months were able to achieve HbA_{1c} levels near 7 percent or less on reduced doses of exogenous insulin (Hirshberg, Rother, Digon, et al., 2003). In another study, HbA_{1c} remained elevated in one patient despite measurable C-peptide and reduced insulin requirements (Hering, Kandaswamy, Harmon, et al., 2004 [In press]).

In the largest series, post-transplant fasting and stimulated C-peptide levels increased to near those of nondiabetic controls, but post-transplant stimulated glucose levels remained higher than controls, although lower than pretransplant (Ryan, Lakey, Paty, et al., 2002; data not shown). Although an attempt was made to abstract metabolic outcomes data across centers, results were not reported consistently for one or a few specific tests to allow comparison (Evidence Table 3). Metabolic outcomes await standardization and routine data collection.

Interestingly, Paty, Ryan, Shapiro, and co-workers (2002), reporting on a subset of seven patients with prolonged insulin independence and absence of hypoglycemic symptoms from the University of Alberta series, found that glucagon responses to hypoglycemia were similar to those of nontransplanted type 1 diabetic patients and that epinephrine response and hypoglycemic symptom recognition were not restored. The glucagon results are similar to those reported for pre-Edmonton islet transplants (Meyer, Hering, Grossmann, et al., 1998), although in this study, glycemic thresholds and/or peak incremental responses of epinephrine,

norepinephrine, and cortisol, as well as symptom recognition, improved in islet transplanted patients. In contrast, glucagon responses to hypoglycemia and symptom recognition reportedly were fully restored and maintained long-term in whole pancreas transplant patients (Kendall, Rooney, Smets, et al., 1997; Paty, Lanz, Kendall, et al., 2001).

Evidence Table 3. Types of metabolic testing reported by transplant centers.

	Hirshberg, Rother, Digon, et al., 2003	Kaufman, Baker, Chen, et al., 2002	Goss, Schock, Brunicardi, et al., 2002	Markmann, Deng, Huang, et al. 2003	Hering, Kandaswamy, Harmon, et al., 2004 (in press)	Ryan, Lakey, Paty, et al., 2002
N	6	1	1–3	7	4–5	17
IV arginine-stimulated C-peptide	X				X	X
Oral glucose stimulated C-peptide		X				
Oral glucose stimulated plasma glucose					x	X descriptive
Mean amplitude of glycemic excursions, pre- vs. post-treatment			X			X
Mixed meal stimulation, glucose levels			X 1 of 3 patients, descriptive	X descriptive		X
Mixed meal stimulation, C-peptide levels				X descriptive		X
IVGTT: • Acute insulin response to glucose						X
• Glucose disposal						X descriptive
• AUC for insulin						X
• AUC for C-peptide						X descriptive
• Homeostasis model assessment of insulin sensitivity						X descriptive

Quality of Life

No general measures of pre- versus post-islet transplant quality of life have been published; only one publication reports limited data on specific measures. Johnson, Kotovych, Ryan, and co-workers (In press) summarized results of patients in the University of Alberta series who completed the Hypoglycemia Fear Survey (HFS) and other quality of life indices at baseline (pretransplant), between the first and second islet infusions, at 1, 3, 6, and 12 months, and annually thereafter. Forty-six patients completed baseline surveys and 35 transplanted patients completed additional surveys. Results of the last survey for each transplant patient were compared to baseline results. Transplant patients had slightly lower fear of hypoglycemia by HFS at 1 month than pretransplant patients (Evidence Table 4) but a much larger reduction by

month 3. Overall, HFS in pretransplant patients was significantly higher than for post-transplant patients at a median followup of 11.9 months ($p < 0.0001$).

The authors note that these data are limited by the small sample size and their cross-sectional nature. They represent the beginning of longitudinal data collection on a growing population of patients. As presented at the Annenberg Second Annual Symposium (Johnson, 2002), Johnson and colleagues are collecting data from both general and disease-specific quality of life instruments for eventual analysis of quality of life trends over time.

Evidence Table 4. Results of Hypoglycemia Fear Survey post-islet transplant compared to baseline.

	Pretransplant	**1 month**	**3 months**	**Median 11.9 months**
Median Hypoglycemia Fear Survey score	47	30	6.5	5

Long-Term Diabetic Complications

Only Ryan, Lakey, Paty, and colleagues (2002) reported on long-term diabetic complications. Of 17 subjects who had completed the transplant protocol at the time of this publication and were followed for 3 years or less, three patients had progression of their retinopathy requiring laser photocoagulation. Nine patients either started or increased antihypertensive therapy. Cholesterol rose in 15 patients and in 11 required statin therapy. There were no major changes in neuropathy. Serum creatinine and urine protein did not change significantly except for two patients with pre-existing renal impairment who suffered serious deterioration in renal function; both patients' renal dysfunction was stabilized by withdrawing potentially nephrotoxic tacrolimus.

Adverse Events

Portal vein hypertension, thrombosis and hemorrhage. One center reported branched portal vein thrombosis (main portal veins remained patent in all patients) in two of 34 transplanted patients (Ryan, Lakey, Paty, et al., 2002; Casey, Lakey, Ryan, et al., 2002; Owen, Ryan, O'Kelly, et al., 2003). One of these patients also developed a hepatic hematoma requiring surgery, but without other long-term consequences. Four additional patients transplanted early in this series experienced hemorrhage from percutaneous portal vein access (Ryan, Lakey, Paty, et al., 2002). Of six patients described in the initial experience at the U. S. National Institutes of Health (NIH) between December, 2000 and June, 2001, symptomatic portal vein thrombosis occurred in one and intra-abdominal hemorrhage requiring transfusion occurred in another (Hirshberg, Rother, Digon, et al., 2003). Various measures have been adopted to minimize risks of these complications (Goss, Soltes, Goodpastor, et al., 2003; Owen, Ryan, O'Kelly, et al., 2003; Baidal, Froud, Ferreira, et al., 2003; Froud, Yrizarry, Alejandro, et al., [In press]). Four other groups did not encounter portal vein thrombosis or hemorrhage among 24 transplanted patients (Evidence Table 2; Hering, Kandaswamy, Harmon, et al., 2004 [In press]; Markmann, Deng, Huang, et al., 2003; Goss, Soltes, Goodpastor, et al., 2003; Kaufman, Baker, Chen, et al., 2002).

Nearly all of 26 patients evaluated for pressure changes during the procedure experienced transient moderate increases of portal venous pressure that correlated with the volume and number of islets transfused (Casey, Lakey, Ryan, et al., 2002). However, only one of the two

patients with thrombosis had a detectable post-infusion change in main portal venous pressure. Investigators attributed the hepatic hematoma in a third patient to a higher dose of anticoagulant therapy used to moderate increases in portal venous pressure. No patients showed evidence of sustained portal vein hypertension over 17 months of followup.

Other acute procedural complications. The Edmonton group reported transient acute bradycardia in two of 30 transplanted patients (Ryan, Lakey, Paty, et al., 2002). A second group reported moderate abdominal pain in 71 percent and nausea in 59 percent of eight transplanted patients (Goss, Soltes, Goodpastor, et al., 2003). Of six patients transplanted at the University of Minnesota, one experienced a severe rash attributed to antifungal therapy and one had a transient but severe elevation of liver transaminase activity in the serum (Hering, Kandaswamy, Harmon, et al., 2004 [In press]). The remaining three centers reported no other serious procedural complications among 16 transplanted patients (Markmann, Deng, Huang, et al., 2003; Kaufman, Baker, Chen, et al., 2002; Hirshberg, Rother, Digon, et al., 2003).

Adverse effects of continued immunosuppression. Published studies reported no instances of post-transplant lymphoproliferative disorder (PTLD), other malignancy, reactivation or transfer of cytomegalovirus (CMV) infection, opportunistic infections, or other long-term consequences of immunosuppression (Evidence Table 2). The absence of CMV infection is noteworthy since at least 16 CMV-negative patients were transplanted with islets from CMV-positive donors in two of the series (Ryan, Lakey, Paty, et al., 2002; Hirshberg, Rother, Digon, et al., 2003). In contrast, nearly 85% of similarly mismatched solid organ transplants (CMV-positive donor to CMV-negative recipient) reportedly developed CMV infection (Preiksaitis, Lakey, LeBlanc, et al., 2002). The absence of PTLD is encouraging but may reflect the small sample size thus far; incidences in the first year after kidney or heart transplant are 0.2% and 1.2%, respectively (Riddell, 2001).

Three studies reported effects of immunosuppressive therapy. In the largest series, mouth ulcers (n = 15), diarrhea (n = 10) and anemia (n = 8) were most common among 17 patients who completed the protocol (Ryan, Lakey, Paty, et al., 2002). Other adverse events included nausea and vomiting (n = 2), arthralgias, and rheumatoid arthritis (n = 1, each).

The first two doses of anti-CD3 humanized monoclonal antibody (Ala-Ala) used for immunosuppression at the University of Minnesota were associated with mild-to-moderate infusion reactions (Hering, Kandaswamy, Harmon, et al., 2004 [In press]). They also reported transient neutropenia in three of six patients, and mild-to-moderate mouth ulcers and weight loss in an unspecified number.

Recurrent oral ulcers, episodic diarrhea, and normocytic anemia occurred in all six patients in the initial NIH experience (Hirshberg, Rother, Digon, et al., 2003). Leg edema and generalized fatigue each occurred in five of six patients; transient, mild thrombocytopenia in four; and two patients experienced severe neutropenia that recovered after myeloid growth factor treatment or when a myelotoxic antibiotic regimen was discontinued. Infections of the skin and urinary tract each occurred in one patient. One patient developed interstitial pneumonitis from sirolimus toxicity, and one experienced severe diarrhea and fatigue.

Patient tolerance of immunosuppressive regimens has been a concern for some, but not all groups. Markmann, Deng, Huang, et al. (2003) discontinued immunosuppression without completing the transplant protocol for one patient due to concern that sirolimus might have been preventing healing of a traumatic foot wound. Immunosuppression was discontinued for one

NIH patient due to sirolimus-related pneumonitis, resulting in loss of most graft function. A second NIH patient with graft function but requiring some exogenous insulin elected to discontinue immunosuppression due to intolerable diarrhea, fatigue, weight loss, and renal dysfunction, but also retained minimal islet function (Hirshberg, Rother, Digon, et al., 2003). Similarly, two patients transplanted at the University of Minnesota discontinued immunosuppression while having partial islet function and subsequently rejected their grafts (Personal communication, Hering B, December 2003). No patients who completed the transplant protocol at the Universities of Miami or Alberta discontinued all immunosuppression (Personal communication, Alejandro R, December 2003; Personal communication, Shapiro J, December 2003).

Autoantibodies and sensitization. Only 2 centers reported on the development of islet autoantibodies. Of six patients followed by Hering, Kandaswamy, Harmon, and colleagues (2004 [In press]), three were positive for glutamic acid decarboxylase (GAD) and/or islet cell antigen (ICA) autoantibodies to pancreatic islet cells pre- and post-transplant and two additional islet recipients became GAD-positive post-transplant (only one of four islet cell autoantibody-positive patients did not achieve insulin independence). Insulin autoantibodies were positive in six patients pretransplant, and in five patients post-transplant.

Of 17 Edmonton patients who completed the transplant protocol at the time of the publication, three lost C-peptide secretion and two of these had developed GAD and ICA autoantibodies (Ryan, Lakey, Paty, et al., 2002). One patient with continued C-peptide secretion but requiring exogenous insulin had a rise in GAD and ICA antibodies.

Only one center reported on allosensitization to donor leukocyte antigens (Markmann, Deng, Huang, et al., 2003). All nine patients were negative for panel reactive antibodies (PRA), a test to measure what percentage of a patient serum sample reacts to a panel of known human leukocyte antigens, both pre- and post-transplant. One patient became PRA-positive after terminating immunosuppression. While these are insufficient data for conclusions, the lack of PRA is encouraging. In kidney and kidney-pancreas transplants, as much as 20% PRA has been detected (Pelletier, Hennessy, Adams, et al., 2002) and patients who lose their first transplant and develop broadly reactive antibodies (>50% PRA) have poorer graft survival upon retransplant than those who do not develop broad reactivity (Cecka, 1996).

Hepatic tissue changes. One study reported that periportal steatosis was detected by magnetic resonance imaging (MRI) after islet transplant in two of four patients (Markmann, Rosen, Siegelman, et al., 2003). Steatosis correlated with post-transplant functional islet grafts and may be a consequence of locally elevated insulin concentration in the portal tracts where functioning islets are located. Long-term consequences, if any, of the tissue changes are uncertain although the Edmonton group noted normal liver function tests in patients whose MRI scans showed evidence of steatosis (U.S. Food and Drug Administration, 2003). Additionally, similar hepatic changes observed in patients transplanted with autologous islets reportedly had no clinical consequences through 18 years of followup (U.S. Food and Drug Administration 2003).

Supplemental Evidence

Overview

This section of the Results chapter supplements the published reports with evidence from recent meetings and discusses more robust data on key outcomes such as insulin independence at 1 and 2 or more years of followup, glycemic control, and adverse events. Where abstracts from the same patient series were presented at different meetings, only the abstract with the most recent and/or detailed information was selected. Where different outcomes for the same group of patients were reported in different abstracts, both were selected and summarized. Abstracts that duplicated information available from published papers were excluded. Selected abstracts from the four most recent meetings are summarized in Evidence Tables 5 and 6. These meetings are:

- American Transplant Congress, 2003: The Fourth Joint American Transplant Meeting, May 30, 2003 - June 4, 2003, Washington, DC

- 63rd Scientific Sessions of the American Diabetes Association, June 13-17, 2003, New Orleans, LA

- 9th Congress of the International Pancreas and Islet Transplant Association, July 8-11, 2003, Dublin, Ireland

- 1st Islet Transplant Congress, November 13-16, 2003, Miami, FL

Because summary data from the Collaborative Islet Transplant Registry is not yet available, a summary of results from transplant groups attending the 2002 Annenberg Second Annual Symposium, in Rancho Mirage, CA represents the only available effort to date to collate islet transplant data from active centers (Evidence Table 7).

Meeting Abstracts

Islet transplantation alone. The abstracts in Evidence Tables 5 and 6 reported on 134 patients entering an islet transplant-alone protocol, including five reported by Berney, Bucher, Mathe, and co-workers (2003a; 2003b) and five reported by Cagliero (2003), but not including the 32 patients from the Immune Tolerance Network (ITN) trial reported by Shapiro, Hering, Ricordi, and colleagues (2003) or the 75 patients combined from 3 centers and reported by Shapiro (2003b) that are most likely included in some individual centers' reports. Not all abstracts reported the number of patients that completed the transplant protocol. Patients were selected primarily for severe hypoglycemia unawareness.

Of four centers that have followed 104 patients for 12 months or more, insulin independence at the time of the report and with variable followup times ranges from 50 to 90 percent (Shapiro, 2003; Shapiro, Hering, Ricordi, et al., 2003; Alejandro, Ferreira, Froud, et al., 2003; Alejandro, 2003; Hering, Kandaswamy, Parkey, et al., 2003; Maffi, Bertuzzi, De Taddeo, et al., 2003). Results beyond 1 year have been reported by the Edmonton transplant center: Shapiro, Lakey, Paty, and co-workers (2003) report Kaplan-Meier projections of 84 percent insulin independence at 1 year (30 patients with 1 or more years of followup), and 64 percent at 2 years (15 patients

Evidence Table 5. Clinical islet transplantation: Patient and transplant characteristics reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003.

Study	N	N completed protocol	Follow-up (mos.)	Patient description	Donor organs/pt	Infusions/ pt	IEq/kg, average of all infusions/pt
Islet-alone transplantation, combined results from multicenter trials							
Shapiro, Hering, Ricordi, et al., 2003 (ATC #3) Multicenter ITN trial	32	17		Metabolic lability, severe recurrent hypoglycemia, or progressive complications	1.5		
Shapiro, 2003 1st Islet Transplant Congress Combined data from U Alberta, U MN, U Miami	75	75	12–36	Metabolic lability, severe recurrent hypoglycemia			
Islet-alone transplantation, single-center reports							
Shapiro, Lakey, Paty, et al., 2003 (ADA #284-OR) U Alberta	48	30	≤36	Type 1 diabetes mellitus			
Shapiro, 2003 1st Islet Transplant Congress Data from U Alberta only	59		≤48				

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Evidence Table 5. Clinical islet transplantation: Patient and transplant characteristics reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003. (continued)

Study	N	N completed protocol	Follow-up (mos.)	Patient description	Donor organs/pt	Infusions/ pt	IEq/kg, average of all infusions/pt
Islet-alone transplantation, single-center reports (continued)							
Goss, Brunicardi, Feliciano, et al., 2003 (IPITA #011) Baylor College	9	5	mean 6	Type 1 diabetes mellitus w/ history of severe hypoglycemia and metabolic instability	2	2	>10,000
Alejandro, Ferreira, Froud, et al., 2003 (ATC #568)	15	13	<18	Type 1 diabetes mellitus		1.8	13,667
Alejandro 2003 1st Islet Transplant Congress U Miami	16	16		Type 1 diabetes mellitus	2 + 5 supplemental in 5 patients	2 + 5 supplemental in 5 patients	13,007 for 1st+ 2nd infusions; 8,713 for 3rd
Hering, Kandaswamy, Parkey, et al., (submitted for ATC 2004) U Minnesota	20	20	Mean 23 (2-40)	Type 1 diabetes mellitus with hypoglycemic unawareness	18 single donor; 2, 2 donors	18-1 2-2	8,300 for single-donor recipients

Evidence Table 5. Clinical islet transplantation: Patient and transplant characteristics reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003. (continued)

Study	N	N completed protocol	Follow-up (mos.)	Patient description	Donor organs/pt	Infusions/ pt	IEq/kg, average of all infusions/pt
Islet-alone transplantation, single-center reports (continued)							
Zavala, Hanaway, Peddi, et al., 2003 (ATC #1452) U Cincinnati	6		3	Type 1 diabetes mellitus with hypoglycemic unawareness	1	1	
Maffi, Bertuzzi, De Taddeo, et al., 2003 (IPITA #063) San Raffaele Scientific Institute, Milan	10		18	Type 1 diabetes mellitus, "brittle," with hypoglycemia unawareness and chronic complications		1.7	5,200/ infusion
Larsen, 2003 1st Islet Transplant Congress Emory U	4	3	1-9	Type 1 diabetes mellitus >5 years with hypoglycemic unawareness	2 (n=2) 1 (n=1) 1 awaiting 2nd transplant	2 (n=2) 1 (n=1)	12,100 for completed protocols

Evidence Table 5. Clinical islet transplantation: Patient and transplant characteristics reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003. (continued)

Study	N	N completed protocol	Follow-up (mos.)	Patient description	Donor organs/pt	Infusions/ pt	IEq/kg, average of all infusions/pt
Islet and kidney transplantation							
Berney, Bucher, Mathe, et al. 2003b (ATC #401)	4 2 1		3	islet alone islet-kidney islet after kidney			>5,000/infusion
Berney, Bucher, Mathe, et al. 2003a (IPITA #014) U Geneva	5 2 3			islet alone islet-kidney islet after kidney			
Berney, Bucher, Kessler, et al., 2003 (IPITA #013) GRAGIL IB Multicenter trial	9	7	3-12	Type 1 diabetes mellitus with prior kidney transplant; tapered off corticosteroids			target 10,000+
Froud, Ferreira, Hafiz, et al., 2003 (IPITA #061) U Miami	3		0.5-4.5	islet after kidney	1	1	8,511

Evidence Table 5. Clinical islet transplantation: Patient and transplant characteristics reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003. (continued)

Study	N	N completed protocol	Follow-up (mos.)	Patient description	Donor organs/pt	Infusions/ pt	IEq/kg, average of all infusions/pt
Islet and kidney transplantation (continued)							
Lehmann, Weber, Zuellig, et al., 2003 (ADA #285-OR) U Hosp Zurich	8	6	mean 15	Type 1 diabetes mellitus of 40 +/- 9-year duration; Islet-kidney transplant			
Cagliero, 2003 1st Islet Transplant Congress Harvard-Mass Gen	5 5	5 3	3-23	Islet after kidney Islet alone	~2 (1-IAK,1 donor; 2-IAK, 3 donors)	~2 (1-1 infusion, 2-3 infusions)	mean 13-14,000 (mean 19,546 for 3 combined infusions, n=2)

Evidence Table 6. Clinical islet transplantation: Outcomes reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003.

Study	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	HbA1c, most current (%)	Hypo-glycemic reactions	#Pts withdrawn	Comment	Complications
Islet-alone transplantation, combined results from multicenter trials									
Shapiro, Hering, Ricordi, et al. 2003 (ATC #3) Multicenter ITN trial	32	17	?	__/14 of 17 completing protocol			2	30 of 32 (94%) C-peptide positive UPDATE: after median 9.4 mos., 52% insulin-free[a]	15-severe adverse event 4-hemorrhage 2- severe neutropenia 40%-statin therapy for new-onset hypercholesterolemia
Shapiro, 2003 1st Islet Transplant Congress Combined data from U Alberta, U MN, U Miami	75	75	12-36	__/64 of 75 (85%) at 1 year	6.1 1yr n=34 6.2 2yr n=18 6.5 3yr n=10			All patients receiving cultured cells; ~same protocols for all; 99% demonstrated primary function; 96% C-peptide positive at 1 year	3 left branch thrombus (U Alberta); 0 main portal thrombosis; 0 deaths; 0 cancer, PTLD; 0 CMV, EBV
Islet-alone transplantation, single-center reports									
Shapiro, Lakey, Paty, et al., 2003 (ADA #284-OR)	48	?	≤36	1 year-84% (30 pts with 1+ year data) 2 year-64% (15 pts with 2+ year data) by Kaplan-Meier analysis	6 in insulin-indep pts			4 patients became C-peptide negative due to recurrent autoimmunity, rejection, or islet exhaustion	0-deaths, malignancy, PTLD or CMV 11% liver bleeds w/ transfusion 2% hemobilia 5% severe neutropenia 2% portal thrombosis

[a]Ault, 2003

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Evidence Table 6. Clinical islet transplantation: Outcomes reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003. (continued)

Study	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	HbA1c, most current (%)	Hypo-glycemic reactions	#Pts withdrawn	Comment	Complications
Islet-alone transplantation, single-center reports (continued)									
Shapiro, 2003 1st Islet Transplant Congress Data from U Alberta only	59		≤48	1 year-90% cultured islets, 95% non-cultured; 2 year-79% cultured islets; 4 year-2 of 3; all by Kaplan-Meier analysis				88% C-peptide positive, 16-48 months liver bleeds early, preventable complication; protocols have been modified to avoid	14% liver bleeds 5% gallbladder problem 2% hemobilia 3% severe neutropenia 3% pneumonia 3% ileal ulcer 2% sensitization various mild to moderate adverse events of immunosuppression in 23-87% of patients
Alejandro, Ferreira, Froud, et al., 2003 (ATC #568)	15	13	≤18	13/8	6 (all pts)	None in insulin-independent pts		69% of initially insulin-free pts remained so at 1 year; pts on insulin (31%) still had significant islet function	(Not reported)
Alejandro 2003 1st Islet Transplant Congress U Miami	16	16		14/10; 1 year: 80%				5 required supplemental 3rd infusion at 1 yr or later; of these, 3 are insulin indep	1-severe gastroparesis 1-parvovirus both discontinued immunosuppression 1-tacrolimus toxicity, changed to MMF
Goss, Brunicardi, Feliciano, et al., 2003 (IPITA #011) Baylor College	9	5	mean 6	5/5	Normal (all pts)	None (all pts)		4 awaiting 2nd tx reduced insulin by >75%	no technical complications from procedure or unexpected adverse effects from immunosuppression

Evidence Table 6. Clinical islet transplantation: Outcomes reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003. (continued)

Study	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	HbA1c, most current (%)	Hypo-glycemic reactions	#Pts withdrawn	Comment	Complications
Islet-alone transplantation, single-center reports (continued)									
Hering, Kandaswamy, Parkey, et al. (submitted for ATC 2004) U Minnesota	20	20	Mean 23 (2-40)	1 year: 85% of 20 of 18 single donor recipients, 16 initially insulin independent; 11 >1 year	of 11 insulin-indep: 1 yr-5.5 2 yr-5.1 (n=7) 3 yr-5.5 (n=3)			Recipients participated in 4 pilot clinical trials	Of 20: 0-portal vein thrombosis 0-bleeding 0-opportunistic infections 0-malignancies 7-severe transient neutropenia 1-transient anemia 1-acute cholecystitis
Zavala, Hanaway, Peddi, et al., 2003 (ATC #1452) U Cincinnati	6	1	3	1/1		None in insulin-independent pts; improvement with 50% insulin reduction		3-50% insulin reduction 2-25% insulin reduction	1-portal vein thrombosis and later re-admission for rectal ulcer
Maffi, Bertuzzi, De Taddeo, et al., 2003 (IPITA #063) San Raffaele Scientific Institute, Milan	10		18	_/5	6.8 at 1 year (all pts)			8 pts reduced insulin by >50%; 3 pts lost islet function by 3 mos.	1-portal thrombosis 2-deteriorating renal function 10-mouth ulceration 6-acne-like lesions controlled by decreased sirolimus dose no hypertension, dyslipidemia or severe neutropenia/leukopenia

Evidence Table 6. Clinical islet transplantation: Outcomes reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003. (continued)

Study	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	HbA1c, most current (%)	Hypo-glycemic reactions	#Pts withdrawn	Comment	Complications
Islet-alone transplantation, single-center reports (continued)									
Larsen, 2003 1st Islet Transplant Congress Emory U	4	3	1-9	3/2				1 pt resumed insulin meal boluses at 9 weeks, awaiting 3rd transplant; Edmonton immunosuppression	of 4: 3-mild anemia 3-grade I-II leukopenia mild ulcers, diarrhea, elevated LFT common
Islet and kidney transplantation									
Berney, Bucher, Mathe, et al. 2003b (ATC #401)	4 2 1		<u>3</u>	_/5	6.3 (?all pts)			All pts C-peptide positive; pts received 2nd infusion if not insulin-independent by 3 mos.; 1 pt scheduled for a third infusion	1-died 2° to OKT3 2-acute rejection episodes 1-bleeding after portal access 1-acute pyelonephritis 1-severe tubulopathy 3-mouth ulcerations 6-dyslipidemia, statin therapy
Berney, Bucher, Mathe, et al. 2003a (IPITA #014) U Geneva	5 2 3			_/6					1-died 2° to OKT3 2-acute rejection episodes 2-bleeding after portal access 1-severe tubulopathy 6-mouth ulcerations 8-dyslipidemia 7- leukopenia

Evidence Table 6. Clinical islet transplantation: Outcomes reported in meeting abstracts from the American Transplant Congress (ATC), June, 2003; the 63rd Scientific Sessions of the American Diabetes Association (ADA), June, 2003; and the 9th Congress of the International Pancreas and Islet Transplant Association (IPITA), July, 2003 and the 1st Islet Transplant Congress, November, 2003. (continued)

Study	N	N completed protocol	Follow-up (mos.)	#Pts insulin independent initially/ remaining	HbA1c, most current (%)	Hypo-glycemic reactions	#Pts withdrawn	Comment	Complications
Islet and kidney transplantation									
Berney, Bucher, Kessler, et al., 2003 (IPITA #013) GRAGIL IB trial	9	7	3-12	6/1				4 retain graft function; 3 lost graft function; no corticosteroids, but not Edmonton protocol; islets shipped	1 death: severe pneumonopathy 1-intraperitoneal hemorrhage 1-partial, reversible portal thrombosis 1-severe mouth ulcerations
Froud, Ferreira, Hafiz, et al., 2003 (IPITA #061) U Miami	3		0.5-4.5	1/1[b]	5 (1 pt)			85% mean insulin reduction; mild deterioration in renal function	mild deterioration of renal function in all patients (0.13 mg/dL mean elevation of serum creatinine)
Lehmann, Weber, Zuellig, et al., 2003 (ADA #285-OR) U Hospital Zurich	8	6	mean 15	5/5	5.8 (n=8)			treated with continuous subcutaneous insulin infusion initial 2 mos.	1 kidney rejection resolved with reinstitution of immunosuppression rejection rate no different than for SPK
Cagliero, 2003 1st Islet Transplant Congress Harvard-Mass Gen	5 5	5 3	3-23	3 IAK insulin independent 1 IA insulin independent	6.8 (n=8)		1 graft failure	2-IAK, 25-30% of pretransplant insulin, awaiting 3rd transplant; 1-IA weaning off insulin after 3rd transplant	

[b] In presentation, information updated to 3 of 3 completing protocol were insulin independent, one with a single donor (Alejandro R, personal communication).

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with 2 or more years of follow-up) in patients who completed the transplant protocol. Of particular note, Hering, Kandaswamy, Parkey, and colleagues (submitted for ATC 2004) reported that of 18 single-donor transplant recipients, 16 were initially insulin independent and 11 remained so at more than 1 year of follow-up. Other centers report on small numbers of patients with less than 1 year of follow-up. In general, for patients who did not achieve or retain insulin independence, centers reported decreases in pretransplant insulin doses of 25 to 75 percent.

Other notable results include 79 percent insulin independence at 2 years for patients receiving cultured islets at the Edmonton center, and 2 of 3 patients remaining insulin independent at greater than 4 years post-transplant (Shapiro, 2003). Ninety-nine percent of 75 patients pooled from 3 transplant centers (Universities of Alberta [Edmonton], Minnesota, and Miami) demonstrated primary islet function, 96 percent were C-peptide positive at 1 year, and 85 percent insulin independent at 1 year (Shapiro, 2003). For 32 patients entered into the ITN trial, Shapiro, Ricordi, Hering, and colleagues (2003) noted that results varied by center, with 90 percent insulin independent at three centers with long-standing experience, 67 percent at a fourth center, but a much lower average across remaining centers.

Where reported, insulin-independent patients experienced no hypoglycemic reactions (Alejandro, Ferreira, Froud, et al., 2003; Goss, Brunicardi, Feliciano, et al., 2003; Zavala, Hanaway, Peddi, et al., 2003). HbA_{1c} was reported primarily for insulin-independent patients, in whom mean levels decreased to well under 7 percent and, in most cases, less than 6.5 percent. In two series (Shapiro, 2003; Hering, Kandaswamy, Parkey, et al., submitted for ATC 2004), HbA_{1c} was maintained at or below 6.5 percent for up to 3 years post-transplant (total n = 13).

Adverse events (islet transplantation alone). Evidence Table 6 summarizes data on adverse events reported at recent meetings by three multicenter groups (the ITN trial and the Edmonton/University of Minnesota/University of Miami and Baylor/University of Miami collaborations) and six single institutions (Universities of Miami, Minnesota, Cincinnati, Alberta, and Emory, and the San Raffaele Institute). These abstracts report on more than 124 patients.[4] None reported CMV infection or PTLD in any patients given islet-alone transplants. A recent summary presented to the FDA's Biologic Response Modifiers Advisory Committee confirmed that neither adverse event has been reported after islet transplant (U.S. Food and Drug Administration, 2003).

Serious adverse events ranged from none (Goss, Brunicardi, Feliciano, et al., 2003, IPITA #011) to 15 of 32 patients (Shapiro, Hering, Ricordi, et al., 2003; ATC #3, Multicenter ITN trial). Frequent complications included hypercholesterolemia or other dyslipidemia, hemorrhage, and neutropenia and/or leukopenia (n = 121). Occasional complications included portal thrombosis, mouth ulcerations, mild deterioration of renal function, and acneiform rash. Hemobilia, severe tubulopathy, acute pyelonephritis, and interstitial pneumonitis each occurred in one patient.

Islet and kidney transplantation. A few transplant centers report on a total of 30 kidney transplant patients who received an islet transplant. Lehmann, Weber, Zuellig, and co-workers

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[4] This total excludes five islet-only patients reported by Berney, Bucher, Mathe, and co-workers (2003) and 5 reported by Cagliero (2003), since the abstracts did not indicate whether adverse events occurred in patients given simultaneous islet-kidney transplants or in those transplanted with islets alone. It also excludes the ITN trial (Shapiro, Hering, Ricordi, et al., 2003) and the Edmonton/Miami/Minnesota collaboration (Shapiro, 2003), since some of these patients are most likely also included in some individual centers' reports.

(2003) performed eight islet/kidney transplants; six patients have completed the islet transplant protocol and five achieved and remain insulin independent after a mean of 15 months. Berney, Bucher, Mathe, and colleagues (2003a; 2003b) reported on 2 simultaneous islet/kidney, and 3 islet after kidney transplant patients, but did not report results separately from islet-alone transplants. C-peptide positivity was achieved in all patients, and insulin independence in some over a short followup time.

The GRAGIL 1B trial used a different glucocorticoid-free immunosuppressive regimen and shipped islet preparations to different transplant centers, but was less successful. In this trial, Berney, Bucher, Kessler, and co-workers (2003) report achieving insulin independence initially in six of seven patients with prior kidney transplants tapered off glucocorticoids, but after 3–12 months' followup only one remained insulin independent. Froud, Ferreira, Hafiz, and co-workers (2003) report three of three islet after kidney transplants achieved and remained insulin independent, one after a single islet infusion. Cagliero (2003) reported on five islet-after-kidney transplants, followed for 3 to 23 months; three are insulin independent and two require 25 to 30 percent of their pretransplant insulin doses while awaiting a third transplant.

No centers reported on hypoglycemic reactions. Where reported, HbA_{1c} levels were normal for most patients, even if some insulin was needed to maintain good glycemic control.

Two deaths were reported, both in patients given simultaneous islet/kidney transplants. One died from a reaction to the OKT3 antibody used for immunosuppression (Berney, Bucher, Mathe, et al., 2003a, 2003b; ATC #401/IPITA #014). The other died from severe pneumonopathy; it is uncertain whether an investigational drug included in this patient's immunosuppression regimen contributed to the adverse outcome (Berney, Bucher, Kessler, et al., 2003; IPITA #013, the GRAGIL 1B trial). Acute rejection episodes occurred in three patients given simultaneous islet/kidney transplant, but rejection of the renal allograft reversed when immunosuppression was modified.

Annenberg 2002 Data Summary

At the "Islet Transplantation 2002 and Beyond: 2nd Annual Symposium," December 5-7, 2002, at the Annenberg Center for Health Sciences, Rancho Mirage, CA, a number of islet transplant centers pooled their data for a brief summary, shown in Evidence Table 7. At that time, 14 centers reporting had performed 263 islet infusions on 155 patients; 113 of these patients had completed the centers' transplant protocols. At 3 months, after one infusion, 32 patients were insulin independent and after two infusions 65 were insulin independent. This summary does not supply sufficient information to allow the calculation of insulin independence or euglycemia percentages, but reflects the experience of several transplant centers that are using a variety of protocols.

At the 1st Islet Transplant Congress, November 13-16, 2003, in Miami, FL, it was reported that over 75 centers worldwide have initiated transplant programs, and that over 300 patients have received islet transplants since 1999. However, no overall summary of outcomes for all these patients has as yet been reported.

Evidence Table 7. 2nd Annenberg Islet Symposium: Transplant Center Results as of December, 2002.

Center	#Infusions	#Patients	#Completed	#Insulin-free by 3 mos., 1 infusion	#Insulin-free by 3 mos., 2 infusions	#Using insulin but free of hypoglycemia and with normal HbA1c 1 infusion	#Using insulin but free of hypoglycemia and with normal HbA1c 2 infusions
Boston	9	6	4	1	4	3	0
Cincinnati	6	6	1	1		4	0
Edmonton	85	43	33	4	28	26	15
Geneva	28	16	12	1	8	1	3
Houston	16	7	5	3	0	0	0
London	3	1	0	0	0	0	1
Memphis	6	3	3	1	2	2	1
Miami	35	21	17	1	12	0	4
Minneapolis	19	18	16	15	1	1	0
NIH	10	6	6		3		2
Philadelphia	12	9	7	5	2	0	0
Seattle	8	6	0	0	0	2	1
St. Louis	12	7	4	0	2	0	0
Uppsala	14	6	5	0	3	0	3
Total	**263**	**155**	**113**	**32**	**65**	**39**	**30**

Conclusions

Published data on clinical outcomes of islet alone transplantation are limited by small patient numbers, few transplant centers, short duration of followup, and by lack of standardized methods of reporting outcomes. Data are also lacking on quality of life outcomes. Meeting abstracts and presentations supplement published reports with larger numbers of patients and reporting transplant centers. Efforts are ongoing to update and expand long-term transplant results and quality of life data, disseminate protocols to additional centers, and standardize reporting of outcomes. From the available data, the following summary statements can be made:

- Islet-alone transplantation has been used in a highly selected population of type 1 diabetic patients. The existing evidence reports on patients who have been selected for transplantation based on 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.

- There are sufficient data to conclude that there is a high rate of technical success for islet alone transplantation. Five centers published reports on 47 patients who completed a transplant protocol. Of these, patients 44 (94 percent) achieved insulin independence over the 3-month post-transplant period.

- Clinical outcomes from presently available data can be summarized as follows:

  - Published data from three centers report that 28 of 37 patients (76 percent of those completing a transplant protocol) maintained insulin independence for 1 year. Recent abstracts from four centers that followed 104 patients for at least 12 months report insulin independence in 50 to 90 percent of patients.

  - Only one published study (from the Edmonton group) reported on patients with 2 years of followup: four of six patients remained insulin-independent. In one abstract from Edmonton, 48 patients were transplanted and 15 of these were followed for 2 or more years. Kaplan-Meier analysis estimated that the probability of remaining insulin-independent at 2 years was 64 percent.

  - Two institutions published detailed information on 23 patients who completed a transplant protocol and had at least one year of followup. Of these, 19 (83 percent) were euglycemic, without hypoglycemic episodes, and free of or on reduced insulin. Meeting abstracts and presentations offered no additional data on this outcome.

  - All published series report that hypoglycemic episodes were abated in insulin-independent transplant patients. In three series reporting on 26 patients completing the transplant protocol, hypoglycemic episodes were also abated in nine patients with continuing C-peptide secretion, but who were not insulin independent at 1 year. Abstracts report this outcome less consistently but where reported, hypoglycemic episodes were eliminated in insulin-independent patients.

- In each published series and for all insulin independent patients, mean HbA_{1c} decreased from greater than 7 percent to less than 6.5 percent; 7 percent or less is recommended to avoid or delay progression of diabetic complications. Where reported in meeting abstracts, mean HbA_{1c} after transplantation is in most cases less than 6.5 percent and in two series was maintained for up to 3 years post-transplant (total n=13).

- Data are scant on effects of islet transplantation on long-term diabetic consequences. In one publication the Edmonton group reported on 17 subjects who completed the transplant protocol. Retinopathy progressed in three and required laser photocoagulation. Nine patients either started or increased antihypertensive therapy. Cholesterol rose in 15 patients and in 11 required statin therapy. There were no major changes in neuropathy. Serum creatinine and urine protein did not change significantly except for two patients with pre-existing renal impairment.

- Infrequent but serious adverse events (e.g., portal vein thrombosis, hemorrhage) have occurred in patients given islet transplants, but it is not possible from present data to estimate their frequency. Recent modifications of the procedure reportedly minimize risks of these adverse events. No procedure-related deaths have been reported among patients transplanted with islets alone. Notably, no publication or abstracts reported CMV infection or PTLD in any patients given islet-alone transplants.

- Available evidence is insufficient to evaluate long-term consequences of immunosuppression, any as yet unknown long-term effects of the islet graft, and the potential need for and consequences of supplemental islet transplants.

- The majority of transplants using the newer protocols have been islet alone. Reported mainly in meeting abstracts and presentations (with the exception of one published case report), 30 islet transplants after or simultaneous with kidney transplants have been attempted; in most cases, followup is less than 1 year. Present evidence is insufficient to permit conclusions for this type of transplant.

Chapter 4. Discussion

The available evidence demonstrates the technical feasibility of islet transplantation using the Edmonton and subsequent protocols, with procedural success that is far superior to earlier protocols. Where 1-year follow-up has been reported, most patients are insulin independent and free of severe hypoglycemic episodes. At present, 100 or more patients have been followed for 1 year post-procedure, and the Edmonton group recently reported on 15 patients followed for 2 years or more. Evidence on longer-term outcomes or durability of the procedure is not yet available. Presently, it is not possible to assess the effects on diabetic complications or the consequences of life-long immunosuppression. However, this systematic review represents the current state of the evidence, recognizing that the major islet transplant centers continue to actively accrue and follow patients.

Presently, the best data on the long-term benefits of replenished islet function comes from uremic diabetic patients who receive simultaneous kidney and pancreas transplants compared to those who receive kidney transplant alone. Whole-organ pancreas transplantation has favorable effects on hypoglycemic and renal complications, hypertension, and may stabilize retinopathy; effects on neuropathy, cardiac function, and quality of life are not yet clear. Data from one study of long-term successful islet transplants from the pre-Edmonton era suggest significantly reduced cardiovascular mortality and renal damage.

Candidates for islet transplant are type 1 diabetic patients with severe metabolic disease or hypoglycemia despite strict medical management such that the risk of adverse effects of long-term immunosuppression is acceptable. Similar patients transplanted with an intact pancreas are currently being evaluated for long-term benefit. However, an analysis of United Network for Organ Sharing (UNOS) data found that at about 4 years post-procedure "survival for those with diabetes and preserved kidney function and receiving solitary pancreas transplant was significantly worse" than wait-listed patients receiving conventional care (Venstrom, McBride, Rother, et al., 2003). A recent summary of the NIDDK experience with islet transplantation highlights some of the difficulties of long-term immunosuppression. Neither report should lead to the conclusion that either solitary whole-organ pancreas transplants or islet transplants is ineffective, but both show the urgency of evidence-based assessment of the benefits and risks.

Reports from the Collaborative Islet Transplant Registry (CITR) are expected to be available in the near future. The Registry will provide systematic data on outcomes of patients treated at the major islet transplant centers and over time will accumulate data on long-term outcomes. The CITR plans to collect data on patient characteristics at transplantation (post-Edmonton protocols only, and including retrospective data) as well as long-term follow-up data on the secondary complications of diabetes. The addition of data on the baseline status of retinopathy, neuropathy, and other diabetic complications prior to transplantation would aid interpretation of long-term results. Randomized, controlled trials of islet transplant do not exist and are unlikely to be conducted. Thus pre- and post-procedure evaluations, which are likely to be the only source of evidence to evaluate this procedure, should proceed with the utmost rigor.

As is the case with many procedures, outcomes may vary by center, perhaps due to experience or protocol. Moreover, such variation can be difficult to ascertain when the number of procedures is small and perhaps lacking in statistical power. Center-specific data will complement aggregate data in evaluating outcomes of islet transplant, benchmarking performance, and improving outcomes.

Long-term follow-up will delineate the durability of islet graft function and the need for repeat procedures. Uncertainties remain: Should patients who fail to maintain insulin independence be administered additional islet transplants? Does reactivation of autoimmune reactions against beta cells affect the success of subsequent transplants? Do the risks of the procedure increase with successive transplants?

At present, the supply of donor pancreata stringently limits the availability of islet transplants. However, refining the islet isolation and transplant procedures, could promote more vigorous efforts at organ collection, and perhaps make islet transplantation more available. Simultaneous islet and kidney transplant is being attempted and may yield another population of patients eligible for islet transplantation. Ongoing research on innovations in nondiabetogenic immunosuppression regimens, prevention of rejection, and tolerance induction, may eventually improve the benefit to risk ratio of the procedure; and methods of in vitro production may increase the availability of islets for transplantation. While whole-organ pancreas and islet transplant are now the only means of achieving physiologic insulin regulation, continuous monitoring and infusion technologies are being developed in hope of someday achieving an artificial pancreas. As innovations in the management of type I diabetes emerge and diffuse, risks and benefits, relative-effectiveness, and cost-effectiveness for various patient populations should be carefully evaluated.

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List of Acronyms/Abbreviations

ACPR: acute C-peptide response to arginine
AHRQ: Agency for Healthcare Research and Quality
ADA: American Diabetes Association
ALG: antilymphocyte globulin
AIR_{arg}: acute insulin response to arginine
AIR_g :   acute insulin response to glucose
ATC: American Transplant Congress
ATG: antithymocyte globulin
AUC_{C-p}: area under the curve, C-peptide
AUC_i: area under the curve, insulin
BLA: biologics license application
BP: blood pressure
CI: confidence interval
CITR: Collaborative Islet Transplant Registry
CMV: cytomegalovirus
DCCT: Diabetes Control and Complications Trial
DM: diabetes mellitus
EBV: Epstein-Barr virus
EDIC: Epidemiology of Diabetes Interventions and Complications
EPC: Evidence-based Practice Center
ER: emergency room
FDA: U.S. Food and Drug Administration
GAD: glutamic acid decarboxylase
G-CSF: granulocyte colony-stimulating factor
HDRF: Juvenile Diabetes Research Foundation
HFS: Hypoglycemia Fear Survey
Hosp: hospital
hr(s).:   hour(s)
IA: islet alone
IAK: islet after kidney
ICA: islet cell antigens
ICR: Islet Cell Resource
IEq: islet equivalents
IEq/kg: islet equivalents per kilogram of body weight
IND: investigational new drug
ITN: Immune Tolerance Network
ITR: International Islet Transplant Registry
indep: independent
IPITA: International Pancreas and Islet Transplant Association
IPTR: International Pancreas Transplant Registry
ITA: islet transplant alone
ITN: Immune Tolerance Network

IVGTT: intravenous glucose tolerance test
JDRF(I):   Juvenile Diabetes Research Foundation (International)
JDFI: Juvenile Diabetes Foundation International
K_G: glucose disposal
KTA: kidney transplant alone
LFT(s):   liver function test(s)
MeSH[®]:   Medical Subject Headings[®]
MMF: mycophenolate mofetil
mo(s).:   month(s)
N, n: number
NCCR: National Center for Research Resources
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIH: National Institutes of Health
OGTT: oral glucose tolerance testing
OPTN: Organ Procurement and Transplantation Network
PAK: pancreas after kidney
PRA: panel reactive antibodies
pt(s):   patients
PTA: pancreas transplant alone
PTLD: post-transplant lymphoproliferative disorder
QoL: quality of life
SD: standard deviation
SIK: simultaneous islet/kidney
SIL: simultaneous islet/liver
SPK: simultaneous pancreas/kidney
TEP: Technical Expert Panel
tx: transplant(ation)
U: University
UNOS: United Network for Organ Sharing
U.S.:   United States
UTI: urinary tract infection
w/:   with
yr(s):   year(s)

APPENDIX A: EXACT SEARCH STRINGS

The MEDLINE database was searched for recently published research articles and for relevant background information. The database was searched initially from 1966 through October 2002; subsequent search updates were performed through October 2003. Additionally, bibliographies of relevant articles were also searched and the project's Technical Expert Panel was queried for any relevant articles omitted from the search results. During the peer review process, reviewers informed the Evidence-based Practice Center (EPC) staff of articles recently published or accepted for publication and in the case of certain imminent publications, provided prepublication manuscripts.

The search strategy selected for review all citations that included any of the following terms:
   "Islets of Langerhans Transplantation"[Medical Subject Heading® (MeSH®)]
   "Islets of Langerhans"[MeSH®] AND "transplantation"[MeSH®]
   islet*[tw] AND transplant*[tw], or
   beta cell*[tw] AND transplant*[tw]

The search was limited to studies on human subjects with English-language abstracts. Papers published in foreign languages were reviewed if the English abstract appeared to meet inclusion criteria.

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