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Huang, et al., 2003; Hirshberg, Rother, Digon, et al., 2003; Kaufman, Baker, Chen, et al., 2002) Older publications superceded by later updates of similar information are not summarized, but the corresponding citations are indicated in footnotes (Shapiro, Lakey, Ryan, et al., 2000;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.

[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	≥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

[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				

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) Berney, Bucher, Mathe, et al. 2003a (IPITA #014) U Geneva	4 2 1		3	islet alone islet-kidney islet after kidney			≥5,000/infusion
	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

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		3	_/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).

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

[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.