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.