Type 1 diabetes mellitus (also known as juvenile diabetes) is an autoimmune disease seen primarily in Western countries. There is a rising incidence worldwide of the disease and in Scandinavian countries it affects up to 1.5 percent of the population. Type 1 diabetes is characterized by hyperglycemia due to the nearly complete destruction of the insulin producing β-cells of the pancreatic islets of Langerhans. β-cell loss is via a T-cell mediated autoimmune attack, a process that usually occurs during childhood or adolescence. Although insulin replacement can lead to acceptable control of blood glucose levels, affected individuals are subject to the development of various complications due to the disease. Diabetic patients have increased risk of premature death, cardiac disease, stroke, retinopathy and blindness, nephropathy and renal failure, peripheral and autonomic neuropathy, and amputation. Although tight glycemic control has been shown to decrease the number of diabetes-related secondary complications, it has also been shown to lead to an increased number of dangerous hypoglycemic episodes.

Transplantation of either the whole pancreas or isolated pancreatic islets are alternatives to exogenous insulin therapy that are currently being used in select individuals with type 1 diabetes. Both options have been studied for over three decades in both animal models and in humans and offer the promise of restoration of normal glycemic control. Although historically both options have had serious limitations, they are currently demonstrating improved success rates compared to the past.

**Pancreatic Islet Transplantation**

Prior to transplantation, islets of Langerhans must be isolated from cadaver donor organs. The isolation of islets involves a multistep process that can be divided into a digestion phase, a collection phase, and a purification phase, all of which are performed under strictly sterile conditions in a GMP facility. The isolation process begins with dissection of the pancreas and removal of all extraneous tissue attached to the gland, including the duodenum, the spleen, and surrounding fat. The pancreas is then injected via the pancreatic duct with a solution containing collagenase. Collagenase is an enzyme derived from cultures of *Clostridium histolyticum*. A specially purified form of collagenase known as “Liberase” is used for human islet isolation. The enzyme is known to disrupt the fine network of collagen that binds the pancreatic exocrine tissue together with the islets. Following injection of the collagenase solution, the pancreas is placed into the Ricordi chamber for the digestion phase, which takes place at 37°C (Figure 1). This chamber is specially designed to allow constant circulation of the collagenase and has a screen that will allow only small pieces of tissue to pass through into the circulating solution. Sampling of this circulating fluid is performed every few minutes during the digestion phase, which is typically 20 to 40 minutes, and these samples are viewed under a microscope for the presence of free islets. Once enough free islet tissue is detected, the collection phase is begun. The collection phase involves circulating five to 10 liters of media through the Ricordi chamber to both “wash out” the tissue that has been digested free from the whole pancreas and to remove the collagenase from the solution to stop the enzymatic reaction. The resulting digested tissue contains free islets within a large amount of contaminating exocrine tissue. The separation phase is then undertaken where islets are purified from the contaminating exocrine tissue using density gradient centrifugation. Usually, Ficoll is used to create these gradients. Following purification, islets are tested for cell viability, purity versus contaminating exocrine tissue, sterility, and endotoxin levels. Only if the preparation is acceptable in terms of these tests, and if a sufficient number of islets have been isolated (generally over 5,000 islets per kilogram body weight of the recipient), is transplantation performed.

An interventional radiologist performs the islet transplant procedure. It involves percutaneous transhepatic access to the portal venous circulation and placement of a catheter into the main portal vein. The islets are infused via this catheter into the
portal circulation, allowing them to embolize in the liver (Figure 2). During the 30-minute infusion period, the portal venous pressure is periodically monitored for significant increases. The recipient receives only a local anesthetic and mild sedation to undergo the procedure, thus the recovery period is relatively rapid.

The initial experiences (1974-1999) with islet transplantation as an isolated procedure, or in diabetic patients that had already undergone a kidney transplant, were generally quite poor. In type 1 diabetic patients, the rate of graft function (some insulin production) was only 25 percent at one year and the rate of insulin independence was only 9 percent at one year. As a result, enthusiasm for this procedure was low. However, the encouraging report in 2000 from the University of Alberta in Edmonton, Canada, has revived the field of islet transplantation. These investigators were able to achieve an insulin independence rate of 80 percent at one year. The improved success was mainly due to a novel immunosuppression protocol that did not use corticosteroids and the transplantation of a larger number of islets than had been used in the past (the Edmonton Protocol). To transplant this larger islet number, recipients typically needed to undergo two of these transplant procedures with islets from two different donors.

Whole Organ Pancreas Transplantation

Whole organ pancreas transplantation was performed first at the University of Minnesota in 1966, and since that time over 19,000 pancreas transplants have been performed worldwide. Pancreas transplantation can be divided into three categories—simultaneous pancreas and kidney (SPK, 85 percent of cases), pancreas after kidney (PAK, 10 percent of cases), and pancreas transplant alone (PTA, 5 percent of cases). The SPK and PAK procedures are performed in type 1 diabetic patients who have concomitant renal failure but are otherwise good candidates. Since the SPK and PAK patients require immunosuppressive therapy for the kidney transplant, the added benefit of normal glycemic control from a pancreas transplant is thought to be worthwhile. Of interest, the pancreas graft has been demonstrated to protect the transplanted kidney from recurrent diabetic nephropathy. In addition, these patients show stabilization of progressive retinopathy and reversal of peripheral and autonomic neuropathy. The main indications for PTA are hypoglycemic unawareness, with frequent episodes of seizures or loss of consciousness, and hyper-labile diabetes with frequent hospital admissions for ketoacidosis. In the small subset of diabetic patients that qualify for PTA, it is felt that the risks of a pancreas transplant and the associated immunosuppression are outweighed by the benefit of avoiding these dangerous periods of low blood glucose.

Early experience with pancreas transplantation demonstrated that the procedure carried a high morbidity rate and a high graft-loss rate due to thrombosis or rejection. However, newer immunosuppressive agents and refinement of the surgical techniques have allowed overall improvements in graft survival and significant reduction of morbidity. As a result of these modifications, nearly 80 percent of patients are insulin independent at three years follow-up in both the SPK and PAK categories. Unfortunately, the rate of insulin independence for PTA is significantly lower at only 50 percent at three years.

The surgical technique has undergone two major revisions over the past decade. The first was a change from bladder...
drainage of the pancreatic exocrine secretions to enteric drainage. Although the former procedure allowed close monitoring of graft function via measurements of amylase levels in the urine, the associated metabolic acidosis, dehydration and cystitis that often developed in these patients led to a decrease in quality of life. With enteric drainage, these side effects were eliminated, and a majority of centers have adopted enteric drainage. The second surgical modification has been a change in the venous drainage of the pancreas into the superior mesenteric vein rather than the iliac vein. Proponents of this technique believe the rate of graft thrombosis is lower and metabolic control of diabetes is improved since secreted insulin drains into the portal venous circulation similar to the native pancreas, rather than into the systemic venous circulation. However, controversy exists over the benefits of this technique, and most centers have not yet switched to portal venous drainage of the pancreas.

**Patient Selection and Evaluation**

Under current protocols, patient selection is quite different between isolated islet and whole pancreas transplantation. Isolated islet transplantation is primarily for type 1 diabetic individuals without significant end-organ damage. The selected recipients often suffer from hypoglycemic unawareness and the risks of the procedure are outweighed by the benefit of achieving normal glucose control and thus avoiding hypoglycemia. The selection of recipients has been biased towards smaller individuals with daily insulin requirements of less than 40 units. There is increased effort recently to perform islet transplantation following a successful kidney transplant, however, the outcome in these patients is currently unknown.

Whole organ pancreas recipients are primarily those patients with renal failure from diabetic nephropathy that are undergoing a SPK transplant or have already had a kidney transplant from a living donor and are undergoing a PAK transplant. In addition, isolated whole organ pancreas transplantation is used on rare occasions for patients with hypoglycemic unawareness. Although whole organ pancreas candidates often have secondary complications from diabetes, they must have sufficient cardiac reserve to tolerate a major operation. Cardiac contraindications include the presence of non-correctable coronary artery disease, ejection fraction below 50 percent, or myocardial infarction within the past six months.

For either type of transplant, a potential recipient must have a thorough history and physical examination, with particular emphasis on the insulin regimen the patient requires and the glucose control this regimen achieves, including the presence of extremely labile or dangerously low glucose levels. In addition, the secondary complications of the disease should be assessed. Aside from standard laboratory testing of a chemistry panel, CBC and coagulation studies, the potential recipient should have the diagnosis of type 1 diabetes confirmed by measurement of insulin C-peptide level in the serum, which should be less than 0.3 ng/ml. The glycosylated hemoglobin fraction (hemoglobin A1c), an indication of the degree of glucose control over the prior three-month period, should also be measured. Finally, the presence of anti-HLA antibodies should be measured to assess if there are specific antibodies against potential donor antigens that the patient would mount a strong immune response to in the transplant setting. Prior to transplantation, a T and B cell crossmatch is also performed between the donor cells and the recipient serum to avoid transplantation across a positive crossmatch.

The evaluation of a patient for either whole organ pancreas or isolated islet transplantation should consider the pros and cons of each procedure (Table 1). Islet transplantation remains an experimental procedure that is only being conducted under research protocols, whereas pancreas transplantation is a procedure that is widely available. Another difference between the two is the requirement for a major surgical procedure in whole organ transplantation, the morbidity and potential mortality associated with the procedure, and the recovery period from the operation. In contrast, isolated islet transplantation only requires that the patient undergo a minimally invasive procedure that is performed with local anesthesia and sedation. The results of whole organ

### Table 1

**Comparison of whole pancreas and islet transplantation**

<table>
<thead>
<tr>
<th></th>
<th>WHOLE PANCREAS TRANSPLANTATION</th>
<th>ISLET TRANSPLANTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Diabetics with renal failure</td>
<td>Diabetics with hypoglycemic unawareness</td>
</tr>
<tr>
<td></td>
<td>(95% of cases)</td>
<td></td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Widely available</td>
<td>Research protocols only</td>
</tr>
<tr>
<td><strong>Procedure</strong></td>
<td>Major abdominal operation under general anesthesia</td>
<td>Percutaneous procedure performed with local anesthesia</td>
</tr>
<tr>
<td><strong>Metabolic control</strong></td>
<td>Normal</td>
<td>Good—still on a diabetic diet</td>
</tr>
<tr>
<td><strong>Longevity of transplant</strong></td>
<td>80% function at 3 years</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Effect on secondary complications of diabetes</strong></td>
<td>Stabilization and improvement</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
transplantation currently exceed those of islet transplantation in terms of overall metabolic control. Patients with a functioning pancreas transplant are essentially “normal” and are generally allowed to eat a regular diet, whereas even successful islet patients must continue to remain on a diabetic diet. Diabetic complications stabilize or improve after whole organ transplantation; however, the same is not known for islet transplantation. Finally, the durability of islet graft function is not known, whereas whole organ pancreas graft survival is 80 percent at three years, with many patients having over 10 years of function.9

**Future Therapies**

Results with islet transplantation should improve as isolation techniques improve, immunosuppressive agents are developed that are not diabetogenic, and clinical experience with this therapy is gained. This therapy will probably become the preferred transplant option for individuals with type 1 diabetes.

However, islet transplantation is already limited by the supply of donor organs and an alternate source of islets is needed, with the two most obvious choices being porcine islets and human stem cells. The vigorous immune responses to xenogeneic tissues with not only the presence of preformed antibody, but also the brisk cellular immune response, will limit the use of porcine islets until these processes are better understood and can be controlled.12 There is great interest in finding a β-cell progenitor or stem cell source that can be expanded to a large enough quantity in culture, allowed to differentiate, and then transplanted. There have been several groups that have reported some initial success in creating insulin producing islet-like clusters from both mouse and human stem cell sources.13 Although the initial results have been encouraging under culture conditions, little evidence of function in animal models has been demonstrated thus far.

Another active area of interest is identification of individuals at risk for developing diabetes before the onset of hyperglycemia and intervention to halt the progression of the disease. Numerous studies have attempted to slow or stop the development of diabetes in at-risk patients by using immunosuppression, antigen exposure, antioxidant therapy and other techniques.14,15 Although no “silver bullet” has been identified yet in preventing type 1 diabetes, it is the hope that some day prevention will be possible, making transplantation a treatment of the past.

**References**


**Help Support the International Immunogenetics Summer School**

The International Immunogenetics Summer School will be held for the first time in 2004. This small course is designed to educate PhD candidates and recently graduated postdoctoral fellows in the latest advancements in subjects such as transplantation, autoimmunity, the host-pathogen response, innate immunity, and the evolution of the immune response. The school will be held in Europe in 2004 and will move to other locations in following years.

To keep costs to a minimum for the students, the course planners have received commitments of support from ASHI, EFI, and ASEATTA. Now they need your help. At its 2003 Annual Meeting, ASHI will hold a silent auction to benefit the International Immunogenetics Summer School. We are asking for donations of unique, attractive and useful items that can be auctioned off at the banquet. Gift baskets, works of art, bottles of wine, jewelry, and gift certificates are just some of the many items that could be contributed. Please contact Donna Phelan (dlp2368@bjc.org) or Amy Hahn (hahna@mail.amc.edu) to let us know what you’ll be contributing or if you have any questions.

We hope that ASHI and the International Immunogenetics Summer School can count on your support as we train tomorrow’s leaders in the field of Immunogenetics.