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# Islet cell transplantation

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ABSTRACT

Islet transplantation has become a promising treatment for selected patients with type 1 diabetes. Here we provide an overview of the procedure including its history, the process of donor selection, and the techniques and procedures involved in a successful transplant. A brief overview of the current immunosuppressive regimens, the long-term follow-up and the reported outcomes will also be discussed. While islet transplantation is currently generally reserved for adults with type 1 diabetes with severe hypoglycemia or glycemic lability, we herein consider the possibility of its application to the pediatric population.



## Introduction

Diabetes is a tremendous medical burden worldwide. It currently affects more than 200 million people worldwide, with projections to 5% of the world population by 2025.[1] The most severe form of this disease, type 1 diabetes, representing approximately 10% of all cases of diabetes, results from the autoimmune destruction of β-cells within the islets of Langerhans. Since the discovery of insulin, diabetes has become a treatable condition. However, even with optimal insulin therapy, many patients still suffer from a multitude of complications of diabetes including nephropathy, neuropathy, retinopathy, peripheral vascular disease, and coronary artery disease. Intensive insulin therapy was formally tested in the Diabetes Control and Complications Trials (DCCT).[2–4] While this therapy does partially mitigate cardiovascular disease, retinopathy, and nephropathy, there was a substantial increase in the number of adverse hypoglycemic events.[3] Innovative means to tighten glycemic control with insulin pumps, dynamic continuous glucose monitoring, and closed loop systems have recently been developed and offer promise of improved control, reduced hypoglycemic risk, and maybe improved protection from secondary diabetic complications but still fall short of a robust cure for diabetes. In parallel, efforts to preserve and restore endogenous beta cell (and islet) mass have continued, both with whole vascularized pancreas transplantation and with islet transplantation. Whole pancreas transplantation was first attempted in 1966,[5] and while early results were dismal, considerable advances in surgical technique, immunosuppression, and management have considerably improved the safety and efficacy of this approach. However, whole pancreas transplantation requires a major intra-abdominal surgical procedure, with significant morbidity and mortality. In addition, conceptually, it is really only the endocrine tissue that people with type 1 diabetes need replacing, and therefore a whole pancreas involves the transplantation of about 98% of pancreatic tissue that is not required. The presence of the exocrine pancreas also contributes to the risk of peri-operative infection, graft thrombosis, and graft pancreatitis. Transplantation of the islets of Langerhans alone therefore, is considered to be more refined and less risky for patients, but has, until the last decade, resulted in poor clinical success. We herein focus on clinical and experimental islet transplantation and discuss its possible applicability to the pediatric population.

## History of islet transplantation

While islet transplantation in adults has advanced considerably in the first decade of the 21st century, the first recorded attempt at islet transplantation occurred in 1893 in a 13-year-old child dying from the ravages of diabetes. A physician and surgeon at the Bristol Royal Infirmary in the UK implanted “minced” pieces of a recently slaughtered sheep's pancreas beneath the subcutaneous tissues in an attempt to reverse his ketoacidotic state—almost 30 years before the discovery of insulin.[6] While the child inevitably succumbed three days after the first attempt at an islet xenograft, this represented the first attempt at transplantation of β-cells. The discovery of insulin in Toronto in 1922 and its subsequent miraculous ability to bring patients with type 1 diabetes back from death's door inevitably led to further attempts at beta cell

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transplantation being placed on the "back burner." It took nearly 20 years for the euphoria to wear off, with the eventual realization that aside from the inconvenience of repeated glucose measurements and insulin injections, many patients with diabetes suffered devastating secondary complications. Whole organ pancreas transplantation was developed as a means to potentially combat these complications and provide restoration of normal β-cell reserve.

Moskalewski[7] and colleagues first began to isolate pancreatic islets for experimental study using collagenase to digest away the exocrine pancreas in guinea pigs. Hellerstrom used a fine dissecting microscope around the same period also with the aim of isolating islets for physiological studies. Paul E. Lacy, the "Godfather of islet transplantation," was the first to completely cure chemically induced diabetes in rats, and his group went on to compare different sites for islet implantation and found that the portal vein was a very favorable site for injection of islets, especially compared with free intraperitoneal implantation.[8,9] Further refinements including islet purification using density gradient separation[10] coupled with intraportal islet embolization led to the complete reversal of experimental rodent diabetes.

While diabetes reversal in these murine models had become routine, the case was not the same for the early attempts at clinical islet transplantation during the 1970s and 1980s. The translation of murine islet isolation to the human pancreas was not straightforward, with substantial risk of portal hypertension and disseminated intravascular coagulation in the early experience.[11] These risks, coupled with a complete lack of efficacy in most cases in the clinic, gave islet transplantation a tarnished reputation that it struggled to overcome. Researchers turned to large animal models to further improve the procedure, with total pancreatectomy and islet autotransplantation. Here, techniques for pancreatic digestion and islet isolation were optimized[12–14] and islets could indeed function in the intraportal implantation site,[12] even for long periods.[15] Others were even able to provide long-term islet function in large animal allotransplantation models using ciclosporin.[16]

The transition to clinical islet transplantation still required a major leap, as the techniques used in the large animal models failed to yield sufficient islet mass to have any utility in the clinic. In 1989, Dr. Camillo Ricordi developed the so-called "automated digestion method," with intraductal collagenase, by chopping the pancreas and vigorously shaking the pancreatic tissue during digestion within the "Ricordi Chamber."[17] Improvements in techniques for islet purification from the Leicester Group in the UK led to the introduction of the COBE 2991 cell apheresis system for continuous density gradient purification of human islets.[18] This step was also crucial, as it reduced the volume of the islet-containing purified tissue down to a few milliliters, thereby avoiding risks associated with portal vein thrombosis. The first reported case of insulin independence after islet transplantation was reported by David Scharp and colleagues from Dr. Paul Lacy's group in St. Louis, USA in a type 1 diabetic patient.[19] While the freedom from insulin only lasted about a month, subsequent clinical attempts by others including groups in Edmonton, Pittsburgh, Giessen in Germany, and the Milan group led to occasional startling successes, with insulin independence lasting up to 2 years in the odd case.[20,21] The importance of autoimmunity as a factor in graft loss was highlighted in the high rate of insulin independence in the Pittsburgh series of islet allotransplants in cluster liver–small bowel and islet transplants in those with surgically induced diabetes from pancreatectomy at the time of neuroendocrine malignancies, using Ricordi's automated method, with up to 50% of subjects insulin free at 1 year, or until the patients succumbed from recurrence of their malignancies.[22] Outcomes were much less promising though in subjects with autoimmune type 1 diabetes, with poor islet function in combined kidney–islet transplantation.[23]

The quest for insulin independence continued in the 1990s. Several islet transplant centers in Europe, including Giessen, Milan, and the Geneva group, achieved insulin independence in up to 30% of recipients within the first year.[24] At this point, there had been over 450 attempts at islet transplantation, with less than 8% of patients achieving insulin independence.[25] It was very difficult to justify the use of potent immunosuppression and portal vein islet infusion in most type 1 diabetics. Indeed there was waning optimism as the millennium drew near.

This all changed in 2000 when the Edmonton Group published a series of seven consecutive patients—all of whom became insulin independent after islet transplantation, a completely unprecedented outcome at that time.[26] The regimen that they used became known as the "Edmonton Protocol" and this was soon implemented by other groups around the world. Keys to this success included transplantation of an adequate islet mass (> 10,000 islet equivalents per kg recipient body weight), immediate infusion of islets following islet isolation, and the avoidance of corticosteroids. Immunosuppression in this series consisted of sirolimus, low-dose tacrolimus, and an anti-CD25 antibody (daclizumab). These promising results reinvigorated the entire field of clinical islet transplantation. An international multicenter trial funded by the National Institutes of Health and the Immune Tolerance Network was subsequently published in 2006 with 58% of subjects attaining insulin independence and 36% remaining insulin independent at 2 years.[27] Some sites achieved 100% success, while others less experienced in islet preparation and management of systemic immunosuppression had much more limited success.

While the Edmonton Protocol provided considerable momentum in driving islet transplantation forward, it was the decades of dedicated research prior to that which allowed this milestone work to come to fruition. The early Edmonton success led to widespread enthusiasm, but the waning of complete insulin independence by 3–5 years after transplantation raised further concerns that islet transplantation could not deliver a permanent reversal of the diabetic state in patients. Improved donor selection, optimized techniques for organ donation and preservation, and the use of alternate cell sources, including xenotransplantation, stem cell therapy, and β-cell regeneration, may all help improve the long-term results of islet transplantation, enabling this treatment to fulfill its undoubted potential in the coming decades.

## Donor selection

While the success of the Edmonton Protocol centered around the avoidance of corticosteroids and the transplantation of an adequate islet mass,[26] there has been an increased understanding that the selection of an optimal pancreas donor can make a dramatic difference in outcomes. Both the number of islets obtained and the quality of these islets can be affected by a number of donor characteristics, including age, body mass index (BMI), and the cold ischemic time.

A study by Lakey et al.[28] retrospectively reviewed human islet isolation preparations and studied the effects of donor age on islet yield and function (insulin secretory capabilities). Older donors (51–65 years old) were more likely to yield an adequate amount of islets (83% compared to 37% in 19–28-year-old donors), however the secretory capabilities of these islets were significantly reduced. Others have confirmed these results and shown higher rates of diabetes reversal in immunodeficient diabetic mice receiving human islet grafts from younger donors.[29] While this would point to younger donors as "ideal" one must also realize that digestion of a young pancreas is technically more difficult. The more fibrous nature of the pancreatic substance of young donors considerably