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# Islet Transplantation – The Canadian Perspective

*A. M. J. Shapiro*

Clinical Islet Transplant Program, University of Alberta, Edmonton, Canada

*Corresponding Author*: A.M. James Shapiro, MD, PhD; e-mail: jshapiro@ualberta.ca

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**Abstract**

**This commentary discusses the evolution of islet transplantation in Canada over the past two decades and discusses the challenge and opportunity for more widespread availability of this therapy in other coun-tries, especially in the US.**

**Abbreviations**

IEQ: Islet Equivalents, T1D: Type 1 diabetes, HbA1c: Hemoglobin A1c, FDA: Food and Drug Administration, BLA: Biological Licensure, NIH: National Institutes of Health, cGMP: Clinical Good Manufacturing Practice.

On March 11th 1999 a 54-year-old schoolteacher with incapacitating recurrent hypoglycemic reactions and a 35 year history of type 1 diabetes underwent percutaneous intraportal delivery of over 370,000 islet equivalents (IEQ) in Edmonton. His hypoglycemic reactions resolved instantly, and his insulin requirements fell by half. A month later he received another 360,000 IEQ, and became the first patient to achieve insulin independence with a new steroid-free, sirolimus-based immunosuppressive protocol, known subsequently as the *Edmonton Protocol*. Six subsequent patients achieved similar success with stabilization of glycemic control, correction of hemoglobin A1 (HbA1c), with sustained periods of insulin independence[1]. This success was not Edmonton's alone, but built collaborative upon a prior quarter-century of innovation beginning with Paul Lacy's seminal islet transplants in mice, Camillo Ricordi's semi-automated method for high yield islet extraction from human donor pancreata, improved quality of collagenase enzymes, better techniques for islet purification and culture, advances in interventional radiology and advances in potent, 'islet-friendly' immune suppression[2].

Fortunately for us, on April 1st 2001 the Alberta Government rapidly embraced the effectiveness of islet transplantation, and in less than a year from the *New England Journal of Medicine* publication, our clinical islet program became a government-funded, non-research 'standard-of care' therapy, as part of the Province Wide Services transplantation portfolio. The regional organ donor programs across Canada strongly supported these efforts, ensuring that all pancreata across Canada were offered for islet isolation if they could not be used locally for whole pancreas transplantation. Since organ donation programs are funded provincially but supported and coordinated nationally in Canada, no charges are made for organ donation. We were further able to use commercial airline transportation through Air Canada without charge to the program. This provided many advantages and facilitated the integration of a busy islet isolation and transplant centre hub in Edmonton. Over the past 20 years, we have completed 669 intraportal islet transplants in Edmonton in 285 grateful T1D patients. While enthusiasm for islet transplantation grew locally within the province of Alberta, we still face difficulty with national recognition of islet transplantation as a non-research therapy in other remote provinces. This has more recently created challenges for non-Albertans seeking cell transplantation in Edmonton, as Alberta Health Services became increasingly reluctant to continue to offer a national transplant treatment to the rest of Canada without appropriate inter-provincial reimbursement. The still remains a challenge for our program and is definitely rate limiting in our ability to offer appropriate therapy. An innovative clinical islet program led by Garth Warnock in Vancouver BC established an important randomized cross-over controlled trial that further proved the benefit of islet transplantation in stabilizing retinopathy and nephropathy in patients with longstanding T1D[3]. A third newer clinical islet program led by Steven Paraskevas in Montreal QC is growing.

The big remaining question is why have islet programs in the US south of our borders have thus far failed to adopt clinical islet transplantation in a similar manner? It certainly is not through lack of desperate T1D patients – there are at least 10 times more brittle T1Ds in the US than in Canada. It is not through lack of technical expertise in islet manufacture[4], or in clinical interest at several leading centers[5]. And it certainly is not for lack of proof of efficacy of clinical islet transplantation. Indeed, a US led, National Institutes of Health (NIH) funded, major phase 3 trial by the Islet Consortium trials proved beyond doubt that islet transplantation is highly effective in eliminating risk of hypoglycemia with correction of HbA1c[6]. A randomized controlled study of islet vs. insulin in several European centers similarly proved superior metabolic outcomes[7].

Many of us assumed naively that within weeks of publication of the US phase 3 trial that the Food and Drug Administration (FDA) would grant Biological Licensure (BLA) to many of the US programs that participated in that trial. The NIH invested over $75 million in conducting that trial, with the expectation that a BLA would be rapidly forthcoming, and that the costs of routine islet transplantation and care would transfer to Medicare and Medicaid. In practice, this has been far more complex to deliver than anticipated. Individual university islet clinical good manufacturing practice (cGMP) centers have been expected to take on the role of an industrial manufacturing plant with prohibitive license-enabling start-up costs. The costs of obtaining access to good quality human donor pancreas organs remains prohibitive (and almost obscene) in the US. It is difficult to understand how a 15-minute surgical procedure that is already part of a multi-organ retrieval can cost centers upwards of $30,000 - $50,000 per pancreas. The procedure for isolating islets fails to yield sufficient islets for transplant about half of the time, and these costs become rapidly prohibitive. Several islet transplant centers in the US have chosen to bypass these challenges by focusing only on islet autotransplantation in patients with chronic pancreatitis.

While there have been many recent advances in T1D care including better insulins, hybrid closed loop pumps and other wearable technology including continuous glucose monitoring over recent years, only islet (and whole pancreas) transplantation can restore metabolic profiles to near normal. Having been innovators and leaders in islet transplantation for the past 25 years, it is surely high time that the US takes a new and easier path to make islet transplantation more available to those in need.

## Conflict of Interest:

No author declares a conflict of interest.

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