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## REVIEW

## Islet cell transplantation

P Srinivasan, G C Huang, S A Amiel, N D Heaton

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People with type 1 diabetes have normal exocrine pancreatic function, making islet cell rather than whole organ transplantation an attractive option. Achieving insulin independence in type 1 diabetes was the perceived goal of islet cell transplantation. The success of the Edmonton group in achieving this in a selected group of type 1 patients has led to renewed optimism that this treatment could eventually replace whole organ pancreas transplantation. However the long-term results of this treatment indicate that insulin independence is lost with time in a significant proportion of patients, although they may retain glycaemic stability. In this context, the indications for islet cell transplantation, which have evolved over the last 5 years, indicate that the patients who benefit most are those who experience severe hypoglycaemic reactions despite optimal insulin therapy. This review will summarise the history of islet cell transplantation, islet isolation techniques, the transplant procedure, immunosuppressive therapy, indications for islet cell transplantation, current clinical trials, the early UK islet cell transplant experience using the Edmonton protocol, and some of the challenges that lie ahead.

than whole organ transplantation an attractive option. Achieving insulin independence in type 1 diabetes was the perceived goal of islet cell transplantation. The success of the Edmonton group in achieving this in a selected group<sup>4</sup> of type 1 patients has led to renewed optimism that this treatment could eventually replace whole organ pancreas transplantation. Since this initial report a multicentre trial organised by the Immune Tolerance Network has reported reasonable success rates in experienced units.<sup>5,6</sup> However the long-term results of this therapy indicate that insulin independence is lost with time in a significant proportion of patients, although they may retain glycaemic stability. In this context, the indications for islet cell transplantation, which have evolved over the last 5 years, indicate that the patients who benefit most are those who experience severe hypoglycaemic reactions despite optimal insulin therapy. It is also postulated that the degree of metabolic control achieved in these patients should have a positive impact on the advancement of secondary complications, but this remains to be seen in long-term studies. This review will summarise the history of islet cell transplantation, islet isolation techniques, the transplant procedure, immunosuppressive therapy, indications for islet cell transplantation, current clinical trials, the early UK islet cell transplant experience using the Edmonton protocol, and some of the challenges that lie ahead.

The Diabetes Control and Complications Trial<sup>1</sup> (DCCT) in 1993 published the standard of care for patients with type 1 diabetes mellitus. This study concluded that intensive insulin therapy improved glycaemic control and outcomes in terms of secondary complication rates, but at the cost of severe hypoglycaemic reactions in a significant proportion (65%) of patients. More recent improvements in insulin preparations, glucose home monitoring and insulin pump therapy have further helped patients to attain better glycaemic control without frequent episodes of hypoglycaemia. However, achieving normal glycosylated haemoglobin levels is still an issue in these patients.

Parallel success with whole pancreas transplantation in selected patients with type 1 diabetes mellitus and autonomic insufficiency in achieving normal glycosylated haemoglobin levels has prompted the American Diabetes Association (ADA) to recommend the procedure in 2000.<sup>2</sup> In 2003<sup>3</sup> the ADA recommended that simultaneous pancreas transplantation should be considered at the time of kidney transplantation and pancreas only transplantation should be provided for patients with very poor metabolic control, particularly when this presented as intractable recurrent severe hypoglycaemia.

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## HISTORY

Islet cell transplantation was reported as early as 1893 when Watson-Williams and Harshant transplanted minced sheep pancreas into the thigh of a young patient with diabetic ketoacidosis. Although the boy's glycosuria improved transiently for 24 h, the procedure subsequently failed, presumably due to rejection from lack of immunosuppression and ischaemia due to implantation in a poorly vascularised site. In 1921 Best and Banting discovered insulin after abandoning pancreas transplantation experiments; although hypoglycaemic insulin reactions were reported from its early use in 1923, insulin remained the only treatment for insulin deficient diabetes until the 1970s. From the 1980s onward the advent of and improvements in immunosuppression made whole organ transplantation a clinical reality. The next milestone was the

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**Abbreviations:** ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; BMI, body mass index; DCCT, Diabetes Control and Complications Trial; ETDRS, Early Treatment Diabetic Retinopathy Study; IBMIR, instant blood mediated inflammatory reaction; IEQ, islet equivalents; MMF, mycophenolate mofetil; PFCs, perfluorohydrocarbons

reversal of diabetes using islet isografts from normal rats in streptozocin induced diabetic rats reported by Ballinger and Lacey<sup>7</sup> in 1972. Initial attempts at islet autografting in humans were reported in 1980 in a series of 10 patients<sup>8</sup> with painful chronic pancreatitis. Insulin independence was achieved in three patients for 1, 9 and 38 months, respectively. The removed pancreas was digested with collagenase and the non-purified preparation infused into the patient's portal venous circulation within two-and-a-half hours of removal. In 1992, Pyzdrowski reported that 265 000 islets were sufficient to achieve insulin independence<sup>9</sup> (the normal pancreas has roughly one million islets).

A report of allogenic islet cell transplantation in humans appeared in 1980, with the recipient achieving insulin independence with normal glucose levels at 9 months follow-up.<sup>10</sup> Reports of successful islet cell transplantation using conventional immunosuppression have appeared since, but insulin independence at 1 year was less than 10%. Interest in islet cell transplantation was reawakened in 2000 after Shapiro *et al*<sup>4</sup> published successful outcome in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppression regimen. Their novel approach utilised fresh islets from multiple donors injected into the main portal vein on size-restricted, C peptide negative type 1 diabetic patients with hypoglycaemic unawareness, using a steroid-free immunosuppression regimen that included dacluzimab, sirolimus and low dose tacrolimus. Since this initial report a multi-centre trial organised by the Immune Tolerance Network to assess the reproducibility of the Edmonton study has reported that reasonable success rates can be achieved in experienced centres.

## INDICATIONS FOR ISLET CELL TRANSPLANTATION

The ideal candidate for islet cell transplantation in its current form is an insulin-sensitive person with type 1 diabetes, who has poor subjective recognition of hypoglycaemia and is experiencing recurrent severe hypoglycaemic episodes, despite optimised medical treatment. The indication of intractable hypoglycaemia is recognised throughout the global islet transplant community, as it is strongly evidence based.<sup>11</sup> There is yet no firm evidence for the ability of islet transplantation to affect the progression of complications or help with recurrent hyperglycaemia. With current insulin therapy and insulin pump delivery the majority of patients experiencing hypoglycaemia can be managed tolerably with improved glycosylated values and reduced frequency of hypoglycaemic reactions.<sup>12</sup> However, there are a small number of patients who, despite optimal insulin therapy, are unable to control their hypoglycaemia. It is this group who should be considered for islet cell transplantation. Even in the absence of insulin independence after transplantation, the presence of functioning islets appears to protect against refractory hypoglycaemia. Although insulin independence remains the stated aim of islet cell transplantation,<sup>11</sup> it is increasingly recognised that patients who are cured of refractory hypoglycaemia with islet cell transplantation deem the procedure as life changing. These patients may require minimal exogenous insulin, but in the face of normalising HbA1c and the abolition of hypoglycaemia this is increasingly being recognised as treatment success.<sup>13–16</sup>

In view of the current organ shortage, it would be impossible to transplant all patients with type 1 diabetes with islets just to improve glycaemic control, but this procedure is life saving in a highly selected group of patients with severe disabling hypoglycaemic unawareness refractory to intense insulin therapy. These patients are rare, as optimised conservative care<sup>17</sup> eliminates symptoms in the majority.

## Donor evaluation

Successful islet isolation has been correlated with several donor variables including donor age,<sup>18</sup> body mass index<sup>19</sup> and retrieval by the local surgical team.<sup>20</sup> Poor islet yield has been associated with donor hyperglycaemia,<sup>21</sup> increased cold ischaemia<sup>19</sup> and duration/frequency of donor cardiac arrest.<sup>19</sup> Effective separation of islets from exocrine tissue is critical to the recovery of islets following purification; islets from paediatric donors have been reported to be difficult to separate from exocrine components without excessive fragmentation. Isolations from young (2–15-year-old) and old (56–69-year-old) donors when grouped together were reported to be associated with reduced yields as compared with adult pancreases (18–55-year-old).<sup>18</sup> Donors with an increased body mass index (BMI)<sup>19</sup> resulted in a significantly higher recovery of islets, and pancreatic insulin content has been associated with increased donor body surface area. However, the subjective appearance of the pancreas as excessively steatotic or damaged upon arrival is also reported to be associated with reduced isolation success.

Uncontrolled hyperglycaemia with an elevated minimum blood glucose value of >15 mmol/l in donors has been associated with reduced isolation success and in that context it has also been suggested that abnormal donor HbA1c values may predict the potential of type 2 diabetes in donors. The duration of cold preservation for longer than five-and-a-half hours and donor cardiac arrest of greater than 5 min have also been reported to be associated with reduced islet isolation success.<sup>19</sup> The surgical technique by which the pancreas is retrieved is also critical to successful islet isolation.<sup>22</sup> The pancreas must be removed intact, as a damaged organ cannot be adequately distended with the enzymes required to begin the isolation process, as described below.

## Recipient evaluation

Recipient assessment and selection is key to the success of islet transplantation. The following is based on our own experience of the investigation and management of patients with problematic hypoglycaemia,<sup>23</sup> pre-dating our own islet transplant programme and the recommendations of large islet programmes such as Edmonton, Miami and Minnesota. Type 1 diabetic patients enrolled for islet transplantation should be insulin sensitive, C-peptide negative and have a documented problem of hypoglycaemia unawareness and counterregulatory failure associated with recurrent severe hypoglycaemia. The requirement for insulin sensitivity is because the procedure is not sufficiently efficient to overcome any significant insulin resistance. We now use euglycaemic insulin clamping, taking into consideration the therapeutic dose of insulin the patient is using to assess this. The work-up of these patients includes thorough clinical, haematological, biochemical, renal and liver function evaluation in addition to psychological assessment and exclusion of current malignant disease (box 1). Of note, the majority of patients enrolled for islet transplantation have had diabetes for several years and appear to belong to a group of patients that escape end-stage renal failure.

It is important that treatable contributors to hypoglycaemic risk are excluded. Deficiencies in hyperglycaemic hormones, such as occur in Addison's disease (cortisol deficiency), growth hormone deficiency or panhypopituitarism must be actively excluded or treated where present. Hypothyroidism, by reducing insulin clearance, can also increase hypoglycaemia risk. Malabsorption, such as may occur with coeliac disease (being also autoimmune and therefore relatively more common in the type 1 diabetic population), may also underlie hypoglycaemic risk in a small number of patients. Hypoglycaemia associated with excess alcohol intake or other substance abuse is better treated by addressing the root cause. Some patients with diabetes may be on non-physiological insulin regimens and

### Box 1 Pre-operative work-up schedule for islet transplantation patients

#### Inclusion criteria

- Type 1 diabetes, duration >5 years
- Age 18–65 years
- C-peptide negative, <0.16 nmol/l with no increment at 6 min after 1 mg glucagon intravenously
- GFR within normal range for age
- First priority: Recurrent severe hypoglycaemia (SH) of at least one year's duration, with at least 2 episodes of SH (coma, seizure, hospitalisation with intravenous glucose or intramuscular glucagon administration with *documented* evidence of blood glucose concentration <2 mmol/l and no other diagnosis) per 6 months, *despite evidence of compliance with expert medical advice and intensified insulin therapy*
- Second priority: Progression of microvascular complications (pre-proliferative or proliferative retinopathy; macular oedema; worsening microalbuminuria demonstrated to be incremental over at least 2 years, with at least 2 early morning albumin creatinine ratios demonstrating deterioration; painful neuropathy of increasing severity *despite compliance with attempts to optimise diabetes, hypertension and ACE inhibitor therapy under expert medical supervision for at least 6 months*)

Note: patients with untreated proliferative retinopathy or proteinuria will not be eligible

#### Exclusion criteria

- C-peptide positivity (>0.3 ng/ml after stimulation)
- Renal impairment (creatinine >135 µmol/l, or creatinine clearance <85 ml/min/1.73 m<sup>2</sup>)
- GFR above the normal range for age and sex
- Macroalbuminuria (AER >300 mg/24 h)
- Body mass index ≥28
- Insulin requirement >0.7 units/kg body weight per day
- HbA1c >9%
- Untreated proliferative retinopathy
- Requiring steroids for treatment of other medical condition
- High index of suspicion of non-compliance with conventional therapy
- Portal hypertension, gall stones or liver haemangioma on baseline ultrasound
- Active or chronic hepatitis C or B, HIV, tuberculosis
- Active gastric or duodenal ulcer
- Likely allergy to immunosuppressive antibodies
- Neoplasia if not free of relapse >5 years
- Recent myocardial infarction or uncorrected myocardial ischaemia
- Inability to reach hospital within 2 h of notification
- Uncontrolled hyperlipidaemia (fasting LDL cholesterol >3.4 mmol/l, triglycerides >2.4 mmol/l)
- Abnormal liver function tests (persistently >1.5 × upper limit of normal)
- Anaemia
- Addison's disease (untreated) or untreated coeliac disease
- On anticoagulants (excluding aspirin)
- Alcohol or other substance abuse
- Inability to provide informed consent

- Previous transplant or sensitisation
- Pregnancy or plans for pregnancy (including fatherhood)

ACE, angiotensin-converting enzyme; AER, albumin excretion rate; GFR, glomerular filtration rate; LDL, low density lipoprotein.

failure to reduce insulin after alcohol or exercise exposure may contribute to problematic hypoglycaemia. Such issues should be diagnosed and treated as far as possible before committing a patient to a transplant programme.

Our patients have had type 1 diabetes mellitus for more than 5 years, complicated by the following situations that persist despite intensive efforts with insulin management (defined as a minimum of monitoring glucose values at home no less than three times each day and by the administration of three or more insulin injections each day or use of continuous subcutaneous insulin infusion). Such management must be monitored in close cooperation with a diabetologist experienced in intensified therapy and is usually expected to include exposure to structured education in insulin management and a trial of insulin pump therapy if the patient is willing.

The complicating situations despite optimal insulin therapy are:

- Reduced awareness of hypoglycaemia, as defined by the absence of adequate autonomic symptoms at plasma glucose levels of <3 mmol/dl; and
- Metabolic lability/instability, characterised by two or more episodes of severe hypoglycaemia (defined as an event with symptoms consistent with hypoglycaemia in which the subject requires the assistance of another person and which is associated with a blood glucose below 2.5 mmol/dl) in a year. The quality of hypoglycaemia awareness can be assessed by the Clark questionnaire, and the Edmonton group<sup>11–17</sup> have devised a score for quantifying the impact of hypoglycaemia which is proving a useful tool; we also document counterregulatory deficit, using a clamp technique to apply a slow, stepped fall in plasma glucose during which the hormonal, metabolic and cognitive function responses can be assessed.<sup>24</sup> An alternative definition of metabolic instability is the occurrence of two or more hospital visits for diabetic ketoacidosis over the last year, in the absence of a clear predisposing illness; however, this is not an indication we have yet used, in part because these patients tend to have very high glycated haemoglobin which predicts significant insulin resistance, and also because there are often concerns about treatment adherence in this patient group and at present there is no evidence that adherence with non-insulin therapies will be any easier for them. In contrast to the situation of the recurrently hypoglycaemic patient, there is also no evidence yet that this hyperglycaemic instability responds to islet cell transplantation.

The third described indication for islet transplant is defined as progressive secondary complications of diabetes, despite efforts at optimal glucose control as defined by:

- *retinopathy*—a minimum of a three step progression using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system, or an equivalent progression as certified by an ophthalmologist familiar with diabetic retinopathy; or
- *nephropathy*—a confirmed rise of 50 µg/min (72 mg/24 h) of microalbuminuria or greater over at least three months (beginning anytime within the past two years) despite the use of an angiotensin-converting enzyme (ACE) inhibitor; or
- *neuropathy*—persistent or progressing autonomic neuropathy (gastroparesis, postural hypotension, neuropathic bowel or



bladder) or persistent or progressing severe peripheral painful neuropathy not responding to usual management (for example, tricyclics, gabapentin, or carbamazepine).

However, it should be noted that there are as yet no data to show that islet transplantation will effect improvement in rate of complication progression and patients with established nephropathy (proteinuria or glomerular filtration rate (GFR) <60 ml/min are excluded because of the potential nephrotoxicity of the current immunosuppression regimens. In general therefore, islet transplantation is currently most suitable for the hypoglycaemia indication. Careful documentation of all possible diabetic complications before transplantation is essential, to exclude possible contributors to glycaemic instability and to document the effect of islet cell transplantation on progression of complications. It is also important to assess the patient for macrovascular disease, as significant large vessel or coronary disease should probably be treated before transplantation. The psychological assessment is also important both to diagnose (pre-existing) and treat significant disease such as depression and also to allow robust assessment of quality of life pre- and post-transplantation.

### Islet isolation and yield

The total number of islets in a human pancreas has been determined using morphometrical analysis to vary between 3.6–14.8 million. There are 1.5 million islets with a diameter >23 µm and those with a diameter of 100 µm constitute 20% of the total number, but account for 75% of the total islet volume. Islets account for about 1.3% of the volume of the pancreas with a progressive increase in concentration from head to tail. Most centres with an active clinical islet cell transplant programme obtain 300–600 000 islet equivalents (IEQ)/pancreas after purification, which is about 50% of the islet tissue content.

Modern islet cell isolation involves the procurement of healthy pancreas from a brain stem dead, heart-beating donor using standardised techniques<sup>22</sup> developed for retrieval of whole pancreas for transplantation. More recently pancreases from non-heart beating<sup>25</sup> and living donors<sup>26–28</sup> have also been utilised successfully. The pancreas is perfused and preserved in University of Wisconsin solution and transported to the islet isolation laboratory in ice. Given the oxygen-rich environment of the islets in the native pancreas, it is conceivable that islets are highly susceptible to irreversible damage following prolonged ischaemia. The use of continuously oxygenated perfluorohydrocarbons (PFCs), known for their high oxygen-solubility coefficients, in a two-layer culture with standard University of Wisconsin preservation media, has extended the acceptable cold ischaemic time and has now been shown to improve islet cell function.

The pancreatic duct is cannulated and collagenase infused to enzymatically help separate islets from exocrine and ductal tissues. The remnant tissue is purified by Ficoll density-gradient centrifugation. With the currently available technology most of the small sized islets are lost, however, the greater part of the islet volume is successfully retrieved. A number of the largest islets will be damaged during the procedure. These, however, contribute only a small fraction of the total as medium sized islets contribute the most significant volume. Although unpurified islets have been used successfully in islet auto-transplantation, proponents of purification argue that infusion of a smaller volume of cells lowers the risk of portal vein thrombosis and portal hypertension.

Islet yield, purity, and cell viability are assessed using caspase 3, terminal deoxynucleotidyl transferase-mediated biotin-deoxyuridine 5-triphosphate nick-end labelling stain and insulin secretion *in vitro*, respectively. Improving the yield is dependent on a number of variables including the health and medications of the donor, the surgical expertise and care taken by the surgical retrieval team, short cold and warm ischaemia times,

and the timeliness of transportation of the organ to the isolation centre. Transportation of pancreas using the “two layer method”, which sandwiches the pancreas between the bottom layer of perfluorodecalin saturated with oxygen and the top layer of University of Wisconsin preservation solution, has resulted in better function of islets even from marginal donors.<sup>29</sup> Islet culture before clinical transplantation<sup>30</sup> ensures the transplantation of only the more robust cells and is emerging as standard practice in larger volume centres. It allows the transplant procedure to be performed under elective conditions, with earlier establishment of immunosuppression and decreased travel demands on recipients.

### The transplant procedure

The procedure takes place in the radiology suite and involves percutaneous transhepatic placement under local anaesthetic of a size 4 FG catheter into the main portal vein under fluoroscopic guidance or ultrasound guidance, although a laparoscopic approach has also been used. The portal venous pressure is checked and, if normal (8–10 mm Hg), a single preparation lot with a packed cell volume of ≤5 ml of purified islets is gently dispersed in approximately 150 ml of transplant medium (M199-BioWhittaker, Verviers, Belgium) from a suspended bag containing heparin with intermittent portal pressure monitoring. After completion of the infusion the entry tract is plugged with a haemostatic sealant and the catheter withdrawn. It has been suggested that one reason for the previous poor results of allografted human islet tissue was due to the damaging rapid clotting process termed the instant blood mediated inflammatory reaction (IBMIR) that occurs when islets are in contact with blood.<sup>31</sup> This affected the survival of newly infused islets and early attempts did not use anticoagulation with the islet preparation. Heparin has been shown to reduce IBMIR and its addition to the suspension of islets has been suggested as one of the reasons for the success of the Edmonton protocol.

Most patients require only a short hospital stay of 1–2 days. However, studies comparing islet cell to whole pancreas transplantation reported it to be more expensive due to increased costs of isolation and the use of multiple donor pancreases.

The potential complications<sup>32–33</sup> of an infusion into the liver include bleeding, portal vein thrombosis and portal hypertension. More recently the percutaneous tract is plugged with a haemosealant<sup>34</sup> before withdrawing the cannula from the liver to reduce the chance of bleeding. These complications can potentially be life threatening and underscore the importance of a multidisciplinary team that includes a specialist with expertise in the field of interventional liver radiology.

### Immunosuppression

Current success in whole organ transplantation is based on combination immunosuppression using calcineurin inhibitors and steroids. The development of a steroid-free immunosuppression protocol using a combination of sirolimus and tacrolimus by the Edmonton group resulted in a notably improved outcome of islet cell transplantation and led to many transplant centres utilising this regimen. While the combination of sirolimus and low-dose tacrolimus has helped move islet cell transplantation forward, these drugs are not ideal. Both drugs act by binding to FK binding receptors, have similar targets of distribution, and as a result have a number of adverse effects<sup>29</sup> in islet recipients, including painful mouth ulceration, peripheral oedema, proteinuria (sirolimus exerts an antiproliferative effect in renal tubular cells and may hinder recovery of an injured kidney), hypercholesterolaemia and hypertension.

Although the majority of patients are managed long term on the sirolimus and tacrolimus combination, some may require conversion to mycophenolate mofetil (MMF) for side-effects. Successful MMF conversion from sirolimus has resulted in improvements in

pedal oedema, mouth ulcers and nephrotoxicity without compromising graft function. With anticipated progress in current clinical trials it is likely that these immunosuppressants will be replaced by less toxic and more potent therapies in the future.

### Current clinical results

Following the success of the Edmonton steroid-free immunosuppression protocol, over 43 institutions worldwide have transplanted at least 470 patients up to May 2005. The Immune Tolerance Network has organised a nine-centre trial designed to evaluate the reproducibility of the Edmonton protocol in 36 patients. The American Transplant Congress in June 2003 reported on these patients with a median follow-up of 9 months.<sup>5-6</sup> A 90% insulin-free rate was demonstrated in three centres (Edmonton, Minneapolis and Miami) with longstanding experience in the field, while the average rate of insulin independence among the remaining six sites was 23%. Twelve patients achieved insulin independence (five achieving insulin independence after one infusion, five after two infusions, and two patients required three infusions). The overall success rate, in terms of insulin independence, was 52%. In the UK five patients have been transplanted in our centre, with facilities to isolate islets in at other centres in London and Oxford contributing a further five patients to the UK experience. The charity Diabetes UK supports the clinical costs of the procedures and there are plans to expand transplantation centres ideally using the currently active isolation laboratories, if the international successes are reproducible in the UK.

The rates of insulin independence achieved currently vary widely, with experienced centres achieving insulin independence in over 80% of recipients while those with less experience achieving insulin independence in 0–63% at short-term follow-up. Our own centre has achieved insulin independence in two of five recipients transplanted. Post-transplant there appears to be a progressive loss of insulin independence over time, leaving 50% of patients insulin-free at 3 years. Recent reports from Edmonton suggest that although insulin independence wanes with time, 83% of patients demonstrate islet function at 5 years when assessed by C-peptide secretion.<sup>35</sup> Furthermore the HbA1c level was well controlled in those off insulin (6.4%, range 6.1–6.7%) and in those back on insulin but C-peptide positive (6.7%, 5.9–7.5%), and higher in those who lost all graft function (9.0%, 6.7–9.3%) ( $p < 0.05$ ). Those who resumed insulin therapy did not appear more insulin resistant compared with those off insulin and required half their pretransplant insulin dose. However, they had a lower increment of C-peptide to a standard meal challenge (mean (SD) 0.44 (0.06) vs 0.76 (0.06) nmol/L,  $p < 0.001$ ). Furthermore there is demonstrable improvement in symptom control and metabolic stability. In a recent report of islet transplantation compared with whole pancreas transplantation in renal transplant recipients, diabetic control was no different at 3 years between the groups, despite return to insulin therapy in many of the islet recipients.<sup>36</sup> Potential reasons for the decay in rates of insulin independence include chronic allograft rejection, undiagnosed acute rejection, local islet cell toxicity from immunosuppressive drugs, recurrent autoimmunity, intercurrent infection and failure of islet cells to regenerate.

### The steps ahead

With the momentum created by the Edmonton protocol, islet cell transplantation is being performed more widely.<sup>37–39</sup> The challenge is to continue to improve early results and to try to sustain cell function long term. An in-depth study of factors influencing the decay in islet function is looking at serial islet graft biopsies, serological analysis of donor sensitisation, cytokine gene activity (granzyme B) and changes in autoantibody status and T lymphocyte function, and should provide valuable information over time.

The inability to diagnose early rejection in cell transplantation remains a problem, particularly with islets.<sup>40–42</sup> The relatively small mass of cells transplanted means that there is a small functional reserve and it is unlikely that sufficient islets survive a single episode of acute rejection. Newer immunosuppressive therapies may help to suppress acute rejection, such as LEA29Y, a co-stimulatory signal blocker found to be highly effective in primate trials which is currently being evaluated in Edmonton and Emory.<sup>42</sup> FTY720, a lymphocyte homing agent, is effective in controlling autoimmunity in NOD mice and in promoting marginal mass islet transplants in primates, and is due for evaluation in Miami, Minnesota and Edmonton shortly.<sup>43</sup>

The ultimate goal, however, remains the induction of tolerance. Current regimens<sup>44</sup> are using a combination of anti-thymocyte globulin and rituximab (anti-CD20). The non Fc binding HOKT3- $\gamma$ 1-ala-ala- antibody developed by Bluestone *et al* has been effective in abrogating autoimmunity in new-onset diabetes and has facilitated single-donor islet transplant success in ongoing trials at the University of Minnesota. A potent, diphtheria-conjugated anti-CD3 immunotoxin combined with deoxyspergualin has also shown robust tolerance induction in a series of primates at the University of Alabama. The results of these experiments are awaiting evaluation in humans.

Although many implantation sites such as liver, spleen, subcapsular space or cortex of kidney, pleural cavity and thymus have been evaluated, the liver has gained popularity over the spleen largely due to ease of access and lack of major complications. It is possible, however, that the intrahepatic islets are exposed to environmental toxins, particularly medications, absorbed from the gastrointestinal tract. Furthermore, although intrahepatic islets appear to contain healthy  $\alpha$  cells that process and secrete glucagon and respond to intravenous arginine, they fail to respond to hypoglycaemia. This is a relevant factor, as not all recipients remain insulin independent for the rest of their lives and thus would benefit from having a glucagon response. The protection from hypoglycaemia that these patients maintain therefore would seem to be the result of humorally controlled release of insulin in response to hypoglycaemia. Extrahepatic sites that could be considered include the peritoneal cavity and omental pouches where it would be possible to infuse unpurified islets. Reduced purification may increase the chances of  $\beta$  cell regeneration, although this remains to be shown. Islets implanted in biodegradable scaffolding improves the function of extrahepatically transplanted islets compared to islets transplanted without a scaffold and have been shown to restore diabetic animals to normoglycaemia.<sup>45</sup> There is increasing interest in basic science research into the potential use of islet surrogates. These include islet expansion, islet cell microencapsulation in natrium cellulose sulfate encapsulated islet xenografts, human islet cell lines and embryonic stem cells. The establishment of human  $\beta$  cell lines capable of secreting insulin in response to glucose in vivo awaits reproducibility. Selective use of non-heart beating donor pancreas resuscitated by the two-layer preservation appears to be another viable alternative source of islets.

Early graft failure due to islet emboli represents a practical problem following intraportal islet transplantation. The strategy of liver ischaemic-preconditioning to prevent early islet destruction in a model of syngeneic islet transplantation in STZ induced diabetic mice has been reported.<sup>46</sup> Pretreatment of donors with anti-inflammatory and anti-apoptotic agents such as 17( $\beta$ )-estradiol or atorvastatin could potentially mitigate the negative impact of islet damage induced by brain death. Immune depletion of donor passenger lymphocytes by donor pretreatment with agents such as alemtuzumab<sup>47</sup> may enhance islet survival by reducing islet sensitisation.

Finally, to make islet cell transplantation more readily available, there needs to be an increase in donor numbers. United Network for Organ Sharing (UNOS) data in North America revealed that only 23.8% of the potential 6182 multi-organ donors were procured or used for pancreas or islet cell transplantation. The situation is even less promising in the UK.<sup>48</sup> The number of heart beating donors in the UK was 12.3 per million population, which is one of the lowest rates in Western Europe. Spain has an exceptional rate of 33.0 per million population but many other countries in Europe have rates between 13–22 per million population. This could be more effectively addressed by legislation and developing an infrastructure based on the Spanish or “Italian” model which is the result of a presumed consent law allowing organ removal unless the person has opted out of donation. The report of living donor islet transplantation in Japan with better initial graft function holds potential in the longer term for countries where cadaveric donation is not permitted.

In summary, significant progress has occurred in the field of clinical islet cell transplantation over the last 5 years.<sup>49–51</sup> Opportunities lie ahead with the development of potentially “islet friendly” immunosuppressants, the possibility of tolerance induction, new sources of islets, and improvements in islet yield and implantation. Given these emerging opportunities it is likely that insulin sensitive patients with type 1 diabetes will benefit. Currently patients with hypoglycaemic unawareness are considered ideal candidates. The current results justify an evaluation in patients already receiving immunosuppression after kidney transplantation.

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