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Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis

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1. Introduction

Total pancreatectomy (TP) or near-total pancreatectomy with islet auto-transplantation (IAT) to treat chronic pancreatitis (CP) was first done in 1977 at the University of Minnesota (UMN) (Sutherland et al., 1978). The idea evolved from a desire to compare metabolic outcomes between islet autografts in pancreatectomized individuals, who could not reject their graft, and islet allografts done to treat type 1 diabetes, to understand why the latter failed (was it for technical or immunologic reasons? (Najarian et al., 1979). The main rationale from the beginning, however, was to relieve the pain of CP in patients in whom other measures had failed (Morrow et al., 1984), and to preserve beta (β)-cell mass and insulin secretory capacity in order to prevent or minimize the otherwise inevitable surgical diabetes (Blondet et al., 2007; Najarian et al., 1980). Surgical diabetes is often described as brittle (Pezzilli, 2006), in part because of erratic food absorption from exocrine deficiency (Stauffer et al., 2009), but there are reports where metabolic parameters after TP are similar to patients with type 1 diabetes (Fujino et al., 2009).

Although IATs have been done with pancreatic resections for premalignant (Sakata et al., 2008) and malignant (Forster et al., 2004) neoplasias, as well as for acute relapsing pancreatitis (ARP) before evolution to CP occurs (Sutherland et al., 2011a), the major application of TP-IAT has been in patients who have CP and intractable pain (Blondet et al., 2007; Carlson et al., 2007; Dong et al., 2011; Hermann et al., 2010; Matsumoto, 2011; Onaca et al., 2007; Ong et al., 2009; Robertson, 2010a; Sutherland et al., 2011a). TP, with or without (Behrman & Mulloy, 2006; Casadei et al., 2010a; Casadei et al., 2010b; Fujino Y et al., 2009; Gruessner et al., 2008; Heidt et al., 2007; Janot et al., 2010; Muller et al., 2007; Mullhaupt & Ammann, 2010; Stauffer et al., 2009) IAT, may appear to be a radical treatment, but for the CP patients in whom it is done, the alternative is even more radical: persistent pain and/or

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lifetime narcotic use (Ahmad et al., 2005; Braganza et al., 2011; Gachago & Draganov, 2008; Mullhaupt & Ammann, 2010). Thus, an appreciation of the spectrum of the disease, the inconsistency in correlation between imaging and gross and microscopic pathology results and the degree of pain, and the various mechanisms by which CP causes pain are relevant for patient selection and for interpretation of the outcomes in the TP-IAT series reviewed here.

2. Brief review of chronic pancreatitis and treatment options

CP is characterized by progressive, irreversible damage to the pancreas, with varying degrees of inflammation, fibrosis, ductal alteration, exocrine atrophy, and secondary involvement of the islets of Langerhans (Braganza et al., 2011). The clinical manifestations also vary as to the degree of pain, maldigestion from loss of exocrine function, and occurrence of diabetes. Although lost exocrine function can be managed with oral pancreatic enzyme supplements, and diabetes, if it occurs, with insulin, the hallmark of CP is pain, often intractable and debilitating. Pain is the main symptom toward which therapies are directed, all with significant failure rates (Gachago & Draganov, 2008).

The acute and chronic forms of pancreatitis are not totally distinguishable. They have overlapping risk factors and share a common pathogenic origin as a pancreatic autodigestive process. Additionally, they each may manifest as an initial episode of abdominal pain, with elevation of serum amylase and lipase, and with similar nonspecific inflammatory changes. CP is likely the result of progressive pancreatic damage after recurrent episodes of pancreatic necro-inflammation. The sentinel acute pancreatitis event (SAPE) hypothesis (Schneider & Whitcomb, 2002), postulates that the sentinel event is a pancreatic injury that makes the gland particularly vulnerable, in the recovery phase, to additional insults such as alcohol, metabolic, and oxidative stresses. ARP may evolve to CP; patients who are initially pain free between episodes may begin to have underlying interval pain and may cease having episodes altogether. Even one episode of acute pancreatitis may be followed by evolution to CP, or CP may occur without a history of an identifiable episode of acute pancreatitis. Whatever the trigger, progression of CP to end-stage fibrosis occurs at different rates in different people, and can be caused by different mechanisms (Etemad & Whitcomb, 2001).

Traditionally, alcohol abuse has been thought to be the cause of most cases of CP, but this perception may not be correct. Indeed, in the first 135 cases of TP-IAT for CP at UMN, only 16% were attributed to alcohol, and 60% were idiopathic (Jie et al., 2005); in more recent cases (Sutherland et al., 2011b) fewer are classified as idiopathic and more as genetic in origin because of the identification of genes associated with CP as well as pancreatic cancer (Braganza et al., 2011). In the series at the University of Cincinnati, only 14% of the cases of CP were attributed to alcohol (Ahmad et al., 2005; Sutton et al., 2010). Cigarette smoking is also a major risk factor for CP (Maisonneuve et al., 2005; Talamini et al., 1999). Well-defined inherited germline mutations also can cause CP in families (Whitcomb, 2000). Hereditary pancreatitis once was thought to be rare, diagnosed only when other family members are affected. The identification of PRSS1, SPINK1, and CFTR mutations in patients with so-called idiopathic CP, however, indicates that genetic risk factors are much more common than originally envisioned (Braganza et al., 2011; Witt et al., 2011).

These mutations have both autosomal-dominant and recessive patterns of inheritance with variable penetration and may be influenced by certain modifier genes and environmental factors. The discovery of SPINK1 mutations in various types of CP, such as tropical calcific, alcoholic, and autoimmune pancreatitis, blurs the borders between the particular CP subtypes. Other risk factors for CP include biliary lithiasis, anatomical variants like annular pancreas or divisum, hypertriglyceridemia, hypercalcemia, sphincter of Oddi dysfunction, and trauma (Ahmad et al., 2005; Braganza et al., 2011; Jie et al., 2005; Witt et al., 2011;). The key histopathologic features of CP, regardless of the etiology, are varying degrees (Kobayashi et al., 2010; Kobayashi et al., 2011) and combinations of pancreatic fibrosis, acinar atrophy, acute and chronic inflammation, and distorted or blocked ducts (Braganza et al., 2011).

The diagnosis of CP is based mainly on symptoms, imaging studies, and supporting laboratory tests. In certain patients, the diagnosis can be surprisingly difficult, especially in those who have early or mild small-duct or minimal-change variants (Braganza et al., 2011; Layer et al., 1994; Walsh et al., 1992). Serum amylase and lipase levels typically are elevated during attacks early on but might be normal in later phases with progressive destruction of the gland. Imaging studies include (CT), endoscopic retrograde cholangiopancreatography (ERCP) (which is associated with a risk of precipitating pancreatitis), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS) (Kahl et al., 2002). Although all of the studies can detect ductal and textural abnormalities, the specificity and sensitivity of each in diagnosing CP are not defined well, given the difficulty of obtaining histopathologic correlation, and when it was obtained in a large series at UMN, the correlation was poor with CP clearly present in patients with minimal findings on the imaging studies (Vega-Peralta et al., 2011a; Vega-Peralta et al., 2011b).

The treatment of patients who have CP is focused on mitigating their unrelenting or recurring abdominal pain (Braganza et al., 2011; Gachago & Draganov, 2008; Kobayashi et al., 2010). Patients who imbibe alcohol or smoke should stop. Pancreatic enzyme supplementation may help. Non-narcotic analgesics should be tried first, but many need narcotic analgesics; patient comfort takes precedence over concerns of addiction (Ahmad et al., 2006; Andren-Sandberg et al., 2002; Fasanella et al., 2007). Some patients need escalating doses, with the addition of fentanyl patches or even parenteral administration. Celiac ganglion blocks, percutaneous or endoscopic, can be tried but rarely give permanent pain relief, if any at all, and transient responses often cannot be repeated (Warshaw et al., 1998). Patients who require narcotic analgesics, with or without complete relief, are candidates for invasive procedures in an attempt to remove or modify the root cause of the pain. The general progression is from the least to the most invasive procedure, depending on the response.

Pain in CP occurs with or without ductal obstruction. When obstruction, increased intraductal pressure, or a dilated duct can be demonstrated, efforts should be made to relieve the obstruction. If pain persists or recurs, then the next step is pancreatic resection. Because previous surgical drainage procedures (Puestow or Berger or Frey) compromise islet yield if a subsequent TP-IAT is done (Bellin et al., 2010a; Jie et al., 2005; Sutherland et al., 2011b), the current UMN paradigm is to do any indicated drainage procedures endoscopically only (Sutherland et al., 2011b). Then, if the endoscopic drainage is unsuccessful, the authors

proceed to resection rather than surgical drainage. Although two randomized trials of highly selected subgroups of patients who had severe CP cases showed that primary surgical drainage had a better chance of relieving pain than endoscopic drainage (Cahen et al., 2007; Dite et al., 2003), most gastroenterologists, because it is minimally invasive, advocate an initial trial of endoscopic therapy in an attempt to relieve pain in patients who have a dilated duct, stricture, or pancreatic stones (Wilcox & Varadarajulu, 2006). If endoscopic drainage fails, there is little evidence that surgical drainage will be successful in relieving pain. As primary therapy, each approach has a relatively high failure rate; pain persisted in 68% of patients who had endoscopic and 25% who had surgical drainage in the study by Cahen and colleagues (Cahen et al., 2007). Even in those who have initial relief following either endoscopic or surgical drainage, it may not be sustained longer than 5 years (Braganza et al., 2011).

The ideal CP candidates for endoscopic drainage procedures have a focal proximal stricture associated with upstream dilation of the pancreatic duct, or relatively small burden of main pancreatic duct stones that is amenable to extraction with or without extracorporeal shock wave lithotripsy, or a pseudocyst. Endoscopic therapy most often is successful in patients who have moderate disease. Successful treatment of strictures requires aggressive therapy, with repeated dilations and stenting in hope that the stricture resolves. There is wide variability in expertise, aggressiveness, and conceptual approaches to endoscopic therapy, which may influence outcomes (Fasanella et al., 2007; Wilcox & Varadarajulu, 2006). Although the complication rate of endoscopic therapy is relatively low, acute episodes of pancreatitis can occur after sphincterotomy and stent placement, and in some patients, the underlying pain becomes worse; such patients are prime candidates for resection, including TP-IAT.

Pancreas resection is indicated in CP patients who have small-duct disease or those in whom endoscopic drainage fail, ideally with an IAT but many centers do or have done TP without an IAT (Behrman & Mulloy, 2006; Casadei et al., 2010a; Casadei et al., 2010b; Fujino Y et al., 2009; Gruessner et al., 2008; Janot et al., 2010; Muller et al., 2007; Stauffer et al., 2009). A TP is the most likely operation to relieve pain, and for CP patients who are already diabetic, there is little reason not to do it. For non-diabetic CP patients, a TP-IAT reduces but does not eliminate the risk of surgical diabetes. Thus, a case can be made for partial resection (usually a Whipple operation, but a distal pancreatectomy for the rare case with a mid-duct stricture and CP of the body and tail only). If pain is not relieved by a partial resection, a completion pancreatectomy with IAT can be done subsequently (Sutherland et al., 2011b).

Patients tend to be referred for resection late in the course of CP, often with a pain history of years, and many opt for TP rather than a partial resection, wanting the best chance at pain relief without the risk of reoperation. TP-IAT done early in the course of CP avoids the complications of chronic narcotic use and gives the best chance at a high islet yield to prevent or minimize post-pancreatectomy diabetes (Bellin et al., 2010a; Kobayashi et al., 2010; Kobayashi et al., 2011; Sutherland et al., 2011b; Takita et al., 2010).

The authors' experience indicates that TP with preservation of β -cell mass by immediate isolation and intraportal transplantation of islets from the excised pancreas should be

considered as a primary surgical option for patients who have painful CP refractory to less invasive procedures (Blondet et al., 2007; Jie et al., 2005; Sutherland et al., 2011b; Wahoff et al., 1995a). The main criterion for success of the islet autograft per se is whether insulin independence is maintained or surgical diabetes made milder. The overall outcome, however, depends as much on the clinical response as on the metabolic results, specifically whether the patient's pain is reduced or eliminated, narcotic analgesics withdrawn, and the quality of life (QOL) improved (Bellin et al., 2010b; Bellin et al., 2011b; Bellin et al., 2011c; Billings et al., 2011; Rafael et al., 2008; Sutton et al., 2010).

3. Historical context

The first patient in the UMN series (and the world) to undergo an IAT after pancreatectomy (Sutherland et al., 1978), in 1977, remained insulin-independent and pain-free until she died 6 years later of causes not related to her operation (Farney et al., 1991). This case proved that a viable islet preparation could be made from a freshly excised human pancreas. It also showed that the previous failures with islet allografts were caused either by low viability or poor preservation of deceased donor pancreases, or rejection (Najarian et al., 1977).

As of mid-2011 the UMN IAT experience includes more than 400 cases (Sutherland et al., 2011b). The outcomes in the UMN series have been periodically published (Farney et al., 1991; Farney et al., 1998; Gores et al., 1992; Gruessner et al., 2004; Hering et al., 2004; Jie et al., 2005; Morrow et al., 1984; Najarian et al., 1979; Najarian et al., 1980; Najarian et al., 1977; Robertson et al., 2001; Sutherland et al., 1978; Sutherland et al., 1980a; Sutherland et al., 2004a; Sutherland et al., 2009a; Sutherland et al., 2009b; Sutherland et al., 2011b; Wahoff et al., 1995a; Wahoff et al., 1995b), including in children (Bellin et al., 2007; Bellin et al., 2008; Bellin et al., 2010a; Bellin & Sutherland, 2010; Bellin et al., 2010b; Bellin et al., 2011b; Wahoff et al., 1996).

Shortly after the initial report on IAT from the UMN more than 30 years ago (Sutherland et al., 1978), a few other centers also did IAT after total or partial pancreatectomy (Cameron et al., 1981; Fontana et al., 1994; Hinshaw et al., 2011; Mehigan et al., 1980; Mehigan et al., 1980; Memsic et al., 1984; Mirkovitch et al., 1981; Toledo-Pereyra et al., 1984; Traverso et al., 1981) though because they were done without anticoagulation complications of the IAT occurred at some centers (Mehigan et al., 1980; Memsic et al., 1984; Toledo-Pereyra et al., 1984), but inexplicably not at others (Fontana et al., 1994; Hinshaw et al., 2011; Valente et al., 1986). Later several center began programs with low complication rates because of lessons learned from the others (Blondet et al., 2007). To date, more than 30 are known to have done IAT, nearly all by embolization of the isolated islets to the liver by means of the portal vein (Fig. 1). The world literature as of 2011 contains reports of about 700 IATs, including the 400 UMN cases cited previously and those done elsewhere (Ahmad et al., 2005; Argo et al., 2008; Clayton et al., 2003; Dixon et al., 2008; Farkas & Pap, 1997; Garcea et al., 2009; Jindal et al., 1998; Oberholzer et al., 2000; Rodriguez et al., 2003; Sarbu et al., 2005; Sutton et al., 2010; Takita et al., 2010; Takita et al., 2011a; Teuscher et al., 1998; Watkins et al., 2003; Webb et al., 2008; White et al., 1998; White et al., 2001;)[2622]. After UMN, the next largest series are at the University of Cincinnati (more than 100) and the University of Leicester (more than 60).

For historical completeness, segmental pancreatic auto-transplantation is mentioned as another method for preserving β -cell mass after pancreatic resection (Fukushima et al., 1994; Hogle & Recemtsma, 1978; Rossi et al., 1986). The first such case was done around the time of the first IAT (Hogle & Recemtsma, 1978). This approach appears to have been used less frequently than IAT; indeed, no reports have appeared in the literature on segmental pancreas auto-transplants for the past decade.

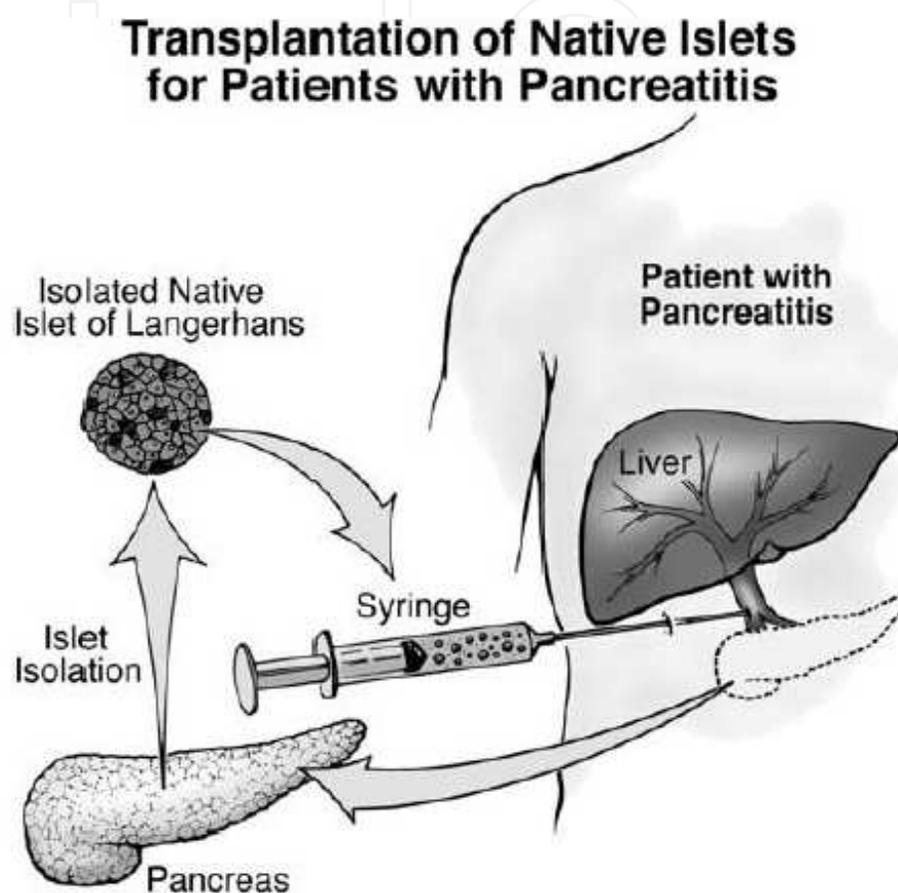


Fig. 1. Sequence of events to preserve beta-cell mass in patients undergoing a total pancreatectomy for benign disease. The resected pancreas is dispersed by collagenase digestion followed by islet isolation. Autologous islets then are embolized to the patient's liver by means of the portal vein (from Blondet et al 2007).

4. Patient selection and pain syndrome

The severity of the gross morphologic changes associated with pancreatitis, as detected by imaging studies, do not correlate necessarily with the degree of pain the patient is experiencing (Noh & Wallace, 2006; Sahai et al., 1998). Nor do normal or near normal imaging studies rule out CP (Gupta et al., 2007; Vega-Peralta et al., 2011a; Vega-Peralta et al., 2011b). Minimal change CP was first described by Walsh and colleagues (Walsh et al., 1992) in patients who had severe abdominal pain with minimal gross morphologic changes but clear histopathologic changes in the gland, with resolution of pain in most patients following pancreatectomy. Layer and colleagues (Layer et al., 1994), also described two forms of CP: early-onset CP, where pain precedes by years the development of gross

pathologic changes, and late-onset CP, where gross changes are already detectable by the time the patient has pain. These two papers were published before the EUS era.

Ideally, EUS should allow minimal change CP to be detected, but because it is standard to require that five of the nine features tested for on EUS (hyperechoic parenchymal foci, strands, hypoechoic lobules, cysts, main duct irregularity, ductal dilation, hyperechoic duct walls, visible side branches, and calcifications or stones) be present for a diagnosis of CP to be made to avoid overcalling (Sahai et al., 1998), the minimal change variety may be present but not diagnosed (Vargas et al., 2001; Vega-Peralta et al., 2011a).

At UMN we have correlated EUS findings (classified using 9 standard criteria) with resected pancreas histopathology in 50 patients with minimal change chronic pancreatic (MCCP) (no calcifications in the pancreas on CT scan) out of 141 undergoing TP-IAT from 1/2008 through 7/2010 because of severe abdominal pain thought secondary to CP (Vega-Peralta et al., 2011a; Vega-Peralta et al., 2011b). MCCP was defined histologically when fibrosis, atrophy or inflammation was found in at least 1 biopsy. . Of pts with histologically confirmed MCCP, 27/45(60%) had $\geq 4/9$ criteria on EUS. 18/21(85%) pts with ≤ 3 EUS criteria and 4/5(80%) pts with 0/9 EUS criteria had MCCP by histopathology. 2/29(7%) pts with $\geq 4/9$ EUS criteria had normal histology. Negative predictive value of a normal EUS was 38%. Positive predictive value of abnormal EUS at ≥ 6 criteria was 72%. Correlation between EUS and histology of MCCP is poor in pts undergoing TP-IAT. This study showed that normal or nearly normal EUS cannot exclude MCCP, and abnormal EUS alone is probably not sufficient for the diagnosis unless ≥ 6 criteria are present. The clinical syndrome is important in MCCP. If it fits the pain pattern seen in CP, treatment, including TP-IAT, should be based on clinical rather than imaging criteria.

Further support for the contention that the current criteria, designed to prevent over-diagnosing CP on EUS (Sahai et al., 1998), may under-diagnose comes from Chong and colleagues (Chong et al., 2007) at the Medical University of South Carolina. They found that a threshold of three criteria gave the best balance between sensitivity (83%) and specificity (80%) for correlation of EUS findings with histological CP. Thus, patients who have an abdominal pain syndrome who have any one of the nine features consistent with CP on EUS may indeed have the disease, probably in the minimal change category. The authors know of no report in the literature that correlates the severity of pain and the morphologic findings of radiologic or pathologic studies.

The pain of pancreatitis is multifactorial (Di Sebastiano et al., 1997; Di Sebastiano et al., 2004; Keith et al., 1985;). Even when there is increased ductal pressure, it is not necessarily the cause of the pain (Manes et al., 1994), and pain in patients who have CP exists in the absence of increased ductal pressure. Indeed microscopic pathology with intrinsic neuritis had the best correlation in at least one study (Keith et al., 1985). Some patients have increased sensitivity to pain of central origin, perhaps explaining the symptoms in minimal-change CP (Buscher et al., 2006).

Thus, at UMN, the authors do TP-IAT in CP patients who have intractable pain, whether the gross morphologic changes detected in the pancreas are minimal or severe. It is almost always worth an attempt at islet isolation, because having even a small beta-cell mass is

better than having none. Occasionally, and especially in CP patients who already have impaired glucose tolerance, the pancreas is such a small atrophic rock that the authors make a decision not to go to the expense and effort of an islet isolation that is almost certain to be ultra-low. In one center, imaging studies of the pancreas correlated with islet yield, being higher in those with MCCP (Takita et al., 2011b).

Patients who have ARP are also candidates for TP-IAT if their episodes are frequent, disruptive, and persist over time, even if they are pain-free between episodes (Sutherland et al., 2011b). Evolution of ARP into CP, where elevated levels of serum amylase and lipase cease but pain persists, is common and often misunderstood as meaning the pain is other than pancreatic. In non-diabetic patients requiring narcotics for their pain who have a history of ARP associated with even minimal criteria for CP on imaging studies, the authors recommend TP-IAT.

Some patients who have CP have diabetes when referred for surgical consultation. In such patients, the decision for resection is easy, especially when exocrine deficiency also exists. Most patients, however, are seen when diabetes does not exist and thus a TP must be undertaken with the acceptance of diabetes as a tradeoff for pain relief and for the chance to discontinue narcotics. If an IAT prevents diabetes, it is a bonus. When a TP is done for CP in a non-diabetic patient, however, an IAT to preserve β -cell mass should be done whenever possible (Pezzilli, 2006).

5. Surgical resection considerations

During TP, the blood supply to the pancreas should be preserved as long as possible to minimize the detrimental effects of warm ischemia on the islets (Corlett & Scharp, 1998; Desai et al., 2011; Sutherland et al., 1980a; White et al., 2000a). To do so, never separate the distal pancreas from the splenic vessels. If the splenic vessels are ligated in the hilum, the spleen may survive on its collateral vessels, but usually it has to be taken. When the spleen is spared, there is a risk of variceal formation in the gastric veins draining the spleen leading to late intestinal bleeding, or splenomegaly that can be painful, so the authors leave it only if it retains an absolutely normal appearance after hilar ligation. It is possible to leave the entire blood supply to the pancreas intact, including the gastroduodenal artery as well as the splenic artery and vein until the pancreas and duodenum is totally mobilized and ready for resection (Desai et al., 2011).

At UMN, early IAT series included cases with the entire duodenum preserved (95% pancreatectomy), but the complication rate was actually lower in patients who had part of the duodenum or the entire duodenum resected (Farney et al., 1991). For the past 20 years, in some cases the authors have done a pylorus- and fourth portion-sparing partial duodenectomy when possible, with orthotopic reconstruction by means of duodenoduodenostomy and choledochoduodenostomy (Fig. 2). The history of this technique for pancreatic head resection or TP has recently been articulated (Farney & Sutherland, 2008).

This is just one method of reconstruction. The proximal duodenum can also be anastomosed to the first loop of jejunum distal to the ligament of Trietz with a choledochoduodenostomy to the distal duodenum. If only the proximal duodenum is spared then it can be

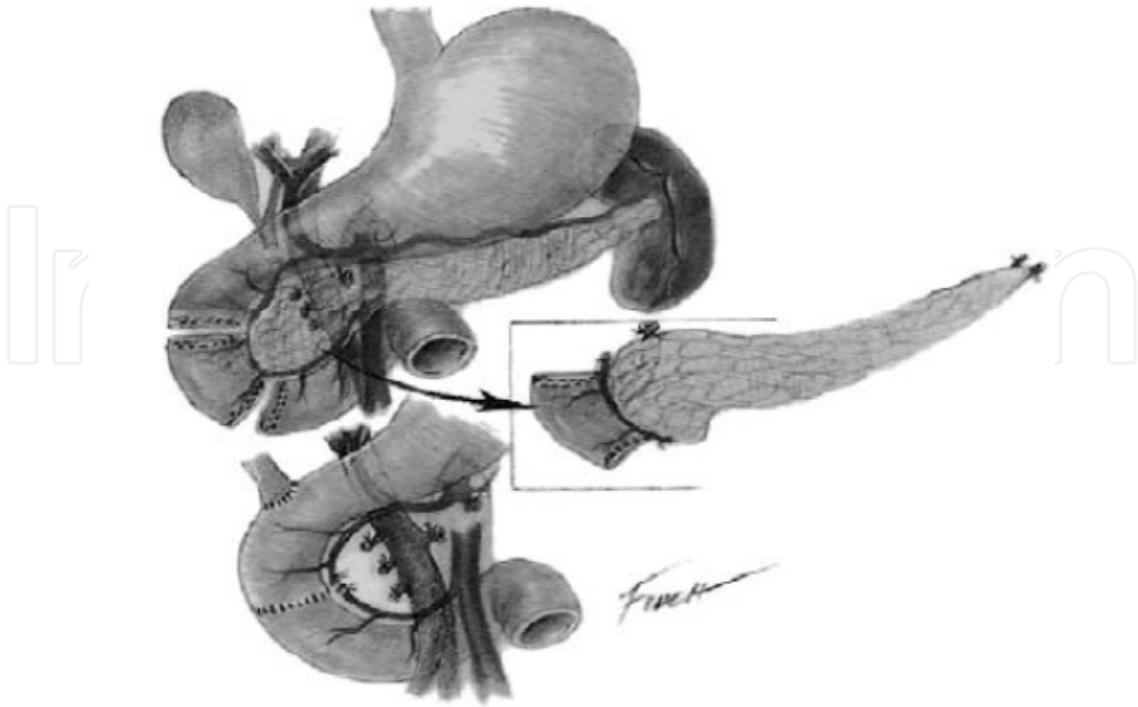


Fig. 2. Surgical technique for total pancreatectomy. Total pancreatectomy and pylorus- and distal-sparing duodenectomy with orthotopic reconstruction by means of duodenostomy and choledochoduodenostomy. (Adapted from Farney AC et al., 1991; with Copyright © 1991, Elsevier.)

anastomosed to the jejunum with a choledochoduodenojejunosomy proximal to it. If the entire duodenum is removed so the pylorus is not spared, then a Roux-en-Y choldechojejunosomy is required to prevent bile reflux via the gastrojejunosomy. The author's current preference when the pylorus is spared is the second method described above but it is best to have all methods in one's armamentarium so one can adjust to the individual circumstances of the surgery

In others cases the proximal duodenum has been anastomosed end-to-side to the proximal jejunum just distal to the ligament of Trietz with a choledochoduodenostomy done to the distal (third or fourth portion) duodenum. Sparing the pylorus is done mainly to prevent bile reflux, but if it is or becomes incompetent enterogastric bile reflux can occur, and if symptomatic enough conversion to a Roux-en-y connection may be required by dividing the jejunum between the ligament of Trietz and the duodenojejunosomy and then performing a jejunojejunosomy 45 cm or more distal to the duodenojejunosomy.

The technique used is surgeon's preference. Some members of our team always remove the entire duodenum with reconstruction via a Roux-en-y gastro- or duodeno-jejunosomy and choldechojejunosomy done so enterogastric bile reflux is not possible. With this method efforts to save the pylorus are unnecessary. The option of doing a cutaneous gastrostomy and feeding jejunostomy also exists, allowing for enteral rather than intravenous nutrition to be provided during the recovery period. Again, this is surgeon preference and can be individualized depending on the anticipation of recovery of bowel function. The impact of

narcotic bowel syndrome, which many of these patients have, must also be taken into consideration (Grunkemeier et al., 2007).

There are many articles on surgical technique of TP (with or without IAT) and the complications there of and these should be read by all who perform such surgery (Behrman & Mulloy, 2006; Casadei et al., 2009; Casadei et al., 2010a; Casadei et al., 2010b; Fujino Y et al., 2009; Janot et al., 2010; Muller et al., 2007; Murphy et al., 2009; Parsaik et al., 2010; Simons et al., 2009; Stauffer et al., 2009). In addition, there are recent reports of pancreatectomy done laproscopically, either hand assisted (Kitasato et al., 2011) or using the DaVinci Robotic Device (Giulianotti et al., 2009; Giulianotti et al., 2011), with the first TP-IAT for CP done at the University of Minnesota in 2008 (Marquez et al., 2010).

There is also the option of trying preserve the spleen at the time of TP (Desai et al., 2011; Wahoff et al., 1995a). In order to preserve blood supply to the pancreas up until the minute it is removed to prevent ischemic injury to the islets, the splenic artery and vein are not taken at their origin and termination respectively until the pancreas is removed and they are left intact without separation from the pancreas. The splenic artery and vein can be ligated in the hilum of the spleen and the spleen than survives on its collateral circulation (short gastric vessels and gastroepiloic vessels) if at all, as originally described for living donors of segmental pancreas transplants (Sutherland, et al., 1980b). Although preserving the spleen gives a theoretical advantage in terms of fighting infection, in a series of TP without IAT done for a variety of reasons, there was no difference in complications and outcomes in the short term in those who underwent splenectomy and those in whom the spleen was preserved (Koukoutsis et al., 2007). In the early part of the TP-IAT series at the University of Minnesota efforts were made to save the spleen (Wahoff et al., 1995a), but the authors rarely do so now unless the collateral circulation is excellent (Sutherland et al., 2011b).

6. Metabolic considerations

In patients who have painful CP referred for resection, baseline metabolic studies to assess β -cell function include fasting and postprandial glucose, baseline and stimulated C-peptide, and glycosylated hemoglobin levels. Patients who have CP often have symptoms of exocrine insufficiency (steatorrhea), but formal evaluation usually is not done. IAT candidates are counseled that exocrine deficiency may be made worse or induced by TP. Exocrine deficiency may be responsible for the more erratic blood sugar control in pancreatic diabetes than type 1 diabetes because of erratic absorption making the predicted insulin dose more difficult to calculate (Jahansouz et al., 2011; Robertson, 2010a; Robertson, 2010b). However, at least one group has reported that diabetic control after TP (for a variety of reasons) without IAT is equivalent to that of patients with type 1 diabetes in their clinic (Jethwa et al., 2006). Nevertheless, the metabolic control does not approach that achieved with an IAT after TP, whether insulin-independent or not (Bellin et al., 2009; Rajab et al., 2008).

Although the authors often try to spare the proximal and distal duodenum during TP, data from the bariatric literature suggest that there may be a metabolic benefit of duodenectomy. GLP-1, produced by L cells in the distal intestinal tract is a powerful incretin. Patients who have a Roux-en-Y gastric bypass have increased levels of GLP-1 with improvement in diabetes, results not seen after restrictive bariatric procedures (Greenway et al., 2002; le Roux et al., 2006). It is possible that complete duodenectomy at the time of TP would

increase GLP-1 levels and mirror the positive impact on insulin sensitivity seen in the bariatric duodenal bypass patients, allowing a reduced islet mass to sustain insulin independence.

As far as metabolic studies after TP-IAT, largely focused on glycemic control and need or lack of need for exogenous insulin and the value of functioning islets even if the mass is insufficient for insulin-independence, many have been published (Ahmad et al., 2005; Bellin et al., 2008; Bellin et al., 2009; Berney et al., 2000; Farney et al., 1998; Jie et al., 2005; Jung et al., 2009; Kendall et al., 1997; Lee et al., 2005; Leone et al., 1998; Ngo et al., 2011; Pyzdrowski et al., 1992; Robertson et al., 2001; Robertson, 2010a; Sutherland et al., 2008; Teuscher et al., 1998).

Tight glucose control is desirable after IAT in order to prevent glucose toxicity to the islet as they engraft (Bellin et al., 2009). Thus the authors usually employ an insulin-drip in the immediate postoperative period after TP-IAT until a transition is made to enteral feeding (Bellin et al., 2009; Sutherland et al., 2011b). A closed loop artificial endocrine pancreas insulin delivery device is another option to use in the early postoperative period to maintain euglycemia (Kobayashi et al., 2010).

7. Islet isolation and infusion considerations

In the United States, islet isolation must be done in a laboratory that meets all of the US Food and Drug Administration (FDA) criteria for processed tissue. Pancreatic surgery centers that do not have an islet isolation facility thus cannot offer IAT or must collaborate with a center that can process and return islets to the center of origin (Langer et al., 2004; Matsumoto, 2011; Rabkin et al., 1997; Rabkin et al., 1999).

After resection, the pancreatic duct is cannulated, and the pancreas is dispersed by collagenase digestion, using the modified Ricordi technique (Gores et al., 1992; Gruessner et al., 2004). At UMN, the authors do not purify preparations with a low tissue volume to maximize the islet yield (Gores & Sutherland, 1993) a situation often found in fibrotic pancreases (Balamurugan et al., 2011b). If the crude tissue digest exceeds 15 mL, the authors usually reduce the volume by purifying all or part of the islet preparation, so that embolization to the liver occurs without any undue rise in portal pressure (Casey et al., 2002; Robertson, 2001; Wilhelm et al., 2011). If portal pressure reaches 20 to 30 cm of water, the residual preparation can be dispersed freely in the peritoneal cavity or transplanted beneath the kidney capsule, or sub-mucosal layer of the stomach, in the hope that the islets engraft (Cameron JL et al., 1981; Wilhelm et al., 2011). The authors' current preference is to purify islets so that the tissue volume is reduced to an amount tolerated by the portal vein, without any undue rise in pressure, but not to the degree that a large number of islets have to be discarded or placed in alternative sites. Sometimes the authors do not purify a high volume digest, because a high percentage of the islets are mantled by, or not cleaved from, a surrounding rim of exocrine tissue, and we will lose most by purification (Wilhelm et al., 2011). In minimal change CP, islet yields are similar to what is obtained from deceased donor pancreases for islet allografts (Soltani et al., 2011b).

Several advances in islet isolation from diseased pancreases have been made in recent years by various techniques, including altering enzyme combinations in the digestion process (Anazawa et al., 2009; Balamurugan et al., 2011a; Balamurugan et al., 2011c) and other maneuvers (Matsumoto, 2011) such as altering the high density gradient process for

purification (Soltani et al., 2011a). There is a clear relationship also to islet yield depending on the severity of the imaging changes of gross pancreatic morphology (Takita et al., 2010) and the severity of the histopathology in both adults (Kobayashi et al., 2011) and children (Kobayashi et al., 2010). In severely fibrotic pancreases of children, ductal neogenesis of islets may be seen (Soltani et al., 2011c), which in some but not all cases is associated with a high islet yield. However, in adults, the presences of nesidioblastosis on histopathology is associated with a statistically lower islet yield than when this feature is absent, probably because its presence is indicative of islet loss from the CP stimulating neogenesis, but the response is inadequate or is itself met by destruction from the pancreatic inflammation and fibrosis (Kobayashi et al., 2011). Predicting islet yield in advance is difficult (Bellin et al., 2010a), but it is clear that prior surgical duct drainage procedures or distal resections compromise yield (Bellin et al., 2011a; Blondet et al., 2007; Jie et al., 2005; Sutherland et al., 2011b). Other factors, such as body mass index (BMI), may also play a role (Takita et al., 2011c). It might be expected that total islet yield is higher with higher BMI, but Takita et al (Takita et al., 2011c) found that even the islet equivalents/kg were higher.

Clinical observations and animal studies indicate that the liver (by means of the portal vein) is the most efficient site for islet engraftment (Gray, 1990; Rajab et al., 2008; Wahoff et al., 1995a; Warnock et al., 1983). Other sites used, such as the renal capsule (Gray et al., 1988; Gray et al., 1989; Matarazzo et al., 2002; Vargas et al., 2001), spleen (Gray, 1990; Gustavson et al., 2005; Sutton et al., 1989), omentum (Ao et al., 1993; Gustavson et al., 2005) and peritoneal cavity (Wahoff et al., 1994a; Wahoff et al., 1994b) rarely have been associated with function of islet autografts in people (Fontana et al., 1994; White et al., 2000b). A recent clinical case report from Sweden demonstrated function (C-peptide positive) of an intramuscular IAT in a 7 year old child undergoing TP for CP (Rafael et al., 2008). The islet yield was high (6400 IE/kg), an amount that usually results in insulin-independence in children if embolized to the liver via the portal vein (Bellin & Sutherland, 2010), suggesting that better islet function might have been achieved if the islets has been placed intra-hepatic.

At any site, the islets initially survive by nutrient diffusion. During this period, they have reduced functional capacity, with function improving once neovascularization occurs (Anderson et al., 1989; Korsgren et al., 1999). There is a correlation between the number of islet equivalents (IE) transplanted per kg (IE/kg) (Sutherland et al., 2008), but there is considerable overlap in functional outcome (Blondet et al., 2007). A few (~7%) IAT recipients of <2500 IE/kg become insulin-independent while about a third with >5000 IE/kg do not (Sutherland et al., 2008). Most likely this relates to differences in viability between different islet preparations: a low islet yield with a high percentage of viable islets will out-perform a high islet yield with a low percentage of viable islets, a hypothesis supported by the studies by Papas et al. (2010) showing the best predictor of islet function in IAT recipients was the *in vitro* oxygen consumption rate prior to implantation (Papas et al., 2010).

To prevent intraportal clotting from the tissue thromboplastin (present in the islet preparation) (Mehigan et al., 1980), the authors have administered heparin since their first cases in the 1970s (Najarian et al., 1979; Wahoff et al., 1995a). Nearly all of the reports of complications related to portal infusion of islets (Mehigan et al., 1980; Memsic et al., 1984; Toledo-Pereyra et al., 1984; Walsh et al., 1982), were published before the standardized semi-

automated pancreas dispersion techniques and before the routine use of heparinization at all centers. A recent analysis of the authors' data indicates that the incidence of complications of IAT is low if less than 0.25 ml tissue/kg is infused (Wilhelm et al., 2011). If the volume is higher, consideration should be given to volume reduction even though some islets are lost, or to simply transplant less than the full unpurified islet mass. There is some risk of heparinization in patients who have heparin antibodies, with one case of heparin induced thrombocytopenia reported after TP-IAT (Rastellini et al., 2006).

In regard to technical aspects of intraportal islet infusion, the most simple technique is to wait for the islets after the enteric and biliary reconstruction has been done following TP and to infuse the islets directly into the portal vein or a tributary and then close the patient (Blondet et al., 2007). However, techniques also exist for intraportal embolization of islet so the liver after abdominal closure has been obtained. The techniques include embolization to a temporarily exteriorized omental vein (Nath et al., 2004); via a recanalized umbilical vein (Pollard et al., 2011) or percutaneous transhepatic access to the portal vein for infusion of the islets (Morgan et al., 2011). The latter approach frees up surgeons and an operating room for other procedures sooner than if the islets are infused in the operating room and thus is thought to be cost-effective at least at one center (Morgan et al., 2011), but the expense incurred by using interventional radiology must also be considered as well as the fact that the abdomen cannot be inspected for bleeding after the heparinization and increased portal pressure that ensue by lieu of the infusion (Blondet et al., 2007).

In islet allograft recipients, one study by Doppler ultrasound showed a 4% incidence of radiologically detected but clinically insignificant portal vein thrombosis (Casey et al., 2002). The risk factors for portal vein thrombosis in islet allograft recipients has been delineated and primarily relates to tissue volume and degree of anticoagulation in the early post-infusion period (Kawahara et al., 2011). In the authors' IAT series, portal vein thrombosis occasionally is detected on ultrasound, but not as a clinical entity (Sutherland et al., 2011b). The authors always administer heparin before islet infusion and usually continue the infusion for a few days if the closing portal pressures are high. Liver function tests typically show a transient rise in serum enzyme levels during the early postoperative period (Gores et al., 1992), with no implication for future hepatic dysfunction. Imaging studies of the liver after IAT often do show changes, such as echogenic nodularity, but such changes do not appear to be associated with any clinical problems and thus are benign (Ong et al., 2008).

8. Intra- and post-operative considerations

The authors maintain euglycemia by an insulin drip during and after the pancreatectomy and IAT (Manciu et al., 1999). Animal studies have shown a decrease in islet engraftment with hyperglycemia; furthermore, glucose toxicity may cause dysfunction and structural lesions in the transplanted islets (Bellin et al., 2009; Clark et al., 1982; Dohan & Lukens, 1947; Korsgren et al., 1989; Makhlouf et al., 2003). The authors promote islet engraftment by an exogenous insulin drip to maintain euglycemia, minimizing insulin secretory demand from the freshly infused islets. A transition to subcutaneous insulin is made when the patient begins to eat or is on a tube-feeding regimen if eating is delayed, with the dose again adjusted to maintain euglycemia; insulin gradually is withdrawn in patients who can achieve euglycemia without it, but this is rarely done before 6 months.

9. Expanding application

IATs have been done after pancreatic resection for focal benign pancreatic processes, including pancreatic pseudocysts (Clayton et al., 2003) cystic neoplasms such as intrapapillary mucinous neoplasms IPMN (Berney et al. 2004; Lee et al., 2005), insulinomas (Berney T et al., 2004; Oberholzer et al. 2003) neuroendocrine and other tumors (Berney T et al., 2004; Ris; 2011). In a series of 14 patients in Seoul, Korea with a mixture of benign tumors, including IPMN (Jung et al., 2009), pathologic evaluation was completed in each before the IAT to confirm that the lesions were benign.

In the UMN series, IATs have been done at the time of distal pancreatectomy for benign cystic tumors in 5 patients (Blondet et al., 2007; Braganza et al., 2011). In these cases the authors are uncertain how well the intrahepatic islets are functioning, because those in the native pancreatic remnant also are functioning.

In the Seoul series mentioned above (Jung et al., 2009), however, the investigators did a formal comparison of 14 patients who had partial pancreatectomy (PP) with an IAT and 6 who had PP without an IAT. Glucose tolerance was abruptly impaired in both groups immediately after surgery, including reduced indices of insulin secretion, but beginning at 6 months and persisting at 24 months, the PP-IAT group had statistically better insulin secretion and glucose tolerance than the PP-alone group. Thus, even with a PP there is a metabolic advantage to doing an IAT; and this would especially be the case if a completion pancreatectomy has to be done later for any reason. The lessons from the Korean experience can be extended to the CP group where a partial pancreatectomy before a completion pancreatectomy is quite common (usually a Whipple, but sometimes a distal).

An IAT also has been reported in a patient with pancreatic adenocarcinoma who had an extended Whipple operation complicated by an anastomotic leak at the pancreaticojejunostomy (Forster et al., 2004). . The leak was treated by an urgent completion pancreatectomy with an IAT. The portion of the pancreas used for islet isolation had margins free of tumor. The patient remained C-peptide positive until death from metastases 2.5 years later, but there was no tumor in the liver.

The risk of doing an IAT when a completion pancreatectomy is done because of a technical complication of a Whipple procedure cannot be calculated from one case, but conceptually the procedure is valid, because the judgment must be that the distal pancreas was tumor-free by leaving it in (otherwise a Whipple operation would not have been done). A case also could be made for doing a TP-IAT, even in situations where a Whipple would otherwise suffice, but where a TP would be safer by avoiding an enteric anastomosis to a soft pancreas that has a higher than average leakage or breakdown probability. These cases are anecdotal and there is at this time no technique to assure that isolated islets are not contaminated by tumor. However, at least for hereditary CP with gene mutations associated with risk for pancreatic cancer, there are no reports yet of cancer arising in the liver after TP-IAT, including those done more than 20 years ago (Blondet et al., 2007).

A case can be made for doing a TP-IAT in patients with hereditary chronic pancreatitis in whom pain is not an issue (for example, "burned out") but has reached the age (>35 years) where the risk of pancreatic cancer associated with the gene mutations is significant and it increases with age (Farrow & Evers, 2002; Whitcomb, 2004; Whitcomb & Pogue-Geile, 2002).

On another note, the authors' TP-IAT series includes a few CP patients whose IATs were done after only a distal pancreatectomy, with the head remaining (Sutherland et al., 2011b). For those in whom a completion pancreatectomy was done later, insulin-independence was preserved, indicating good engraftment at the initial IAT (Blondet et al., 2007).

Transplants of islets isolated from pancreas allografts excised for technical problems or allograft pancreatitis (islet auto-allografts) also have been performed, with one case published by the authors (Leone et al., 1998). This patient remained insulin-independent for more than 1 year while on immunosuppression, but ultimately needed exogenous insulin from decline or loss of islet function for immunologic or non-immunologic reasons. The other islet auto-allografts had limited duration of function (Blondet et al., 2007).

10. Islet autotransplantation in children

CP is less common in children than in adults, but should be treated with the same aim: to relieve pain, eliminate the need for narcotics, and preserve β -cell mass (Schmulewitz, 2011). The first known case of TP-IAT in a child was done at the University of Minnesota in 1989 and was reported in detail by the authors 7 years later with islet function maintained, though the patient was not insulin-independent (Wahoff et al., 1996). The authors have done TP-IAT in more than 40 children since the initial report (Bellin & Sutherland, 2010). Although the experience with TPIAT in children is less extensive than in adults, the data suggests this procedure is particularly successful in the youngest patients with insulin-independence rates of over 50% and the younger the patient the more likely insulin-independence is achieved (Bellin et al., 2008a; Bellin & Sutherland, 2010). Most of the ones that do require insulin retain some beta cell function as manifested by C-peptide positivity and thus are stable. In the historical series, more than three-quarters of the children had islet function after TP-IAT (Bellin et al., 2008a). Brittle diabetes is very rare after TP-IAT unless virtually no islets are obtained because of delaying the TP until nearly all the islets are destroyed by the disease process (Bellin & Sutherland, 2010; Kobayashi et al., 2010).

Most important is the effect of TP-IAT on the CP pain syndrome. Sixty to seventy percent of children completely discontinue narcotic pain medications, while the majority of the remaining patients require only intermittent or low dose narcotics for pain control (Bellin et al., 2008a; Bellin et al., 2011b). Complete discontinuation of narcotics is more frequent in preadolescent patients (younger than 13 years of age) (Bellin et al., 2008a). Over 90% of all children report no pain or significant improvement in pain compared to before surgery (Bellin et al., 2008a). Health-related quality of life, as measured by the Medical Outcomes Study (MOS) Short-Form 36 (SF-36) is nearly two standard deviations below the population at baseline but normalizes on average by 1 year postoperatively (Bellin et al., 2011b).

The islet auto-transplant procedure is the same in children as that performed in adults. Including the cases done outside the University Of Minnesota, IATs have been performed in at least 50 children (not all published) with the majority of islet grafts infused intraportally (Bellin et al., 2008a; Bellin et al., 2011b; Sutherland et al., 2011a). There is one case report of intramuscular autoislet transplant in a 7 year old child; this patient had documented graft function and good metabolic control for over 2 years post-IAT but did not achieve insulin independence (Rafael et al., 2008). In children undergoing intraportal IAT, 40-50% of patients achieve insulin independence in the first 1 year after IAT, with the highest rate of

insulin independence in preadolescent children (Bellin & Sutherland, 2010). In addition to young age, higher islet mass transplanted and lack of prior distal resection and/or lateral pancreatico-jejunostomy are important prognostic factors for insulin independence (Bellin et al., 2008a; Bellin et al., 2011b). More extensive fibrosis and longer duration of disease have been associated with lower islet yields and hence higher risk of insulin dependence in children (Kobayashi et al., 2010). As in adults, baseline glucose, C-peptide (fasting and stimulated), and hemoglobin A1c are measured before surgery. Lower hemoglobin A1c, lower fasting blood glucose, and higher stimulated C-peptide levels are associated with higher islet yields but do not predict the islet count prior to pancreatectomy for any individual patient (Bellin et al., 2010a)

Most important of all is the dramatic improvement in quality of life that can be documented in children undergoing TP-IAT for CP, both retrospectively (Bellin et al., 2008a) and in a recent prospective study at the University Of Minnesota (Bellin et al., 2011b). In the prospective study, nineteen consecutive children (aged 5-18 years) undergoing TP/IAT from December 2006 to December 2009 at the University of Minnesota completed the Medical Outcomes Study 36-item Short Form (SF-36) health questionnaire before and after surgery. Before TP/IAT, the children had below average health-related quality of life, based on data from the Medical Outcomes Study SF-36; they had a mean physical component summary (PCS) score of 30 and mental component summary (MCS) score of 34 (2 and 1.5 standard deviations, respectively, below the mean for the US population). By 1 year after surgery, PCS and MCS scores significantly improved to 50 and 46, respectively Mean scores improved for all 8 component subscales. More than 60% of IAT recipients were insulin independent or required minimal insulin. Patients with prior surgical drainage procedures (Puestow) had significantly lower yields of islets and greater incidence of insulin dependence

Although the number of patients is relatively small, this study (Bellin et al., 2011b) shows that the physical and emotional components that define quality of life significantly improve after TP/IAT in subsets of pediatric patients with CP. Children who have had surgical drainage procedures prior to TP-IAT are disadvantaged in regard to islet yield and none yet have had sustained insulin independence,; however even in this subset some had islet function as manifested by C-peptide positivity or need for only once daily long acting insulin. Children should not be allowed to suffer the pain of CP when it can be relieved by TP and beta cell function preserved by IAT, and quality of life is restored in nearly all cases.

11. Literature review

The largest series published to date on patients undergoing pancreatectomy and IAT have come from the University of Minnesota (Farney et al., 1991; Gores et al., 1992; Gruessner et al., 2004; Jie et al., 2005; Najarian et al., 1979; Najarian et al., 1980; Sutherland et al., 1978; Sutherland et al., 1980a; Sutherland et al., 2004a; Sutherland et al., 2009a; Sutherland et al., 2009b; Sutherland et al., 2011b; Wahoff et al., 1995a) (>400), the University of Cincinnati (Ahmad et al., 2005; Rodriguez et al., 2003; Sutton et al., 2010) (>100), the University of Leicester (Clayton et al., 2003;; Garcea et al., 2009; White SA et al., 1998; White SA et al., 2001; Webb et al., 2008) (>50 cases), but there are many center that are building their series (Argo et al., 2008; Berney T et al., 2000; Desai et al., 2011; Dixon et al., 2008; Jahansouz et al., 2011; Takita et al., 2010; Takita et al., 2011b; Valente et al., 1986) The reports from these centers

largely focus on metabolic outcomes, QOL, and pain reduction., but there are many publications on specialized aspects of TP-IAT as have been referenced in this chapter.

11.1 Insulin independence

The ability to achieve insulin independence after IATs appears to correlate directly with the islet equivalents (IEs) infused. IEs serve as an indirect measurement of β -cell mass, but there is much overlap, in that a small percentage of patients receiving less than 2000 IE/kg will become insulin-independent, while some receiving more than 5000 IE/kg will not (Ahmad et al., 2005; Bellin et al., 2009; Blondet et al., 2007; Dong et al., 2011; Jie et al., 2005; Sutherland et al., 2008; Sutherland et al., 2009a; Takita et al., 2011a). The Leicester group finds very little correlation of insulin-independence with islet yield (Webb et al., 2008). The authors have shown that islet yields are poorest in patients who have prior pancreatic resections (distal pancreatectomies or surgical drainage procedures such as the Puestow procedure) (Blondet et al., 2007; Gruessner et al., 2004; Sutherland et al., 2011b; Wahoff et al., 1995c). In addition, fewer islets are recovered as histopathologic changes of CP increase in severity (Gruessner et al., 2004; Kobayashi et al., 2010; Kobayashi et al., 2011; Wahoff et al., 1995a).

The timing of the procedure has a direct impact on islet yield. Maximal islet yield and insulin independence may be attained more easily if the IAT is performed earlier in the disease course, (Ahmad et al., 2006; Balamurugan et al., 2011a; Bellin et al., 2010a; Kobayashi et al., 2011; Rodriguez et al., 2003; Sutherland et al., 2011; Takita et al., 2010).

In regard to durability of insulin independence when it is achieved after TP-IAT, it is much more durable than in islet allografts, even though the number of islets transplanted is less than for islet allografts (Sutherland et al., 2008). In a retrospective analysis of the first 173 patients to undergo TP-IAT at the University of Minnesota (20 year follow-up on the longest), the incidence of graft function and insulin-independence and decline over time once achieved was calculated and compared to the same calculations made for islet allografts in the Collaborative Islet Transplant Registry (CITR) (Figure 3).

Islet allografts are currently associated with a high rate of early insulin independence, but after 1 year insulin-independence rates have declined relatively rapidly in the CITR analyses overall (CITR; 2009) and at most (Jahansouz et al., 2011) but, more recently, not all (Bellin et al., 2008b) institutions,. The 2008 analysis of islet auto-transplants (IATs) done at the University Of Minnesota over a 30 year period in those who achieved function showed to be relatively durable compared to the islet allografts, despite a lower beta-cell mass (Bellin et al., 2008b). IAT function (full/partial combined) and insulin independence correlated with islet yield. Overall only 65% functioned within the first year, and only 32% were insulin independent, but of IATs that functioned initially, 85% remained so 2-years later, in contrast to 66% of allografts Of IAT recipients who became insulin independent, 74% remained so 2-years later versus 45% of initially insulin-independent allograft recipients. Of IATs that functioned or induced insulin independence, the rates at 5 years were 69% and 47%, respectively. Thus, islet function is more resilient in autografts than allografts. Indeed, in this analysis, the 5-year insulin-independence persistence rate for IATs was similar to the 2-year rate for allografts. Several factors unique to allocases are likely responsible for the differences, including donor brain death, longer cold ischemia time, diabetogenic immunosuppression, and auto- and alloimmunity. IAT outcomes provide a minimum theoretical standard to work

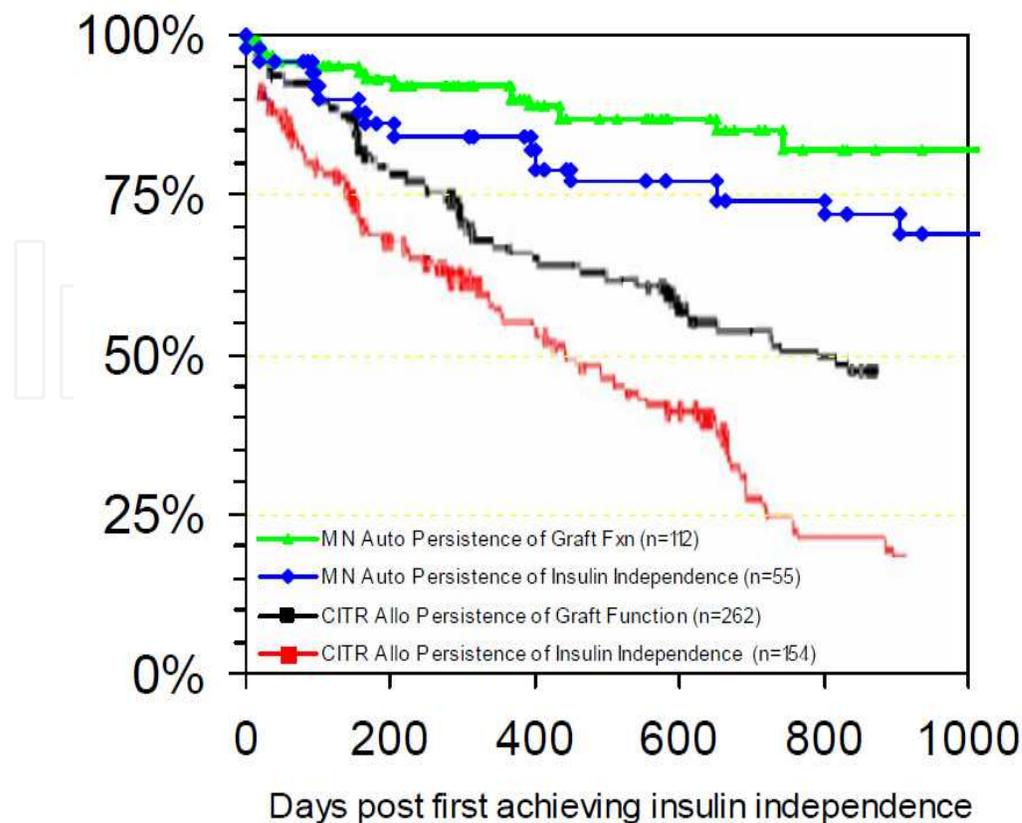


Fig. 3. Rates of loss of islet graft function or insulin independence (II) in University Of Minnesota 1977 to 2007 adult TP recipients of islet AUTO-transplants who achieved islet function or II versus in 1999-2006 type 1 diabetic recipients of islet ALLO-transplants who likewise achieved islet function or II as reported to the Collaborative Islet Transplant Registry (CITR) (Reproduced from Sutherland et al., 2008; with Copyright © , Lippincott Williams & Wilkins, Inc.)

toward in allotransplantation. However, not all islet autografts that initially function continue to do so, and beta cell mass is important, the more the islets, the more durable the function, particularly in adults. Preadolescent children are a special group where even a low islet mass can function long term, and possibly the mass expands in young children (Bellin & Sutherland, 2010).

11.1.1 University of Minnesota series

As referenced above, the University Of Minnesota has published extensively on their series of TP-IAT cases, numbering more than 400 between 1977 and 2011 (Fig 4). In a comprehensive 1995 report (Wahoff et al., 1995a), of the first 50 cases, significant pain relief occurred in >80%. Over half had a period of insulin-independence and a third maintained insulin independence for the 2 to 10 years they had been followed. If over 300,000 islets were transplanted, three-quarters maintained insulin independence by the protocol in place at the time (which did not include adding insulin for perturbations in metabolism as we do now). A major point of this paper (Wahoff et al., 1995a) was that the lowest islet yields were in patients who had a prior Puestow procedure, with only an 18% rate of insulin independence in this group, in contrast to 71% in patients without a prior resection or drainage procedure.

In a later update of the UMN series, at a time when the authors were much more likely to treat even mild hyperglycemia, and nearly all patients underwent a TP, insulin independence was achieved in only 16% of patients with prior resections versus 40% in those without prior resections (Gruessner et al., 2004) . A prior Whipple operation had less effect on the islet yield than a distal pancreatectomy (Sutherland et al., 2004a) .

407 Islet Autografts

University of Minnesota: 1977 – July 25, 2011

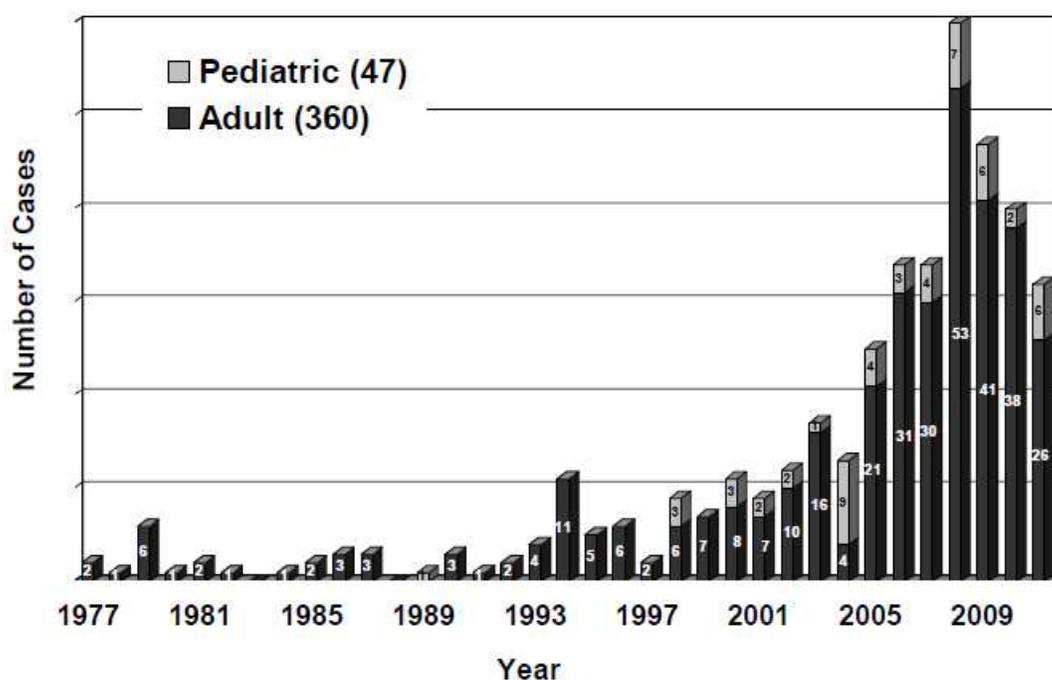


Fig. 4. Islet autograft experience at the University of Minnesota by year, in 407 patients (360 adults, 47 children <18 years old) from February 1977 to July 2011.

The outcomes in the University of Minnesota series were again updated in 2005 when it included 136 patients (97% female) undergoing IAT from 1977 through 2004 (Jie et al., 2005). Further details on this cohort were added in 2007 (Blondet et al., 2007). Patient age ranged from 5 to 70 years (mean 36 years); duration of disease ranged from 1 to 30 years (mean 5.9 years). The etiology of CP was idiopathic in 43%, alcohol in 15%, divisum in 13%, familial in 11%, biliary in 10% and other in 7% of the patients. Most (93%) had had previous operations (cholecystectomy in 42%), 33% directly on the pancreas including duct drainage in 13%, Whipple procedure in 7%, distal pancreatectomy in 9% and combined drainage and resection in 4% . .

A TP or completion pancreatectomy was done in 77% and a near total (duodenal sparing) in 15%, while 10 had a distal pancreatectomy only (some later had a completion pancreatectomy). This analysis (Jie et al.; 2005) confirmed that a prior Puestow procedure was associated with low islet yields (mean of 1531 IE/kg) as compared to no previous direct surgery on the pancreas (mean of 3996 IE/kg). Prior resection was associated with a slightly

lower yield (3687 IE/kg), but the difference was much more striking after a distal pancreatectomy than a Whipple operation. Again, there was a correlation between islet yield and insulin independence. Of patients receiving >2000 IEQ/kg, nearly three-quarters had at least a period off insulin (Jie et al., 2005). Of those completely dependent on insulin, the mean IE/kg transplanted was 1239, while in those in whom it was intermittent it was 3064; in those who maintained insulin-independence it was 5118/kg. About a third of patients fall into each category (Blondet et al., 2007).

Most important was formal patient self-assessment of quality of life after TP-IAT as the University Of Minnesota program progressed (Carlson et al., 2007). Of 90 patients transplanted between 1996 and 2005 with >1 year follow-up in all, 83% reported good to excellent outcome and less than 5% considered their outcomes poor [Figure 5]. This retrospective survey has since been followed by prospective studies of quality of life in both children and adults in the Minnesota series.

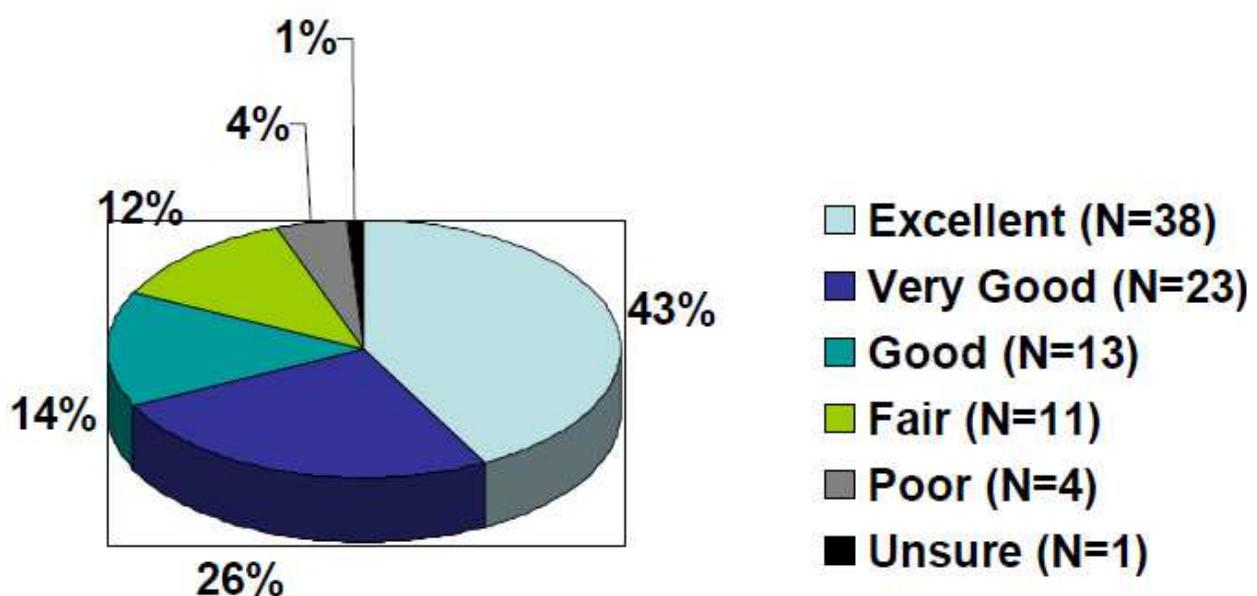


Fig. 5. Patient subjective perception of their outcome post-TP-IAT (1-10 years follow-up) , for 1996-2005 adult cases at University of Minnesota (data from Carlson et al 2007).

Patient survival and durability of IAT graft function (either insulin-independent or on once daily insulin only and C-peptide positive) and insulin-independence in the Minnesota TP-IAT series for 1977-2007 cases (Figure 6) was detailed in a 2008 publication (Sutherland et al., 2008). Patient survival at 1 year was 95% and more than three-quarters were alive at 10 years. More than two thirds had partial or full function of the IAT, with a third achieving insulin independence. At 20 years more than half who exhibited IAT function initially still had function, so overall more than one-third of the original cohort had functioning islets for two decades in this series that includes the earliest cases. Half of those who were insulin independent initially were still so at 5 years; none were insulin-independent at 20 years but at least partial function was maintained for at least this length.(Figure 6). The durability of IAT function (Figure 7) and of insulin-independence (Figure 8) in those who did initially achieve partial or full function, correlated with the number of islets transplanted. For those receiving >5000 IE/kg, more than three quarters still had function (full and partial

combined) 5 years later, while it was slightly less than half for those who received <2500 IE/kg (Figure 7). Similarly, of those who achieved insulin independence, nearly three-quarters of those who received >5000 IE/kg were still insulin-independent 5 years later, while it was less than a third for those who received <2500 IE/kg (Figure 8).

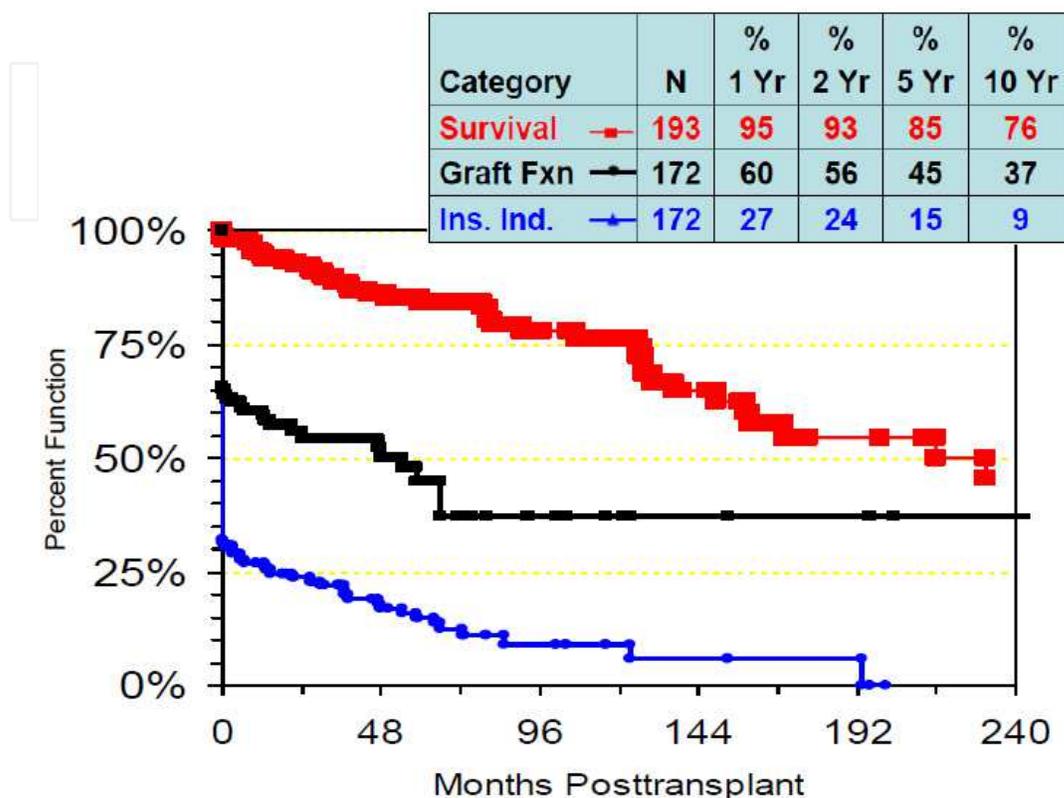


Fig. 6. Actuarial patient survival rates, IAT graft function rates(full-partial combined) and insulin-independence rates from time of transplant for adult Patients undergoing TP-IAT at University Of Minnesota from 1977 to 2007 (data from Sutherland et al, 2008)

Since many modifications in islet isolation, surgical technique and patient selection have occurred over the decades since the first TP-IAT case, the outcomes at the University Of Minnesota in the modern era alone have been the subject of recent analyses of pain relief and quality of life (Sutherland et al., 2009a) and metabolic outcome (Sutherland et al., 2009b). Of 67 adult patients undergoing TP-IAT for CP between January, 2006 and February 2008 (Sutherland et al., 2009a), all had had attempts at pain relief by prior endoscopic duct drainage (EDD) procedures. In all the pain had persisted in spite of the EDD. EDD is a minimally invasive approach that should almost always be tried before major surgery for CP, but in these 67 patients the pain had persisted in spite of the EDD.

The patients were assessed by written surveys and clinic interviews and metabolic testing in 2009, with more than 1 year of follow-up (16-44 months) in all (Sutherland et al., 2009a). Mean age was 36 years and 72% were female. Etiology of CP was unknown in 40%; from pancreas divisums in 14%; genetic in 14%; associated with Sphincter of Oddi dysfunction (SOD) in 12%; with alcohol use in 9%; and other in 11%. Patients were surveyed for outcomes with a median follow-up of 1.7yrs Actual survival at 1 year was 98.5%; actuarial survival at 2 years was 95.5%. The collective number of EDD procedures prior to surgery was 264 (mean of

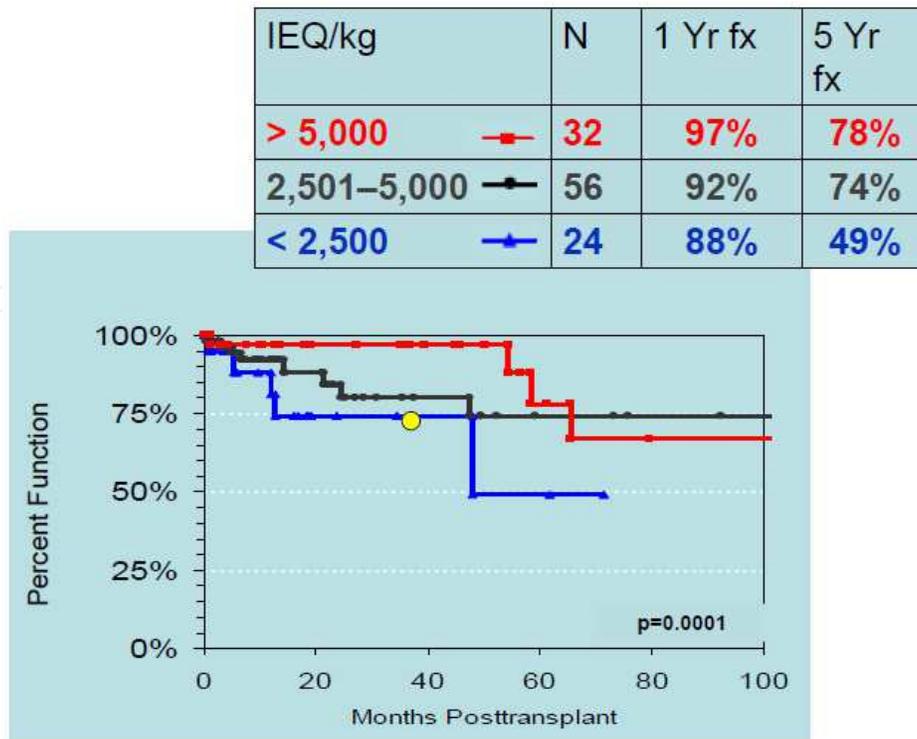


Fig. 7. Actuarial duration of islet graft function (full-partial combined) according to islet yield in adult patients who achieved function after TP-IAT at University Of Minnesota from 1977 to 2007 (data from Sutherland et al, 2008).

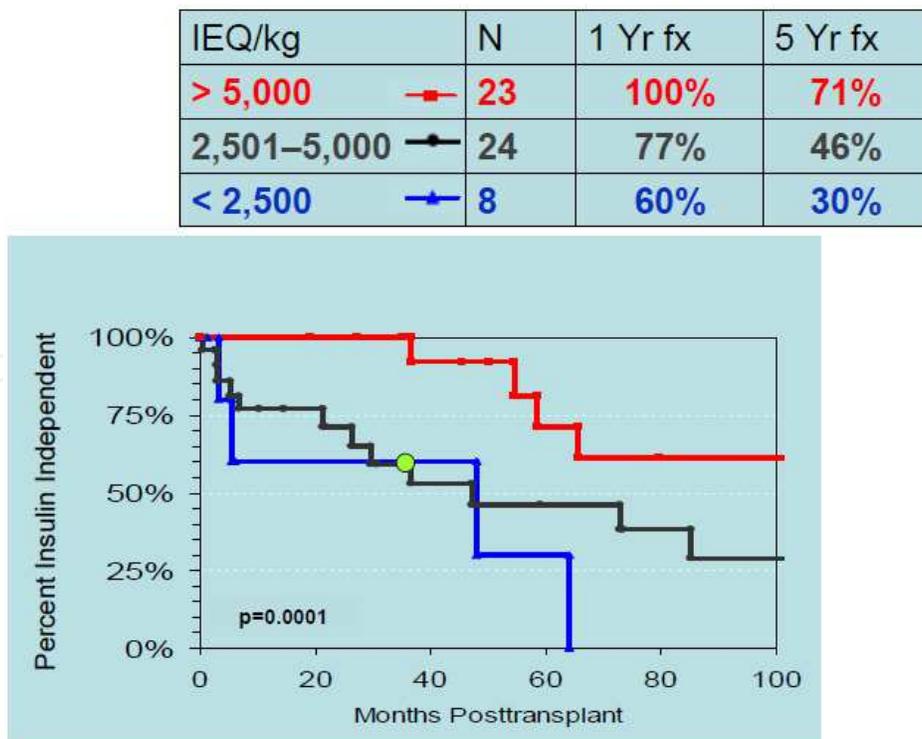


Fig. 8. Actuarial duration of insulin independence according to islet yield in adult patients who achieved insulin-independence after TP-IAT at University Of Minnesota from 1977 to 2007 (data from Sutherland et al, 2008).

4.1/patient; max ~60). Ten patients (15%) had had a partial pancreatectomy elsewhere before a total (completion) pancreatectomy-IAT at the University Of Minnesota, and did not have EDD in the interval.

Patients were assessed at follow-up for pain, narcotic use, quality of life (QOL) and IAT function: full if insulin-independent; partial if euglycemic on once daily long-acting insulin; failed if on a basal-bolus insulin regime). Function was correlated with islet (IE) yield.

Yield was:

<2500 IE/kg in 22 (34%);
2501-5000 IE/kg in 30 (46%);
>5000 IE/kg in 13 (20%).

IAT function was:

Full in 21 (32 %);
partial in 28 (43 %);
failed in 16 (25 %).

IAT function was a combined

full-partial in:100% with >5000 IE/kg;
83% with 2501-5000 IE/kg;
and 59% with <2500 IE/kg ($p<.0011$).

Perception of health was:

good-excellent in 75 %;
fair in 14 %;
poor in 11 %.

Pain was:

better in 85 % (absent in 39 %);
the same in 13 %;
worse in 2 %.

97 % were on narcotics before the TP-IAT; 51 % were on at the time of the post-surgery survey (85% of these were on a wean schedule).

Of those who required insulin, 98% preferred diabetes to the former pain.

Patients rated quality of life (QOL) after TP-IAT as:

excellent-good in 60 %;
fair in 30 %;
poor in 10 %.

QOL change from before to after TP-IAT:

improved in 80 %;
was the same in 15 %;
was worse in 5 %.

Asked would they do the TP-IAT again, 98% said yes.

In these modern era studies (Braganza et al., 2011; Casadei et al., 2010a) in patients with pain after EDD for CP, TP-IAT gave relief in most, preserved meaningful insulin secretion in three-fourths, and improved QOL in four-fifths. Nearly all would do the TP-IAT again, but that fact that not all would indicates an effort is needed to identify in advance patients who will not be made better. Right now that is difficult to do, so to help the many who can be helped, a few will have to be resigned to failure but the percentage is low, and in this study improvement in quality of life was often strikingly dramatic.

The latest analysis of the Minnesota IAT series of IAT includes >400 cases as of mid-2011 (Sutherland et al., 2011b), more than half of them since 2006 (Fig. 3). The results are briefly summarized here.

The etiology of CP in the entire series is currently classified as idiopathic in 44%; sphincter of Oddi dysfunction or biliary in 16%; genetic-in 15%; divisum in 2%; alcohol in only 8%; other in 5%). At least 1 yr follow-up outcomes were available in 313 patients (278 adults, mean age 35.6 yrs.; and 35 children); 74% were female; prior-surgeries had been done in 25%--Peustow- y in 7%, resection in 18%) done before June 2009. Islet-function was considered full for patients insulin-independent; partial if euglycemic on once-daily-insulin; and failed if on a standard-diabetic-regimen even if C-peptide-positive. The SF-36-survey (Quality-of-Life (QOL)) was retrospectively completed by 101 patients done before Sep/2006 and prospectively before and after TP-IAT in 201 patients thereafter.

The results showed actuarial-patient-survival post-TP-IAT was 96% in adults and 98% in children (1-year) and; 89% and 98% (5-years). Overall, IAT-function was achieved in 70% (insulin-independence in 28%); 69% (25%) in adults, 78% (52%) in children. Prior-surgery lowered islet-yield (2712vs4077/kg,p=.003). Islet yield [$<2500/\text{kg}$ (38%); $2501-5000/\text{kg}$ (34%); $>5000/\text{kg}$ (28%)] correlated with glucose control: full-partial rates at 1-year: 26, 79 and 82%, respectively; insulin-independence rates:5, 41 and 65%. All adults retrospectively (1977-2006) surveyed had pain before TP-IAT and 95% were on daily-narcotics. Afterwards, 94% had pain-improvement and 49% ceased-narcotics. 85% of adults stated QOL improved; 8% stated it was same; 5% said it was worse. All children were on narcotics before, 39% at follow-up; pain improved in 94%; 67% became pain-free. In the prospective-QOL-study-since-2006, there was improvement after TP-IAT in all 8 SF-36-subscale-scores ($p<0.001$) with the greatest effect on bodily-pain, as was previously reported in another publication (Bellin et al., 2011c).

In this prospective study of health related quality of life (HRQoL) of patients transplanted since September 2006 (mean age 37, 77% female), prior to surgery, mean Physical Component Score (PCS) was 27 and Mental Component Score (MCS) was 32 (standardized normal=50, SD=10). Both PCS and MCS significantly improved after surgery. At 1 and 2 years, mean PCS scores were 37 and 42 respectively and MCS scores were 42 and 46. Change in PCS from baseline to 1y was greater for children than adults (+15 v. +10). All 8 subscale scores significantly improved over time), with the greatest effect on bodily pain. Children demonstrated more rapid improvement, particularly for bodily pain and role physical.

This prospective study showed meaningful improvement in HRQoL after TPIAT. Although the greatest improvement was in bodily pain, other dimensions of physical, social, and emotional health improved.

This large series, as well as those of others cited above and below, shows definitively that TP can ameliorate pain and improve QOL in patients with otherwise refractory CP, even if narcotic-withdrawal is delayed or incomplete because of prior long-term use. IAT preserves substantial islet-function in >2/3 of patients with insulin-independence occurring in a quarter of adults and half the children.

11.1.2 Cincinnati series

The Cincinnati series of TP-IAT cases (Ahmad et al., 2005; Ahmad et al., 2006; Sutton et al., 2010) is the second largest in the literature with their latest report including 118 cases (Sutton et al., 2010). The early reports from this group (Ahmad et al., 2005; Ahmad et al., 2006) showed a 40% rate of insulin independence after TP/IAT, with a mean follow-up of 18 months. Factors that correlated with postoperative insulin independence included the patient's weight, body mass index (BMI), and gender (Rodriguez Rilo et al., 2003). Patients who had a BMI greater than 28 had a higher chance of insulin dependence (Rodriguez Rilo et al., 2003). Reduction to ideal body weight to minimize insulin resistance may maximize the chance for insulin independence after TP-IAT. Insulin-independent patients had lower mean insulin requirements during the first 24 hours after transplant, possibly relating to the detrimental effect of hyperglycemia on islet function (Ahmad et al., 2006). Of their first 54 CP patients who underwent a TP-IAT, about two thirds had discontinued narcotics at the time of the report and two-thirds had full or partial islet function, (Ahmad et al., 2006). The most recent report from Cincinnati on their TP-IAT series focuses on 16 patients (out of 118, or 14%) with genetic mutations associated with CP (Sutton et al., 2010). At a mean follow-up of 22 months, 69% of patients had good islet function and 25% were insulin-independent. All were on narcotics before TP-IAT while only 37% were at follow-up and at lower doses. An SF-36 survey and pain questionnaire in this cohort demonstrated significant improvement in quality of life and reduction or elimination of pain following TP-IAT for genetically linked pancreatitis. The Cincinnati experience shows that patients with painful hereditary pancreatitis respond well to TP-IAT and should be considered for early intervention in the course of their disease.

11.1.3 Leicester series

The Leicester series of TP-IAT for CP is the third largest in the literature with more than 50 cases since 1996 (Clayton et al., 2003; Garcea et al., 2009; Webb et al., 2008; Ong et al., 2008). Interestingly, early reports from Leicester did not show a correlation between islet yield and insulin independence (Clayton et al., 2003), in contrast to the Minnesota series (Blondet et al., 2007; Sutherland et al., 2009b; Wahoff et al., 1995a). The results may relate to the cause of the CP (mostly alcohol) and possibly to patient compliance issues (Clayton et al., 2003).

The two most recent publications of the Leicester TP-IAT series for CP focus on metabolic outcomes (Webb et al., 2008) and on pain and narcotic reduction or elimination (Garcea et al., 2009), with a comparison in the latter paper to patients with CP who underwent only a TP. In the paper assessing long term IAT graft function in 46 IAT recipients (followup 2-63 months, median 16.5 months), all (100%) were C-peptide function and therefore had functioning islets. Twelve achieved insulin-independence for 2-63 months (median 16.5 months) and 5 remain insulin-independent. Over time insulin requirement tended to increase as did glycohemoglobin levels but all the recipients remained C-peptide positive

for up to 10 years (maximum follow-up). They also assessed renal function over time and it was stable in all suggesting diabetic nephropathy did not occur to any significant degree. The main point of the paper was that even though a decline in IAT function over time could be detected, total loss of function did not occur and protection against diabetic complications was likely (Webb et al., 2008).

In the other recent paper from Leicester (Garcea et al., 2009) the focus was on a comparison of 85 patients who underwent TP for CP, 50 with and 35 without an IAT. In the entire series, 90% of patients were on narcotics at the time of surgery; it fell to 40% by one year and 16% by 5 years. At 5 years insulin requirements were significantly lower in the IAT group, median of 16 units per 24 hours vs. 40 units in the TP alone group and 5 patients in the IAT group were insulin-independent.

The Leicester series complements those of other centers, as described above in the previous sections, in showing the effectiveness of TP in reducing or eliminating the pain of CP and in documenting the metabolic benefit of adding an IAT to the procedure.

11.2 Comments

Insulin independence is only partially the goal of an IAT, because preserving any β -cell mass is beneficial (Pezzilli, 2006; Robertson, 2010a). Indeed, islet allograft recipients who remain insulin dependent but have β -cell function and are C-peptide positive are metabolically more stable and less prone to hypoglycemic unawareness than those who have no β -cell function (Jahansouz et al., 2011; Paty et al., 2006; Robertson, 2010b; Ryan et al., 2002; Ryan et al., 2005). Furthermore, the risk of secondary complications is less in diabetics who receive or are C-peptide-positive (Jahansouz et al., 2011; Johansson et al., 2000; Kamiya et al., 2004). By extrapolation, IAT recipients who are C-peptide-positive, even with an insulin requirement, have a metabolic advantage (Dong et al., 2011). Although only about one-third or less of IAT recipients in the various series are insulin-independent long-term; another third have enough islets to achieve near-normoglycemia with exogenous insulin, usually with one injection daily of the long-acting variety (Bellin et al., 2009; Jie et al., 2005; Sutherland et al., 2009b; Sutherland et al., 2011b), and even those who are on basal-bolus insulin regimens are usually C-peptide positive in the modern era (Sutherland et al., 2011b; Webb et al., 2008).

Although about one third of IAT recipients in the various series require a basal-bolus insulin regimen because of low viable islet yield (Jie et al., 2005; Sutherland et al., 2004a; Sutherland et al., 2011b), as long as pain is relieved or improved, the operation is considered a success. One should only do a TP-IAT in patients who are fully informed about the risk of becoming diabetic, and who accept this risk in exchange for reasonable chances at both pain reduction and narcotic withdrawal. Some patients who became fully diabetic after TP-IAT because of inadequate viable islet yield, and who were particularly labile, have gone on to have a pancreas (allograft) transplant, and thus achieved insulin independence (Gruessner et al., 2004; Gruessner et al., 2008), but at the expense of needing immunosuppression (Sutherland et al., 2001). An islet allograft also could be done in this situation (Sakata et al., 2008), but an enteric-drained pancreas transplant is more attractive, because exocrine deficiency also can be corrected (Gruessner et al., 2004; Gruessner et al., 2008).

12. Long-term metabolic outcomes

One long-term study of metabolic outcomes in six TP-IAT recipients from the authors' center reported that diabetes mellitus was prevented for up to 13 (now 20) years (mean follow-up at study, 6.2 plus or minus 1.7 years) (Robertson et al., 2001). Normal fasting plasma glucose, intravenous glucose disappearance rate (κG), hemoglobin A_{1c} , insulin responses to intravenous glucose and arginine, and insulin secretory reserve were maintained, but insulin responses tended to decrease over time. The intravenous glucose disappearance rate correlated with the number of islets transplanted (Robertson et al., 2001). Another study showed reduced functional β -cell secretory reserve in IAT recipients, as compared with healthy individuals (Teuscher et al., 1998). Still another study showed that intrahepatic islet grafts failed to secrete glucagon in response to sustained hypoglycemia, but did in response to arginine, a peculiarity that may be site-dependent (Kendall et al., 1997). However, a study in dogs by another group indicated that alpha cell function was normal in the liver but not the omentum and spleen (Gustavson et al., 2005), so there are contradictory results. Nonetheless, intraportal islet autografts at least release of insulin appropriately (Pyzdrowski et al., 1992).

In regard to IAT durability, there are case reports in which a long-functioning graft failed when the patient was given steroids for some reason, and often not an essential reason, with glucose toxicity killing the beta cells before it was realized that insulin to protect the stressed islets needed to be given (Ngo et al., 2011). Steroids should nearly never be administered to an IAT recipient. If there is a compelling reason to do so, insulin must be started or increased the moment steroids are begun in order to maintain euglycemia.

It should also be mentioned that exocrine deficiency can be a serious problem after TP, with or without an IAT (Stauffer et al., 2009), and unpredictable absorption can make diabetic management more difficult (Bellin et al., 2009). Exocrine deficiency has more of an impact on diabetic management after TP in those who do not than those that do have an IAT, especially those who are insulin-independent. Patients rank exocrine deficiency more of a problem than endocrine deficiency after TP-IAT (Braganza et al., 2011; Sutherland et al., 2011b).

13. Quality of life and pain relief

Health-related QOL is significantly worse in patients who have CP, as compared with a gender- and age-adjusted general population (Berney et al., 2000). The primary goal in performing TP-IAT is to improve QOL by alleviating pain and giving patients a chance to discontinue narcotics, while preventing or minimizing surgical diabetes. Studies evaluating health-related QOL outcomes after TP-IAT have been recently published. In reports from Cincinnati, QOL as measured by a standard assessment tool (SF-36) showed significant improvement a mean follow-up of .19 months (Rodriguez Rilo et al., 2003), and these findings were confirmed as more patients were included (Sutton et al., 2010).

Prospective studies of quality of life before and after TP-IAT have been conducted at the University Of Minnesota in both children (Bellin et al., 2011a) and adults (Bellin et al., 2011b). Both show significant improvement in QOL, as detailed above in the section on this institution.

As far as abdominal pain from CP that is refractory to high-dose narcotics, the Cincinnati group has published pain scores as assessed before after TP-IAT (Ahmad et al., 2005; Rodriguez Rilo et al., 2003). Narcotic independence was achieved in nearly two-thirds of patients after surgery, with a marked reduction in narcotic use by pre- and postoperative morphine-equivalent determinations (Ahmad et al., 2005).

These findings are similar to those in the University of Minnesota series with pain resolved or improved in nearly all and more than two-thirds able to eliminate narcotics while the remainder needed reduced doses (Bellin et al., 2011c; Carlson et al., 2007; Jie et al., 2005; Sutherland et al., 2009a; Sutherland et al., 2011b; Wahoff et al., 1995a). Similar pain relief statistics are reported for CP patients undergoing TP without IAT (Behrman & Mulloy, 2006; Casadei et al., 2010b; Stauffer et al., 2009).

The patients who cannot withdraw completely from narcotics after TP usually have opioid-induced hyperalgesia (OIH) (Angst & Clark, 2006) from long term use prior to the surgery, a reason to not delay once it is apparent that a patient needs narcotics for pain in spite of other measures to treat the CP. Patients with OIH, are paradoxically become more sensitive to pain, by means of mechanisms originating in afferent neurons and in the spinal cord (Angst & Clark, 2006; Chuet et al., 2006; Dogrul et al., 2005; Gardell et al., 2006; Liang et al., 2006; Mercadante, 2005). OIH may be highly prevalent in patients with long-standing CP and on narcotics for years before being referred for TP-IAT; accordingly, an endpoint such as narcotic independence may not be ideal for assessing postoperative success.

14. Cancer risk of chronic pancreatitis patients

The association between longstanding CP and cancer has been established (Ahmad et al., 2006; Braganza et al., 2011; Farrow & Evers, 2002; Lowenfels et al., 1993; Whitcomb & Pogue-Geile, 2002; Whitcomb, 2004). It is believed that pancreatic cancer develops in the setting of CP, independent of the underlying etiology, but appears to require 30 to 40 years of inflammation before manifesting in an appreciable percentage of patients (Whitcomb, 2004). This increased risk for pancreatic cancer is potentiated by cofactors such as tobacco and likely by genetic factors that are not yet entirely identified (Whitcomb & Pogue-Geile, 2002; Whitcomb DC, 2004).

A TP by itself for CP completely eliminates the risk of pancreatic cancer, but even with an IAT, the risk is lowered considerably, given the marked reduction in pancreatic tissue. The autologous islets infused into the portal system are never totally pure, but the use of tissue at risk for pancreatic cancer must be minimal. Sampling the whole gland for pathologic testing is impossible in the setting of an IAT. Patients who have hereditary and tropical pancreatitis are at higher risk for developing malignant cells than the rest of CP population (Farrow & Evers, 2002; Whitcomb DC, 2004) but again the amount of residual pancreatic tissue after TP-IAT is very small.

In the entire series of TP-IAT patients from UMN, no patients are known to have developed cancer in the liver or in any other site where the islets were auto-grafted, so the risk of cancer appears to be extremely low. In one case of IAT after a TP for pancreatic adenocarcinoma, cancer was not found in the liver at an autopsy two years later in which the patient died with metastatic disease elsewhere (Forster et al., 2004). Thus, the risk of

pancreatic cancer developing in a liver after IAT when the TP is done for benign disease, including genetically linked CP (Sutton et al., 2010), is likely very low.

15. Future directions

A basic but important limitation to more widespread clinical application of IATs is the limited number of centers with the facilities and technology to isolate and prepare human islets. Few centers, including the authors', have used distance processing for both allogenic and autologous islets successfully (Langer et al., 2004; Rabkin et al., 1999; Rabkin et al., 1997). The feasibility of distance processing is enhanced by new preservation methods that extend cold ischemic times and increase islet yield and viability from suboptimal organs (Farrow & Evers, 2002; Fraker et al., 2002; Fujino et al., 1991; Langer et al., 2004; Lowenfels et al., 1993; Liang et al., 2006; Matsuda et al., 2003; Matsumoto, 2011; Mercadante, 2005; Rabkin et al., 1997; Rabkin et al., 1999; Tsujimura et al., 2004; Tsujimura et al., 2004b; Whitcomb, 2004; Whitcomb & Pogue-Geile, 2002).

The long-term success of IATs in patients who have CP (Robertson et al., 2001) contrasts with the apparently less favorable long-term results for islet allotransplants in patients who have type 1 diabetes mellitus (Jahansouz et al., 2011; Ryan et al., 2005; Sabeck et al., 2009; Sutherland et al., 2008), though in some center durable function does occur (Bellin et al., 2008b). The difference in outcomes may be because of the rejection rate of islet allografts, or if allografts are not rejected, to the diabetogenic effect of the necessary immunosuppression (Jahansouz et al., 2011).

Autologous islets are as fresh as possible. They are isolated from a pancreas that, although diseased, is not under the stress of brain death (which in animal models decreases islet yield and function by the activation of proinflammatory cytokines that occurs from central nervous system (CNS) injury (Contreras et al., 2003). A native pancreas removed for IAT also is not subjected to prolonged ischemia or to hours of cold preservation that occur with deceased donor pancreases processed for allogenic islets.

Single-donor islet allografts have resulted in insulin independence in diabetic recipients at UMN (Bellin et al., 2008b; Hering et al., 2005); yet in many cases, multiple donors are required (Jahansouz et al., 2011; Sutherland et al., 2004b). Increasing islet viability for transplants is important; for allografts, one possibility is to use a living donor (Matsumoto et al., 2005; Sutherland et al., 1980a; Sutherland et al., 1980b). This approach should be effective, given the good outcomes in IAT recipients with an islet mass well below that required for a successful outcome with deceased donor islet allografts (Sutherland, 2005; Sutherland et al., 2008).

A comparison of outcomes for IAT and islet allografts provides an opportunity to distinguish between immunologic and nonimmunologic factors that affect declines in, or sustenance of, islet graft function over time. Whatever the variables, it is apparent that currently IATs are more successful than their allogenic counterparts (Sutherland et al., 2008).

16. Summary

TP-IAT has been used to treat painful CP for over 30 years. IAT is safe and prevents or minimizes surgical diabetes after TP for CP or even neoplastic disease in which a non-

diseased portion of the pancreas can be used for islet isolation. Pancreatic resection (even partial) with an IAT always should be considered the primary surgical option for patients who have CP and intractable pain refractory to medical or endoscopic therapy. Pain relief, enabling narcotic discontinuation, is the primary objective; the prevention of diabetes is a secondary goal. The series reviewed here show that both goals are achieved to a reasonable degree in a very difficult disease, CP.

17. References

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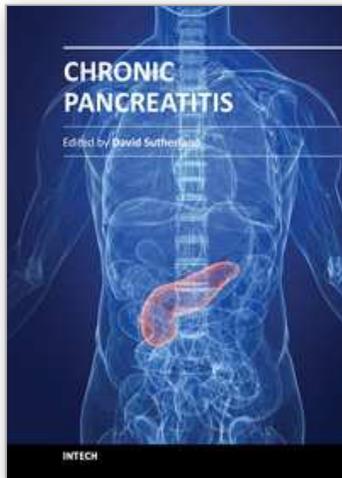
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Chronic Pancreatitis

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ISBN 978-953-51-0011-9

Hard cover, 138 pages

Publisher InTech

Published online 15, February, 2012

Published in print edition February, 2012

Chronic pancreatitis is a disease of diverse etiologies in which pain can be devastating, severely impairing quality of life, and treatment is a challenge. This book covers cutting edge basic science research and clinical diagnosis and treatment issues in chronic pancreatitis. Basic science chapters include studies on amelioration of chronic pancreatitis in rats by bone marrow derived mesenchymal cells; on gene therapy using HSV-Enkephalin to reduce fibrosis, inflammation and pain in a rats; and on pancreatic acinar and island neogenesis according to vascular and matrix dynamics of human and animal tissue. In regard to the clinical aspects, the role of endoscopic ultrasound in detecting the changes of chronic pancreatitis are addressed as well as the endoscopic treatment via duct drainage procedures or stone removal. Finally, the surgical options for chronic pancreatitis (there are well over 20 procedures) are extensively discussed, with a final chapter on total pancreatectomy and islet autotransplant to definitively remove the root cause of the pain with preservation of endocrine function. This book will be valued by basic scientists and clinicians striving to understand the mechanisms of pain in chronic pancreatitis and the treatment options in patients so afflicted.

How to reference

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David E.R. Sutherland, Melena Bellin, Juan J. Blondet, Greg J. Beilman, Ty B. Dunn, Srinath Chinnakotla, Timothy L. Pruett, Martin L. Freeman, A.N. Balamurugan, Barbara Bland, David Radosevich and Bernhard J. Hering (2012). Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis, *Chronic Pancreatitis*, Prof. David Sutherland (Ed.), ISBN: 978-953-51-0011-9, InTech, Available from: <http://www.intechopen.com/books/chronic-pancreatitis/total-pancreatectomy-and-islet-autotransplantation-for-chronic-pancreatitis>

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