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Kidney and Pancreas Transplantation: The History of Surgical Techniques and Immunosuppression

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Additional information is available at the end of the chapter

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1. Introduction

Pancreas Transplantation aims at providing Beta cells replacement in diabetic patients, especially for type 1 diabetes recipients in whom Beta cells had been destroyed by an autoimmune process. The final achievement is to restore a normal physiological control of glucose metabolism in order to halt or reverse the secondary complications of diabetes i.e. retinopathy, neuropathy, nephropathy, micro – and macro - angiopathy [1]. That can be achieved by a vascularised pancreas graft (referred as Pancreas Transplantation, PT) or by islet grafting (referred as Islet Transplantation, IT). The former PT includes transplanting 95% of unuseful cells, the exocrine part from one pancreas, while the last one IP, embolizing into the recipient liver, Islets of Langerhans after digestion and purification of several human pancreases. Three types of PT can be performed: the pancreas and a kidney are simultaneously transplanted with a single induction of immunosuppression (IS) therapy in hoping to correct both uremia and diabetes mellitus (SPK = Simultaneous Pancreas and Kidney Transplantation); the pancreas is transplanted after a successful kidney graft allowing two induction therapies along with the basic IS treatment (PAK = Pancreas After Kidney Transplantation) ; and finally the Pancreas can be transplanted alone in pre-uremic recipients with unawareness hypoglycaemic events or with rapidly evolving secondary complications of diabetes such as proliferative retinopathy, or advanced neuropathy (PTA = Pancreas Transplantation Alone) [1].

Moreover, in SPK, both organs the Pancreas and the Kidney are procured from the same deceased donor, either donor after brain death (DBD) or donor after cardiac death (DCD). In some US institutions, a segmental pancreas and the left kidney, are procured in a living donor [2], using a laparoscopic approach in the more recent year [3]. For PAK, in order to avoid an excessive IS load and two induction therapies, other institutions had proposed whenever possible to keep in stand-by the potential live kidney donor until a cadaver whole pancreatic

compatible graft is available [1]. By contrast, the number of PTA remains limited in non uremic recipients with life-threatening complications of diabetes, in whom one might hope to avoid the hypoglycaemic events with a successful graft. That can also be achieved with IT. But except for rare cases, insulin independence with IT requires more than a single human pancreas and is limited over time [1]. Moreover, IT needs costly materials, chambers and rooms for preparation. That's why IT will not be included in the present report.

2. The history of surgical techniques in pancreas transplantation

The first pancreas transplantation performed by W. Kelly and R. Lillehei on December 17, 1966 at the University of Minnesota was a duct ligated segmental graft which was implanted in the left iliac fossa along with a kidney coming from the same cadaver donor in a 28 year old female uremic recipient with type 1 diabetic nephropathy [4]. It was the first ever SPK (Fig 1). The recipient was insulin-free for six days; later she needed exogenous insulin, the need being attributed to the high doses of steroids given to prevent rejection. However, she also developed graft pancreatitis, that was most likely related to duct ligation, and for which she received 950 Rads graft irradiation. On February 14, 1967, Kelly and Lillehei removed the pancreas and rejected kidney. The recipient died from pulmonary embolism 13 days after pancreas graft removal [4]. This first case exemplified many of the problems that were associated with TP over the following 2 decades: surgical complications, wound infections, and graft rejection.

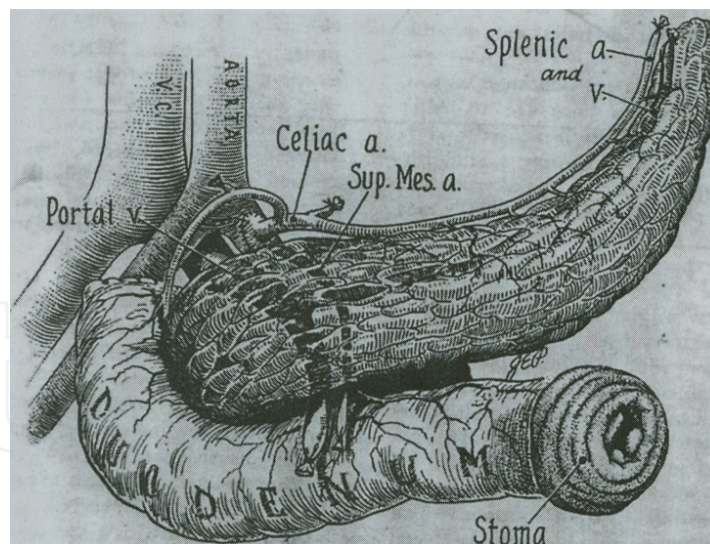


Figure 1. Drawing of the first segmental pancreas transplant (from Kelly et al.) [4].

Lillehei was the lead surgeon in the second pancreas transplant, also done with a kidney (Fig 2). He went on to do a total of 13 cases between the first case of Kelly and 1973, 9 with a kidney and 4 without [5, 6]. Significant changes in surgical techniques were made between the first and the second transplant pertaining to graft size (whole organ versus segmental) and duct management (cutaneous duodenostomy versus duct ligation). Lillehei transplanted the

donor's whole pancreas and attached duodenum extraperitoneally to the 32-Year-old recipient's left iliac fossa (Fig 2). This transplant achieved a more prolonged state of graft function, but rejection treatment had to be instituted three and eight weeks post-transplant. Both rejection episodes affected the graft duodenum. The recipient was on insulin when she died four months post transplant from sepsis.

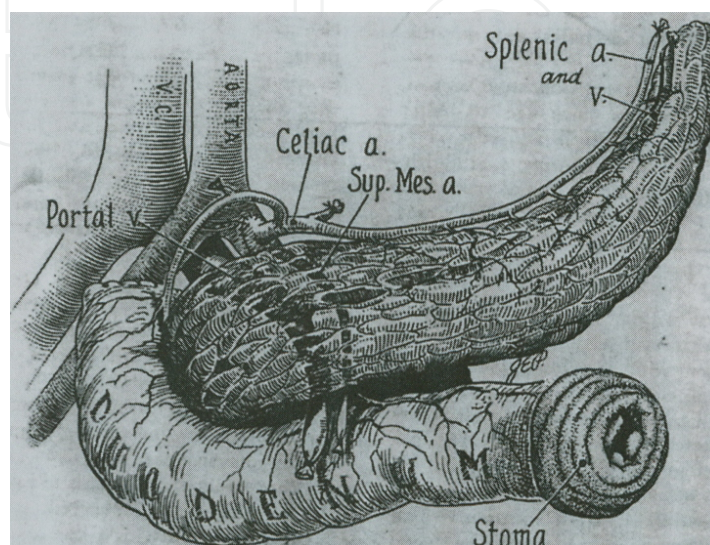


Figure 2. Drawing of the first whole pancreas transplant with cutaneous graft duodenostomy (from Lillehei et al.) [5]

After that series of 13 Pancreas Transplants, R. Lillehei concluded that most complications were associated with kidney graft rejection without pancreas rejection and recipient death [5, 6, 7].

After the first four pancreas transplants at the University of Minnesota, the next four transplants were performed in South America in 1968; [8, 9, 10]; three were performed in Brazil and one in Argentina at the Buenos Aires Hospital. Only one functioned sufficiently to induce insulin-independence and was subsequently lost to rejection at 4 months. [10].

In 1969, two other U.S. institutions performed one SPK transplant each: one at the University of Colorado (Fred Merkel and Thomas Starzl) and one at the University of California, Irvine Medical Center (John Connolly). [8, 11]. The first pancreas transplant in Europe, along with a kidney transplant, was performed in 1972 at Guys Hospital, in London, U.K. (Mick Bewick). [8].

By the 1970s, only 25 pancreas transplants had been performed at six institutions worldwide. Two-thirds of those early pancreas transplants were done along with a simultaneous kidney transplant. Exocrine secretions had been drained by duct ligation, cutaneous duodenostomy, or enteric drainage using a Roux-en-Y loop. Of these 25 grafts, only one, from Lillehei's original series, functioned for almost one year, and none for more than one year.

On November 24, 1971, Marvin Gliedman at Montefiore Hospital and Medical Center in New York performed the first pancreas transplant using urinary drainage via the native ureter [12]. Gliedman and associates performed a total of 11 ureteral pancreas transplants in the early 1970s (Fig 3) with one graft functioning for 22 months and another for 50 months – at that point

the longest pancreas graft survival recorded. [13, 14]. However, ureteral drainage did not find widespread application because of tenuous leakage-prone duct-to-ureter anastomosis; leakage from the pancreas cut surface; and the potential need for ipsilateral native nephrectomy. The main conclusion drawn from that original and historical series was the probable evidence of a hierarchy in rejection, the pancreas being less antigenic than the kidney the latter being less antigenic than the duodenum [15]. Therefore, surgical techniques using a segmental pancreatic graft (body and tail) were developed during the next decade.

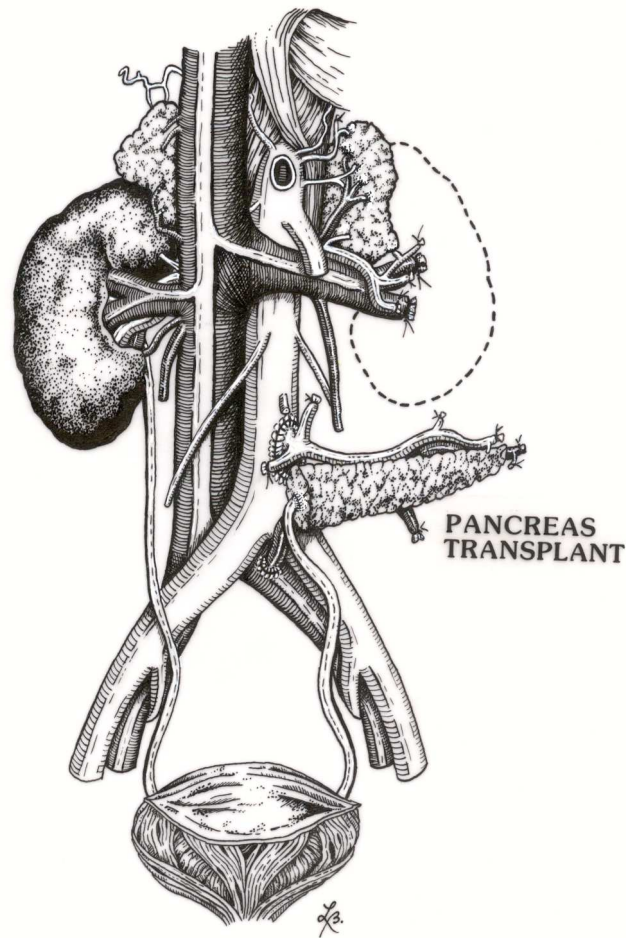


Figure 3. Ureteral pancreas transplant according to Gliedman et al [12] end-to-end distal ureter to pancreatic duct anastomosis.

2.1. The segmental pancreas transplantation reign (from mid 70's to mid's 80's)

In the mid 70's, the segmental pancreas while avoiding the duodenal segment was the most popular technique used for PT [6, 7]. Various procedures were proposed to drain the exocrine secretion: the duct could be left opened with the segmental graft placed intraperitoneally (Fig 4) [16] or blocked by an intraductal injection (Fig 5) of either Neoprene (J.M. Dubernard) [17] or Prolamine (W.Land) [18] or Polyisoprene (P. McMaster) [19] or Silicone (D.E.R. Sutherland) [20].

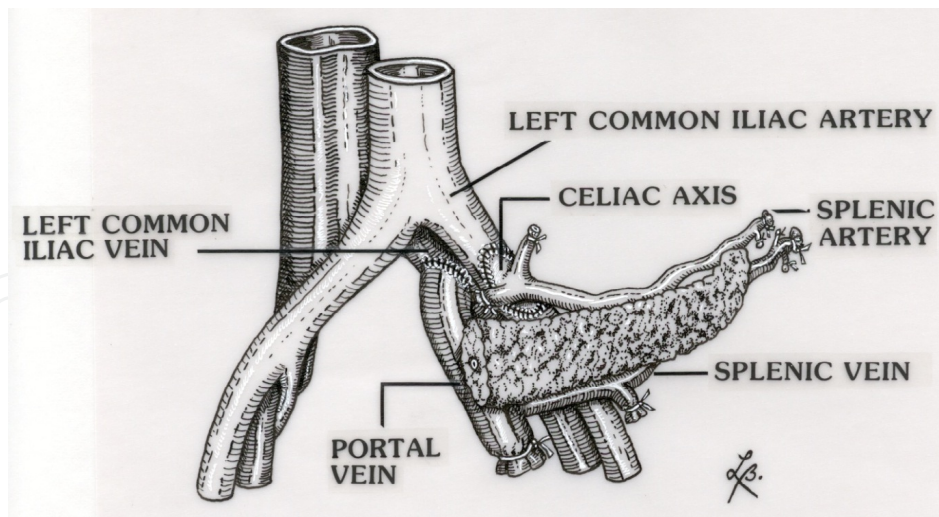


Figure 4. Technique for revascularization in the recipient of a segmental pancreas graft. The celiac axis (on a Carrel patch) and portal vein of the graft are anastomosed to the common iliac vessels of the recipient through the meso-sigmoid [16].

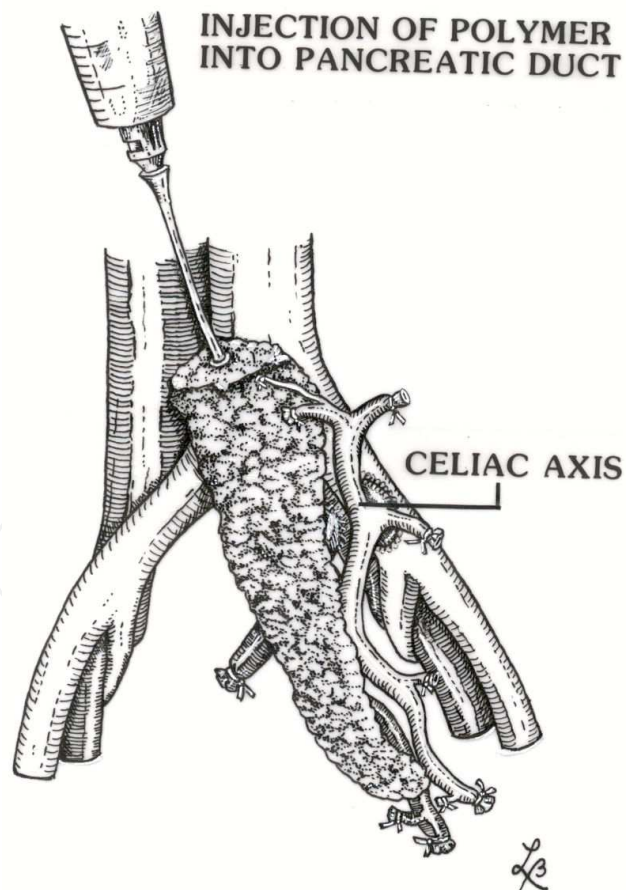


Figure 5. Injection of a synthetic polymer into the duct of a segmental pancreas graft following revascularization. Approximately 4-6 ml of the polymer is injected, followed by ligation of the duct [17-20].

Twelve intraperitoneal open-duct segmental pancreas transplants were performed at the University of Minnesota in a two-year period [16]; four were rejected within 4 months; 3 had to be removed because of peritonitis or ascites. The latter recipient lived insulin-independent for 18 years until in 1996 she died from a trauma, with a functioning graft, the longest duration of function at that time [21].

By contrast the duct occlusion technique became more popular despite numerous leaks, pancreatic fistulae, graft pancreatitis and vascular thrombosis. For managing these complications, Dubernard et al. [17, 7] proposed the omentoplasty in warping the duct-occluded segmental pancreas with the omentum, while Calne et al. [6, 7] was performing an A-V fistula at the distal end of the pancreas tail (Fig 6; panels A and B).

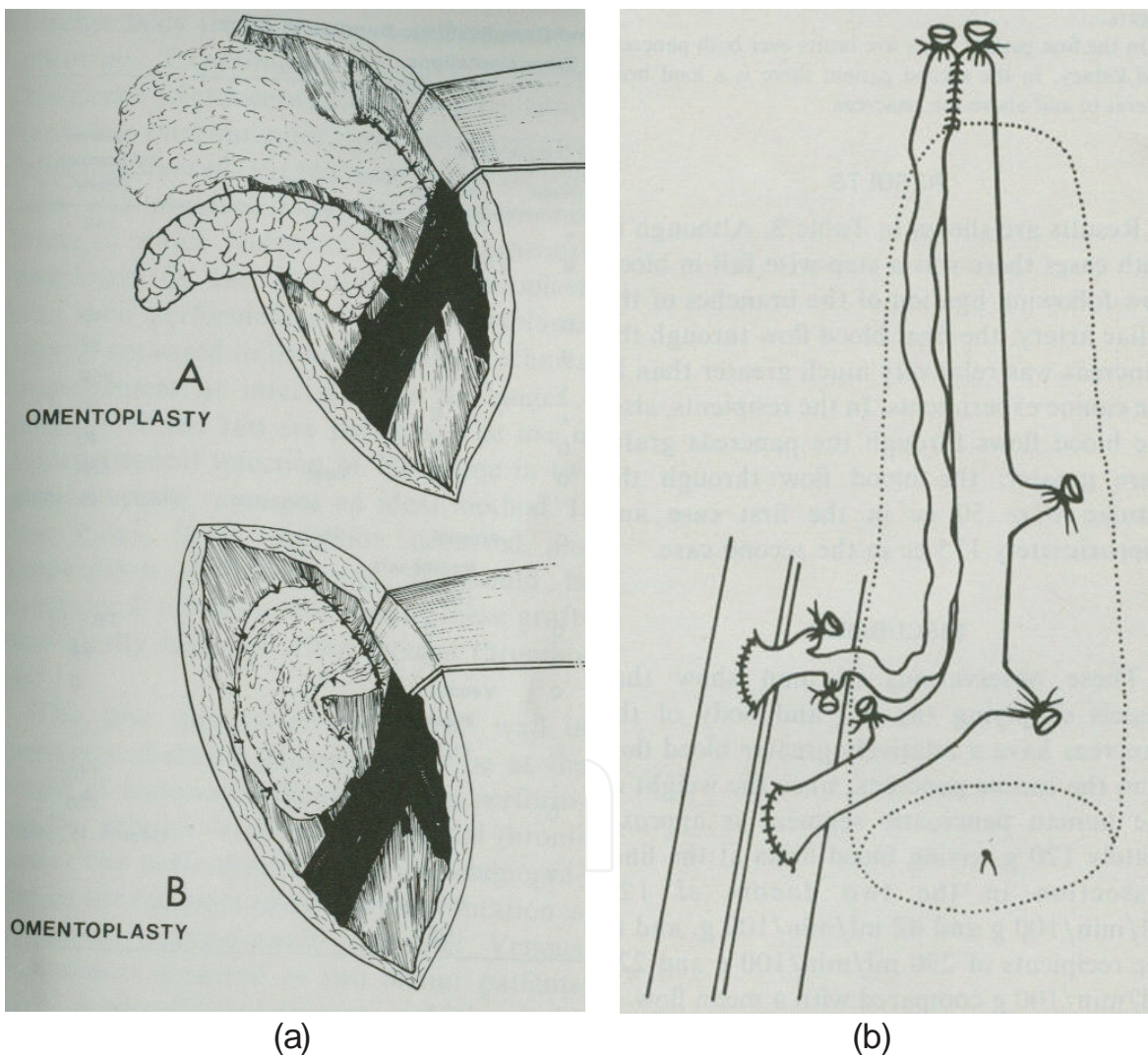


Figure 6. Panel (a): omentoplasty according to Dubernard et al.[7, 17]. Panel (b): AV fistula between the distal splenic artery and vein according to Calne et al. [6, 7].

During the late 70'S, three major events occurred that contributed to the development of PT.

Firstly, in 1979, the clinical use of Cyclosporine A (CsA) by R. Calne et al. [22] as the single immunosuppressant in 36 recipients of cadaveric organs. CsA remained the basic immunosuppressive (IS) drug up to the early 90'S.

Secondly, in 1980, the organization by J.M. Dubernard in Lyon, France, of the first pancreas transplantation meeting, launching the International Pancreas (and Islet) Transplant Registry (IPTR) which was handled by D.E.R. Sutherland at the University of Minnesota [23].

Thirdly and finally, in 1981, the first of a series of 5 workshops – called the Spitzingsee Meeting – organized by W. Land in Kühtai, Austria [24]. The characteristics of these workshops consisted in gathering the world pioneers in PT and allowing them to discuss on not only the successes but also the failures, finding ways to prevent them or improve the results [25]. These meetings were also the basis of creating the International Pancreas and Islet Association (IPITA) and later on, in Europ, the European Study Group in Simultaneous Pancreas and Kidney Transplantation (EuroSPK) [25]. More recently, was created the EPITA, the European Pancreas and Islet Transplantation Association [25].

During one of these workshops, H. Sollinger [26] had the idea to renew an old technique and divert the exocrine secretion of the pancreas into the bladder (Fig 7), while G. Tyden [27] and C. Groth [28] were proposing the enteric drainage (Fig 8). Slowly, both groups moved from the segmental graft [28] to the whole pancreas graft along with a duodenal segment (Fig 9) [26, 27]. This announced the end of the segmental transplantation reign. In the mean time, on November 10, 1982, the first pancreas transplantation was performed in Belgium by J.P. Squifflet and G.P.J. Alexandre [7]. The recipient was a 29 year old female with a 26 year history of type 1 diabetes. She was on peritoneal dialysis since one year and switched to hemodialysis a month before. She received a simultaneous pancreas and kidney transplants from a 22 year old female cadaver donor who died in a car accident from a head trauma. The recipient did not share any HLA antigen with the donor. She received a segmental pancreas graft, anastomosed on a Roux-en-Y loop (Fig 10), according to the technique described by Groth et al. (Fig 8) [23]. The immunosuppressive therapy consisted in a short course of antilymphocytic globulins induction along with cyclosporine A and steroids. She was one of the first few patients who received cyclosporine A in Belgium, at a dose a 14 mgr/kg/day. Following an episode of delayed graft function of the kidney, she fully recovered and was insulin free for a period of 2 years. Than insulin resistance was noticed along with an increase of 15 kg in body weight. Despite Cyclosporin and steroids dose reduction and the introduction of azathioprine, insulin therapy was resumed. She eventually went back on hemodialysis 8 years later and died in June 1992 while waiting for a second kidney transplant. The choice of the surgical technique and IS was based on animal experiments [29–32] but also on the fact that segmental pancreas transplantation was more popular during that period.

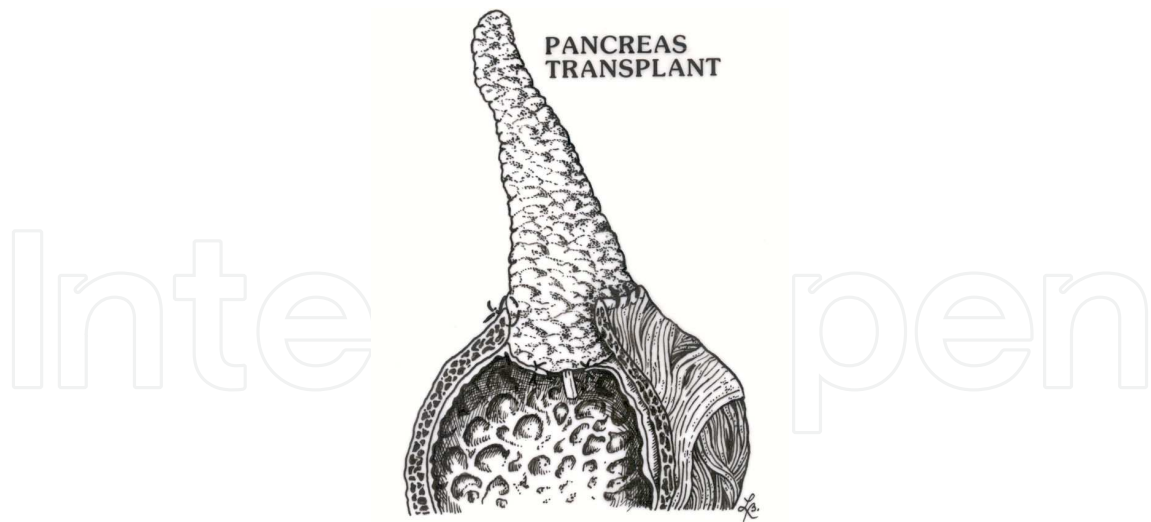


Figure 7. Exocrine secretion of segmental grafts drained directly into the bladder, as first described by Sollinger et al. [26].

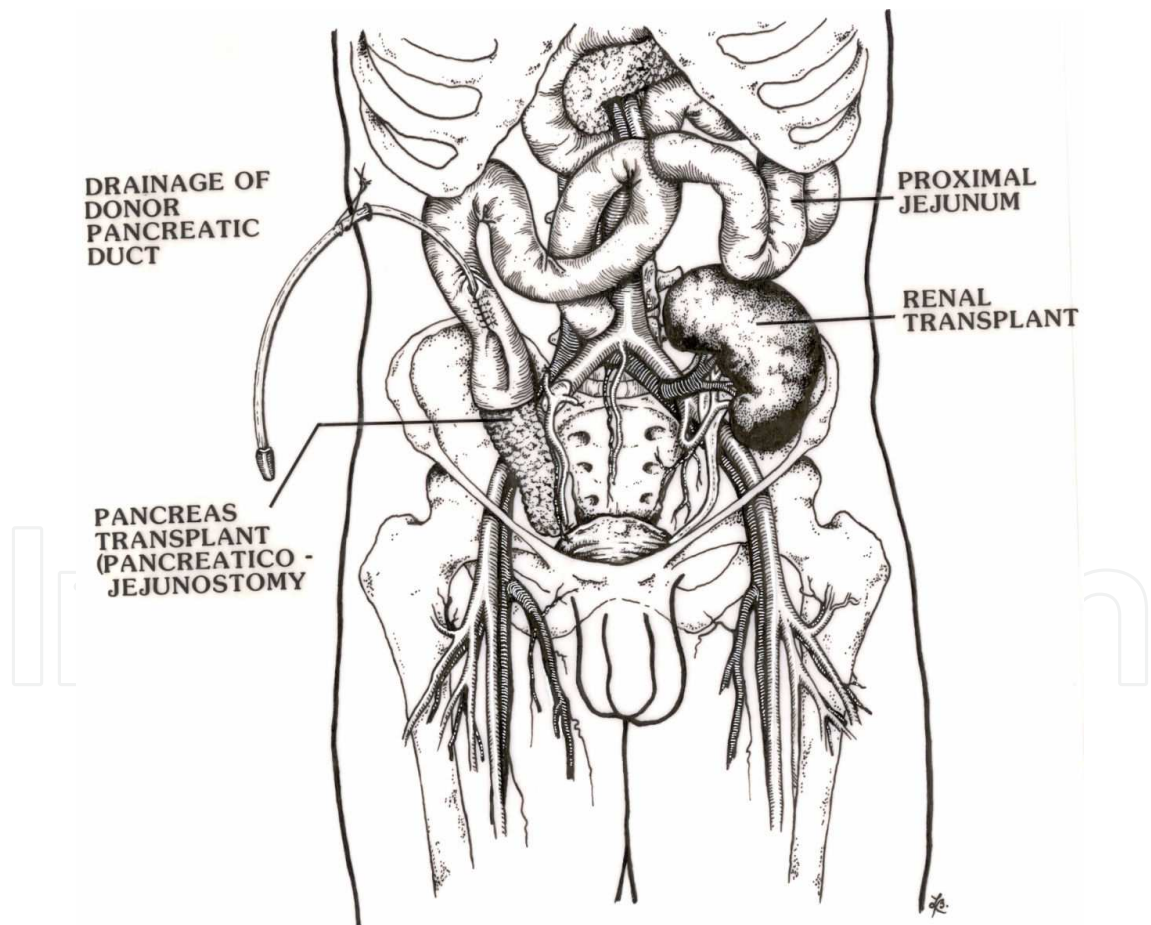


Figure 8. Enteric drainage of a segmental pancreas graft to a Roux-en-Y limb of recipient jejunum. The temporary external drainage of the pancreatic duct secretions to the catheter brought to the Roux-en-Y loop and the abdominal wall is illustrated [28].

2.2. The whole pancreas transplantation reign (from mid 80's)

Thus, in the mid 80's, whole pancreas transplantation with a duodenal segment became the gold standard surgical procedure.

In 1987, Nghiem and Corry at the University of Iowa described the technique of bladder drainage via a graft-to-recipient duodeno-cystostomy for whole pancreaticoduodenal grafts (Fig 9) [33]. Most U.S. and European centers quickly adopted bladder drainage via the graft duodenum. For SPK transplants, the dominant reason to use bladder-drainage was to reduce the risk of anastamotic leaks, since rejection could be monitored by serum creatinine. For solitary pancreas transplants, bladder-drainage had the advantage of urine amylase monitoring for rejection.

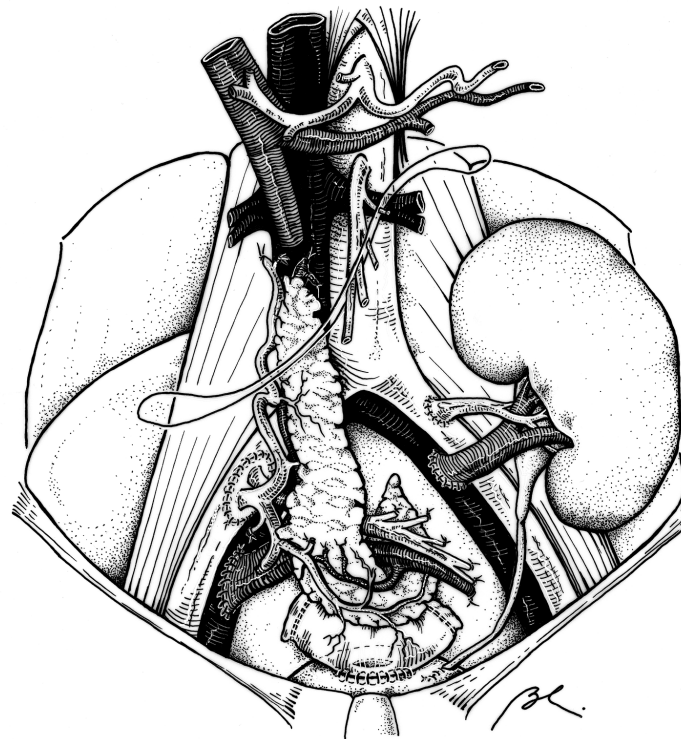
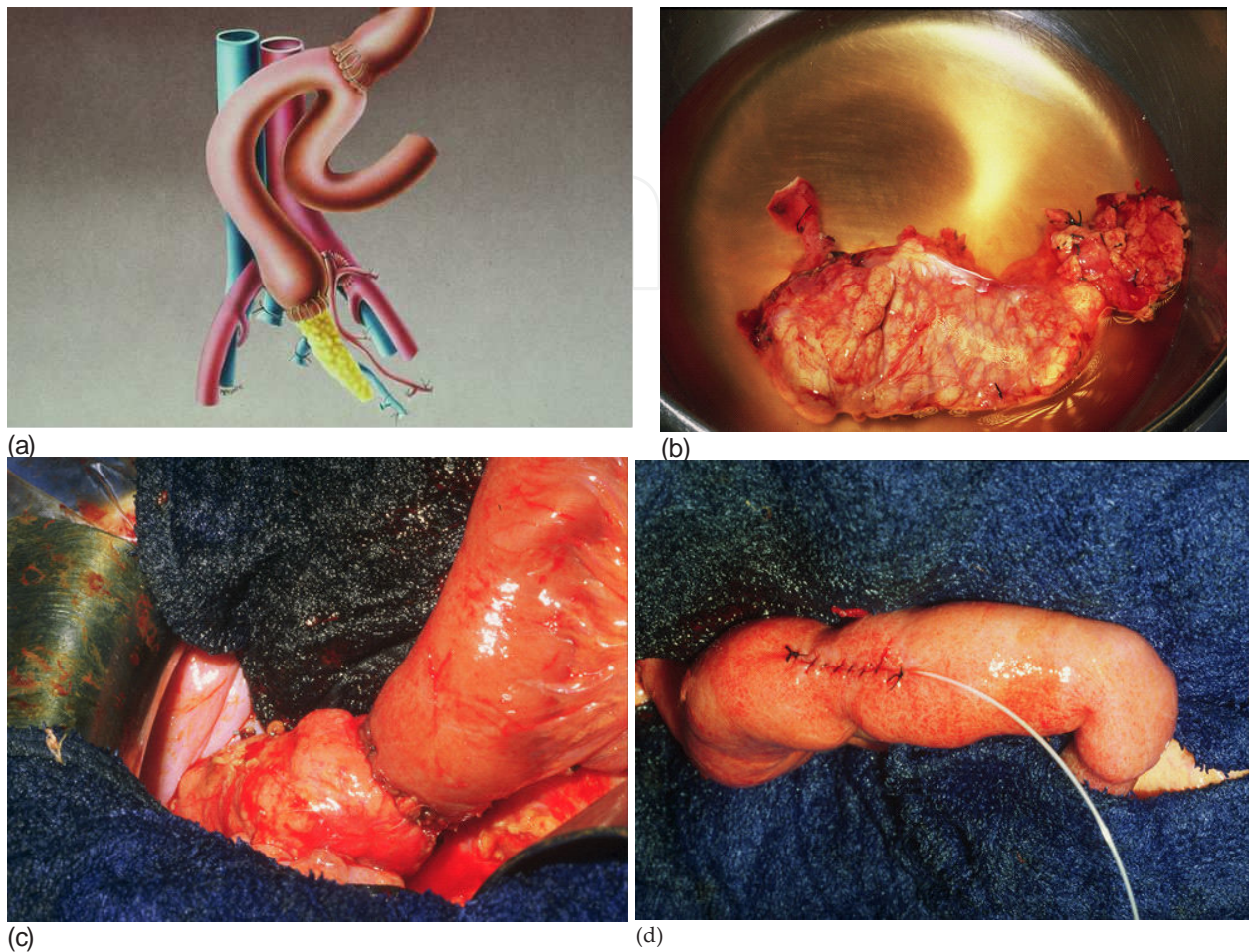


Figure 9. Pancreaticoduodenal transplantation with bladder drainage. A side-to-side anastomosis of the duodenal segment is made to the dome of the bladder [33].

In the mid 80's, Starzl [34] and associates reintroduced in U.S. the technique of enteric-drained whole-organ pancreaticoduodenal transplants, as originally described by Lillehei while the Stockholm group continued to do enteric drainage by direct duodeno-enterostomy [35]. Nearly everyone was convinced that whole pancreaticoduodenal transplants were preferable for PT from cadaver donors, and after en – bloc liver and pancreas procurement (Fig 11), transplant surgeons designed methods for reconstructing the vasculature to both organs (Fig 12) [36 - 39].



a: drawing of the procedure.
 b: the segmental pancreas graft.
 c: the end-to-end pancreas graft anastomosis to the Roux-en-Y loop.
 d: the anastomosis suture was protected by a catheter inserted into the pancreas duct.

Figure 10. Segmental pancreatic transplant in the first Belgian recipient with enteric diversion of the exocrine secretion, in a Roux-en-Y loop.

From the mid-80s to the mid-90s, bladder drainage became the most common technique worldwide (Fig 9). However, because of chronic complications of bladder drainage (urinary tract infections, cystitis, urethritis (Fig 13), reflux pancreatitis, hematuria, metabolic acidosis and dehydration from fluid and bicarbonate losses), leading to conversion to enteric drainage in approximately a quarter of the recipients, in the mid-1990s, surgeons began to shifted to primary enteric drainage (Fig 14), not only for SPK transplants, but at some institutions also for solitary pancreas transplants [40].

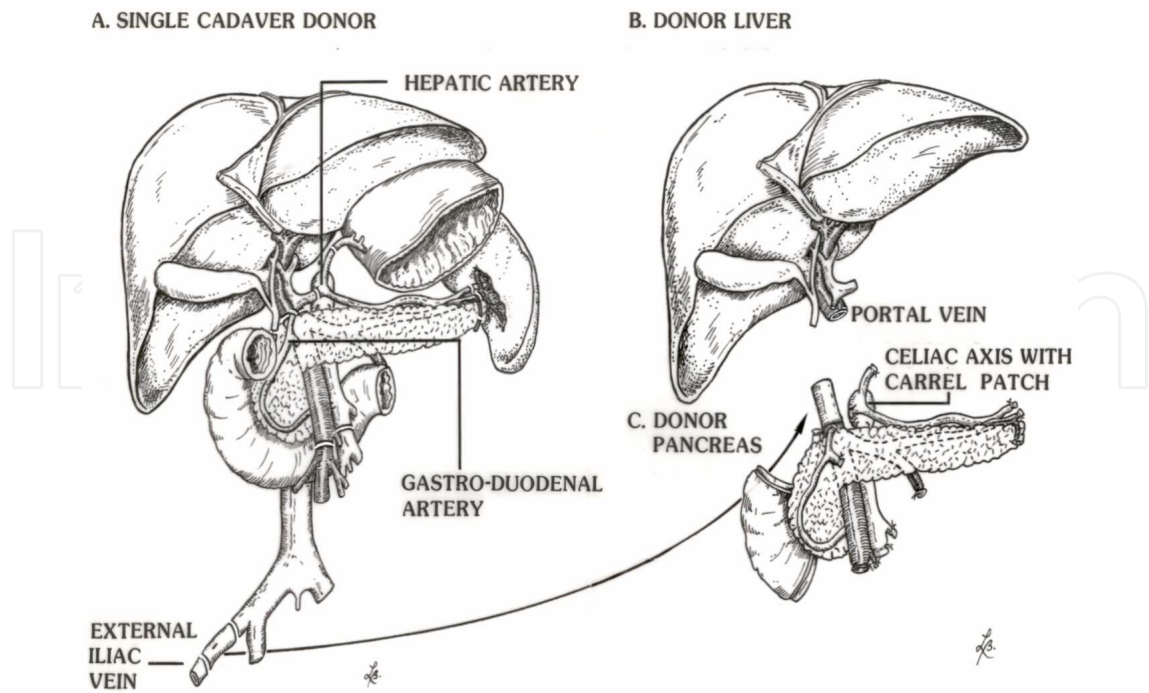
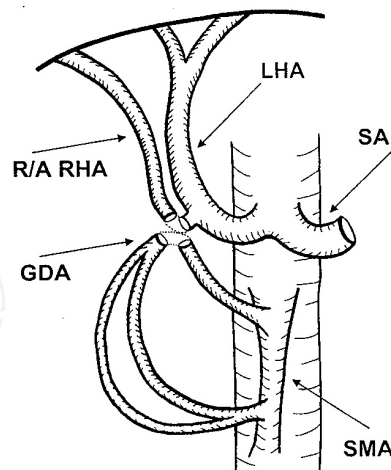


Figure 11. Maneuvers for en-bloc removal of a whole pancreas and a liver from a cadaver donor with normal vascular anatomy. The gastroduodenal artery must be divided so that the common and proper hepatic arteries can remain in continuity and be retained with the liver. The portal vein is divided just superior to the entrance of the splenic vein. Then, the pancreatic portion is lengthened by an iliac vein graft. The celiac and superior mesenteric arteries can remain with the pancreas with a Carrel aortic patch. [38]

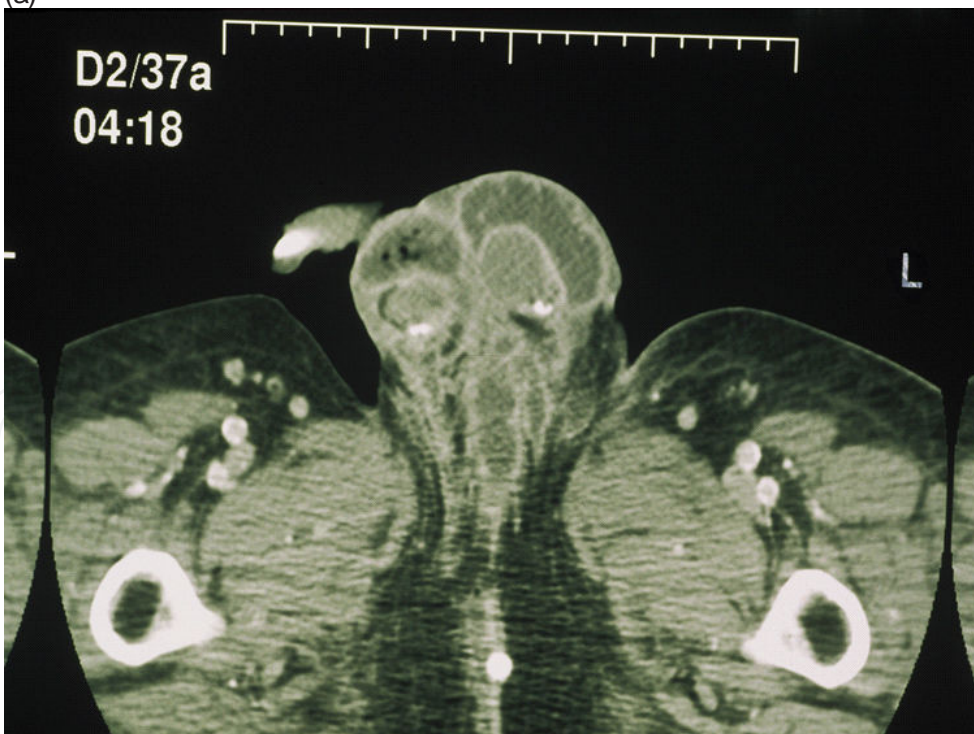


LHA = left hepatic artery.
 GDA = gastroduodenal artery
 SA = splenic artery
 SMA = superior mesenteric artery. [39]

Figure 12. Whole-pancreas procurement and reconstruction of its arterial supply in a donor with a replaced / accessory right hepatic artery (R / A RHA).



(a)



(b)

Figure 13. Chemical urethritis in a pancreas recipient with bladder drainage of the exocrine secretion (Panel (a)). CT scan: same recipient (Panel (b)).

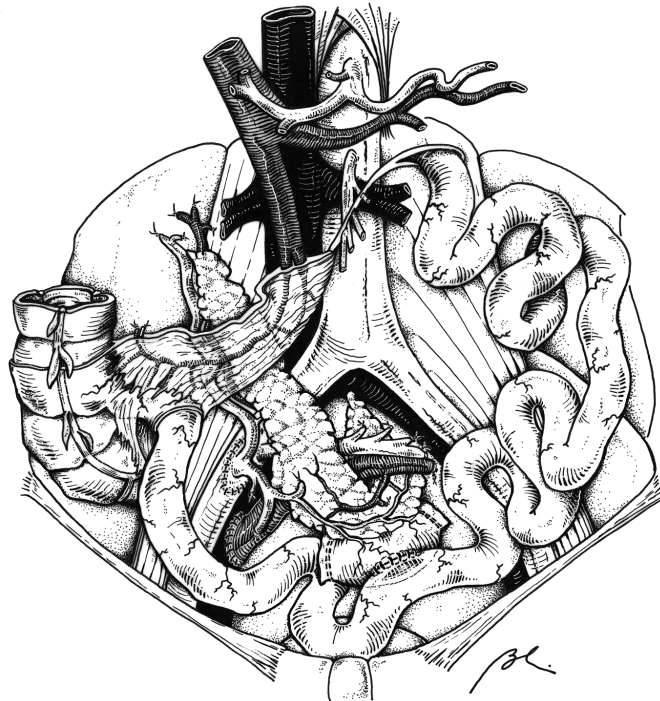


Figure 14. Pancreaticoduodenal transplantation with enteric drainage. A side-to-side anastomosis of the duodenal segment is made to the distal ileon, or the proximal jejunum. It can also be performed on a Roux-en-Y loop [35].

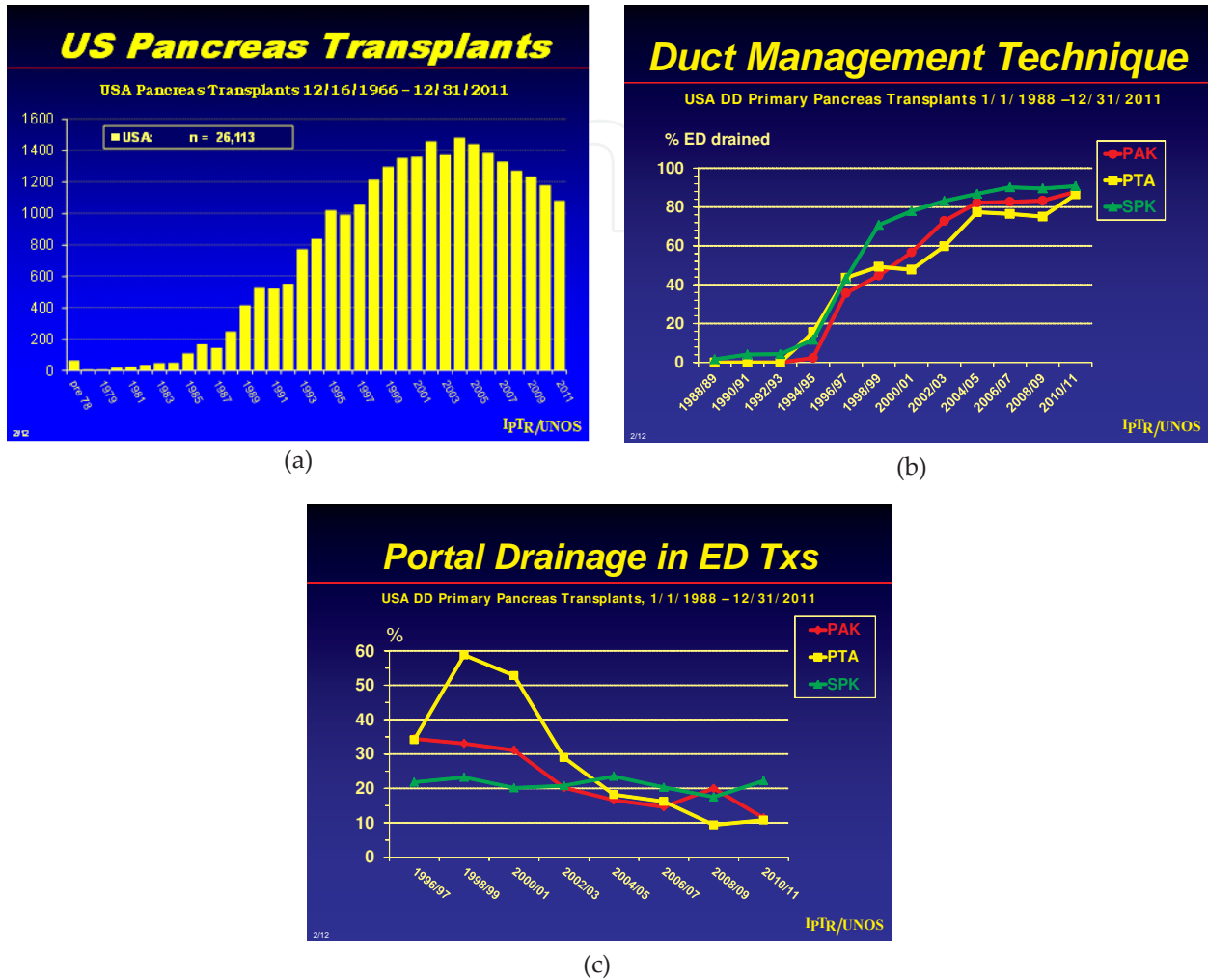
2.3. The modern era of surgical techniques

Either enteric or bladder drainage is now done for virtually all pancreas transplants using a whole pancreas graft with a duodenal segment. The other techniques are virtually never used unless for salvage of a technical situation (e.g., duct injection might be used to manage a leak). With regard to the venous drainage of pancreas grafts, portal would be the most physiological but the systemic venous system was only accessed during the first two decades. Later on, the use of portal drainage at the junction of the recipient's superior mesenteric and splenic vein was favored in recipients of enteric drained whole-organ pancreaticoduodenal transplants (Fig 15). Surgeons reported on its metabolic and possible immunologic advantage, features also noted at the University of Maryland, where a large program existed of conversion to almost exclusive portal drainage [41]. By the end of the 1990's, almost 20 % of pancreas transplants in U.S. and in Europe were being done with portal drainage but the proportion did not increase nearly as much as the proportion of pancreas grafts that were enteric drained, reaching over 80 % for solitary in U.S. and over 90 % for SPK transplants in Europe (Fig 16). Early diagnosis of pancreas rejection had been difficult from the beginning, in particular for solitary pancreas transplants where serum creatinine could not be used as a surrogate marker

like in SPK. That's why there is still room for improvement in surgical techniques. In order to have easy access to the graft for performing biopsies, De Roover et al. [42] proposed recently a technical modification and a side-to-side duodeno-duodenal (D-D) anastomosis while using a whole pancreaticoduodenal transplant with the venous effluent drained into the portal system of the recipient (Fig 17, 18). It offers serial sampling of the duodenal transplant mucosa by simple fibrosopies, a useful tool for monitoring rejection (Fig 18, Panel B). The duodenal anastomosis can be hand-made or performed using a stapler device. But the major drawback of both techniques could be the management of duodenal leaks on graft thrombosis. Our experience in 11 pancreas recipients at the University of Liege, CHU Sart Tilman is summarized in table 1. Peri-pancreatic collections, with or without pancreatitis were managed by surgical exploration and drainage. So far, only one graft thrombosis (PTA) needed prompt removal but was followed by a duodenal leak with cutaneous fistula which required weeks before healing (table 1). Therefore, prospective studies will be useful to specify the place of the D-D and each particular surgical suturing technique.



Figure 15. Pancreaticoduodenal transplantation with enteric drainage and portal drainage at the junction of the recipient's superior mesenteric and splenic veins [41].



*By courtesy from A.E. Gruessner
 Department of Surgery,
 University of Arizona, Tucson, USA.

Figure 16. International Pancreas Transplant Registry * Panel (a): US Pancreas Transplants per year, between 12/16/1966 and 12/31/2011. Panel (b): Duct management techniques (urinary versus enteric drainage) in US primary pancreas transplants, between 1/1/1988 and 12/31/2011. Panel (c): Portal Drainage in enteric drained (ED) transplants. US primary pancreas transplants, between 1/1/1988 and 12/31/2011.

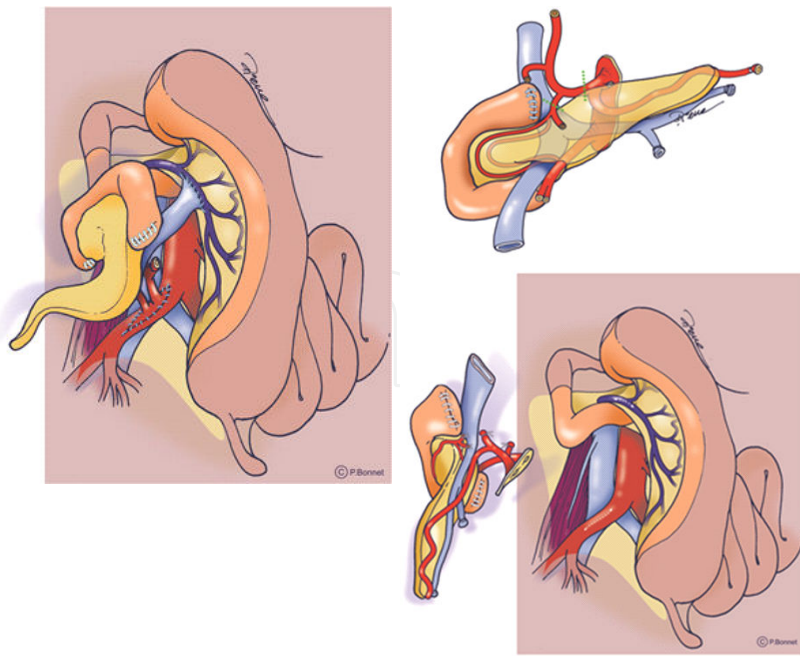


Figure 17. Pancreaticoduodenal transplantation with portal drainage and side-to-side recipient duodenal drainage of the exocrine secretion [23]: schematic representation and positioning.

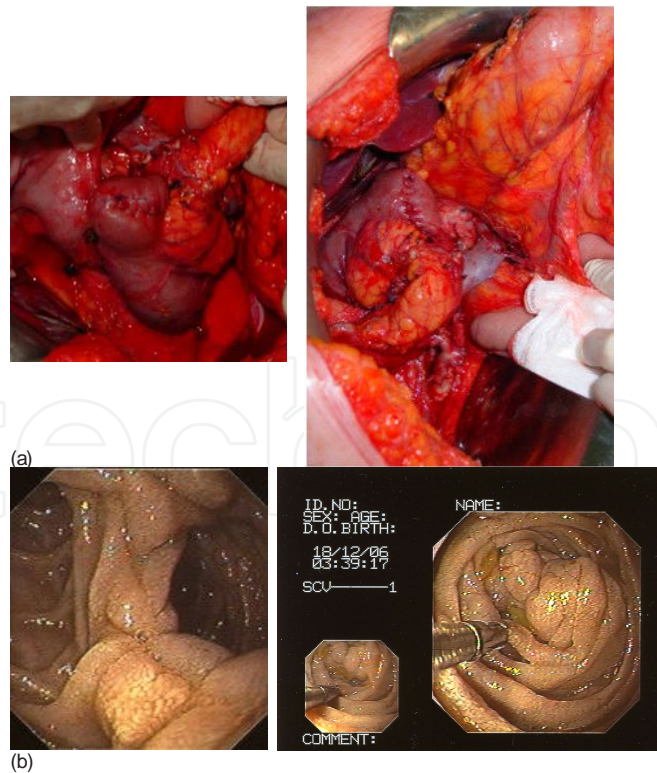
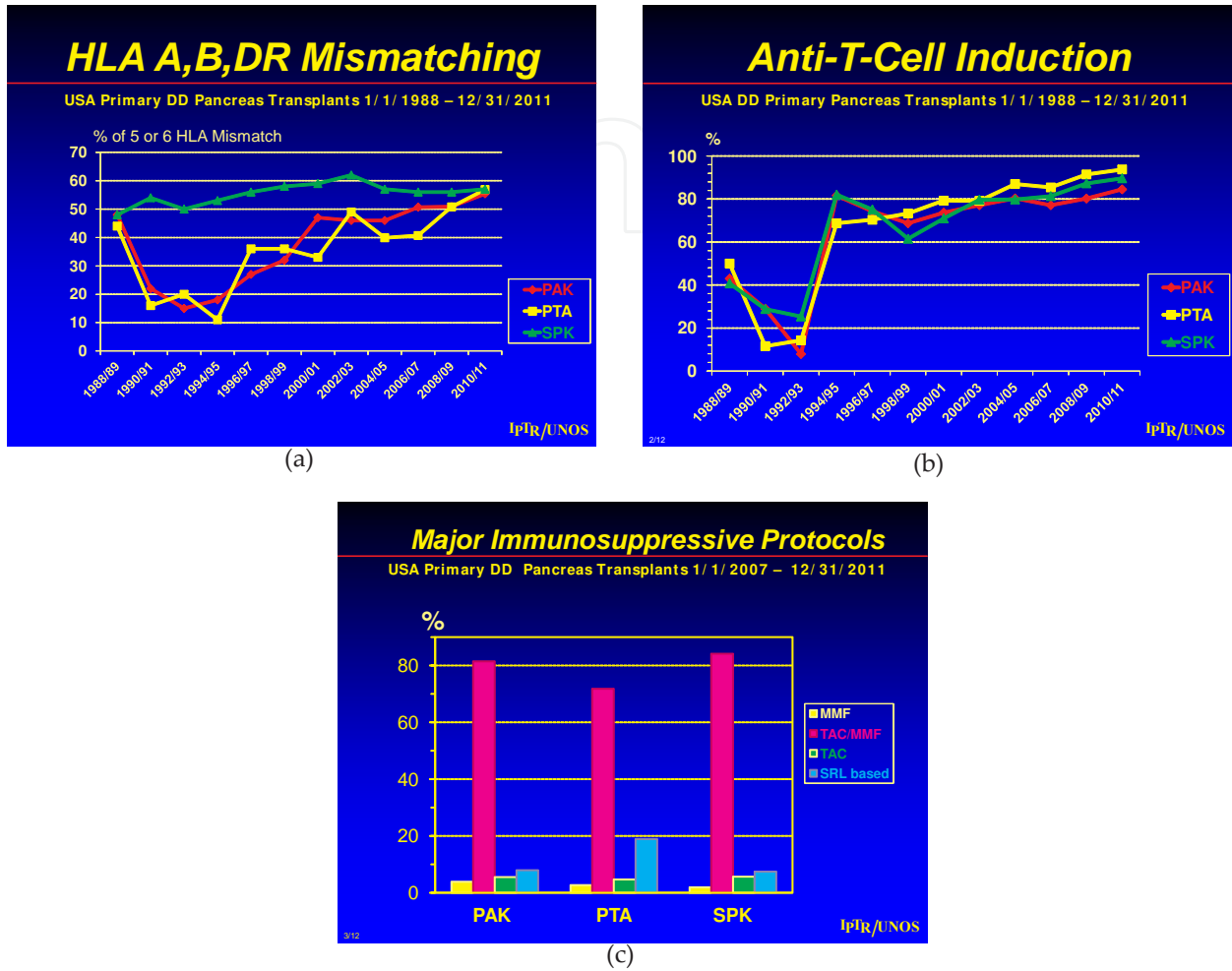


Figure 18. Pancreaticoduodenal transplantation with portal drainage and side-to-side recipient duodenal drainage of the exocrine secretion [23]: Panel (a): per operative view Panel (b): endoscopic view of the duodenum



*By courtesy from A.E. Gruessner
 Department of Surgery,
 University of Arizona, Tucson, USA.

Figure 19. International Pancreas Transplant Registry* Panel (a): Percentage of 5 or 6 HLA A, B, Dr Mismatching in US primary pancreas transplants between 1/1/1988 and 12/31/2011. Panel (b): Anti-T-Cell induction in US primary pancreas transplants between 1/1/1988 and 12/31/2011. Panel (c): Major immunosuppressive protocols in US primary pancreas transplants between 1/1/2007 and 12/31/2011

<ul style="list-style-type: none"> ■ PTA hand-made (n=7): <ul style="list-style-type: none"> ■ Peri-pancreas hematoma + inflammatory syndrome (1)* ■ Graft thrombosis (1)* ■ Pancreatitis + peri-pancreas fluid collection due to partial necrosis of pancreas (1)* ■ PTA stapler (n=0) 	<ul style="list-style-type: none"> ■ Surgical exploration + drainage ■ Transplantectomy ■ Surgical exploration + drainage
<ul style="list-style-type: none"> ■ SPK hand-made (n=1): no. ■ SPK stapler (n=3) <ul style="list-style-type: none"> ■ Peri-pancreas fluid collection + inflammatory syndrome (1)* ■ Digestive hemorrhage due to ulcers of the donor duodenal stump (1) 	<ul style="list-style-type: none"> ■ Surgical exploration + drainage ■ Conservative treatment+transfusion

Table 1. Complications and outcome in 11 recipients of whole pancreas grafts with duodeno-duodenostomy, at the University of Liege, CHU Sart Tilman. The D-D anastomosis was hand-made (n=7) or using a stapler device (n=4)

3. The history of immunosuppression in pancreas transplantation

Advances in immunosuppressive protocols and the introduction of new immunosuppressants have had a major impact on and improved outcome after PT. As already mentioned, in 1979, Calne and associates first reported the successful use of cyclosporine in two pancreas recipients [22]. Due to the large dose of CsA used as a single agent and its nephrotoxicity, Starzl et al. proposed to combined reduced doses of CsA with steroids [43]. Further decreased in CsA dosages by using the synergistic effect of combining CsA to Aza was proposed by Squifflet et al. based on animals experiments [29, 44]. Triple drugs combining CsA, Aza and Steroids and later on quadruple drugs regimen with a short course induction of polyclonal Antibodies was the mainstay IS regimen during the next decade [21]. Starzl and his team first reported the use of Tacrolimus (Tac) in pancreas allograft recipients during the investigative period in 1989. [45] After approval, the first report on the use of Tac for pancreas transplantation was by D. Shaffer and associates, successfully reversing ongoing acute rejection in two SPK recipients. [46].

A major topic of the 4th Spitzingsee Workshop (January 30 – February 02, 1997; Kühtai, Austria) was the IS therapy in PT [25]. At that time, the newly introduced agent mycophenolate mofetil (MMF) was proved to be superior to azathioprine (Aza) for the prevention of acute rejection in kidney transplantation patients [47]. Data comparing Tac with the old (oil-based) formulation of CsA were also available in kidney transplantation, but there were some concerns about Tac having a diabetogenic effect [48], specially for pancreas. A preliminary study investigating the use of Tac in pancreatic transplantation, which was published by Gruessner et al., showed that pancreatic graft survival at 6 months post transplant was higher with Tac (79%) than in a historical group of SPK recipients treated with the oil-based formulation of CsA (65%; $p = 0.04$)

[49]. During the same era, the new micro-emulsion (Me) formulation of CsA (CsA – Me) had been introduced into clinical practice.

At that period, all European participants to the meeting were performing a limited number of SPK per centre. All realized that local studies would not aim solving the IS problems. Therefore W. Land took the opportunity to propose them the first large international prospective multicentre study in the field of PT, comparing Tac to the new CsA – Me, along with MMF, corticosteroids and a short course of induction therapy with Rabbit – antithymocyte globulines (R-ATG, Fresenius, Germany).

The rationale for induction therapy using anti-T-cell agents was triple: minimizing the risks of early rejection episodes, accelerating recovery of renal and pancreatic allograft function (protection against the ischemic reperfusion injury) and perhaps, inducing a tolerogenic effect to donor alloantigens. Before 1994, choices of maintenance IS agents were limited to a “one size fits all” approach with the combined use of Cyclosporin A (CsA), azathioprine (Aza) and corticosteroids. But, with that regimen, rejection rates were about 75 % to 80 %, with a rate of 25 % to 30 % of recurrence. Therefore, during the early 90’s anti-T-cell induction was automatically added in all 3 categories of pancreas transplantation (Fig 19, Panel B). The choice of the anti-T-Cell agent was based more on its accessibility than on any rationale or scientific approach; the anti-T-Cell agents which were used are: MALG®, OKT3®, ATGAM®, R-ATG®, Simulect®, Zenapax®, Thymoglobulin®, Campath®. During the CsA era, single centre studies emphasized the benefit of Quadruple over Triple therapies [50, 51]. Other comparative studies underlined the best efficacy of ATG over OKT3® and MALG® [52 - 54]. During the modern era, during which most centres were using Tacrolimus (Tac), Mycophenolate Mofetil (MMF) and corticosteroids for maintenance therapy, Kaufman et al. designed several multicenter studies [55, 56] in which they confirmed the usefulness of induction therapy in PT. By contrast, the place of Campath®, still remains to be confirmed [57].

The results of the first Euro-SPK study were encouraging [58]. The 1-year incidence of biopsy-proven acute rejection of the kidney or pancreas was lower with Tac (27.2 %) than with CsA-Me (38.2 %; $p = 0.09$). Pancreatic graft survival at 1 year was significantly higher with Tac (91.3 %) than with CsA-Me (74.5 %; $p = 0.0014$). Kidney graft survival was similar in the two groups [58].

At 3 years, fewer patients receiving Tac (36.9 %) than CsA-Me (57.8 %) were discontinued from treatment ($p = 0.003$). The initial episodes of biopsy proven rejection were moderate or severe in just one out of 31 (3 %) Tac-treated patients compared with 11 of 39 (28 %) patients receiving CsA-Me ($p = 0.009$).

While 3-year patient and kidney survival rates were similar in the two treatment groups, pancreas survival was superior with Tac (89.2 vs 72.4 %; $p = 0.002$). Thrombosis resulted in pancreas graft loss in 10 patients receiving CsA-Me and in only 2 treated with Tac ($p = 0.02$). The overall incidence of adverse events was similar in both groups, but MMF intolerance was more frequent with Tac whereas hyperlipidaemia was more frequent with CsA-Me. Acute rejection was more common among CMV-infected patients (66 vs 41 % without infection; $p = 0.001$) and in those not receiving ganciclovir prophylaxis [48, 58].

There were no differences in 3-year kidney pancreas or patient survival between the 0-3 and 4-6 HLA antigen mismatch (MM) groups. Significantly more patients with 0-3 MM (66 %) were rejection-free at 3 years compared to those with 4-6 MM (41 %; $p = 0.003$). The relative risk of acute rejection was 2.6 times higher among patients with 4-6 MM than among those with 0-3 MM [48].

In summary the Euro-SPK study findings provided evidence to support the use of Tac in patients undergoing SPK transplantation.

A second SPK study addressed the issue of the choice of the antiproliferative agent which could be associated to Tac, either MMF or rapamycin (Rapa). Preliminary one and three year results demonstrated more frequent study withdrawal in the Rapa group, due to toxicity [59].

More than 60 % of those patients were rejection free at 1 year. Adequate kidney and pancreas functions were also achieved in both groups while the serum creatinine level was significantly lower in the Rapa group from month 2, the price to pay being hyperlipidemia, delayed wound healing, lymphocele or hernia.

Corticosteroid withdrawal was possible in both studies in 70 % and 50 % of recipients respectively. Therefore, it can be concluded that steroid withdrawal is feasible in SPK transplantation but not in all patients; further studies must be designed to address that issue completely.

4. Conclusion

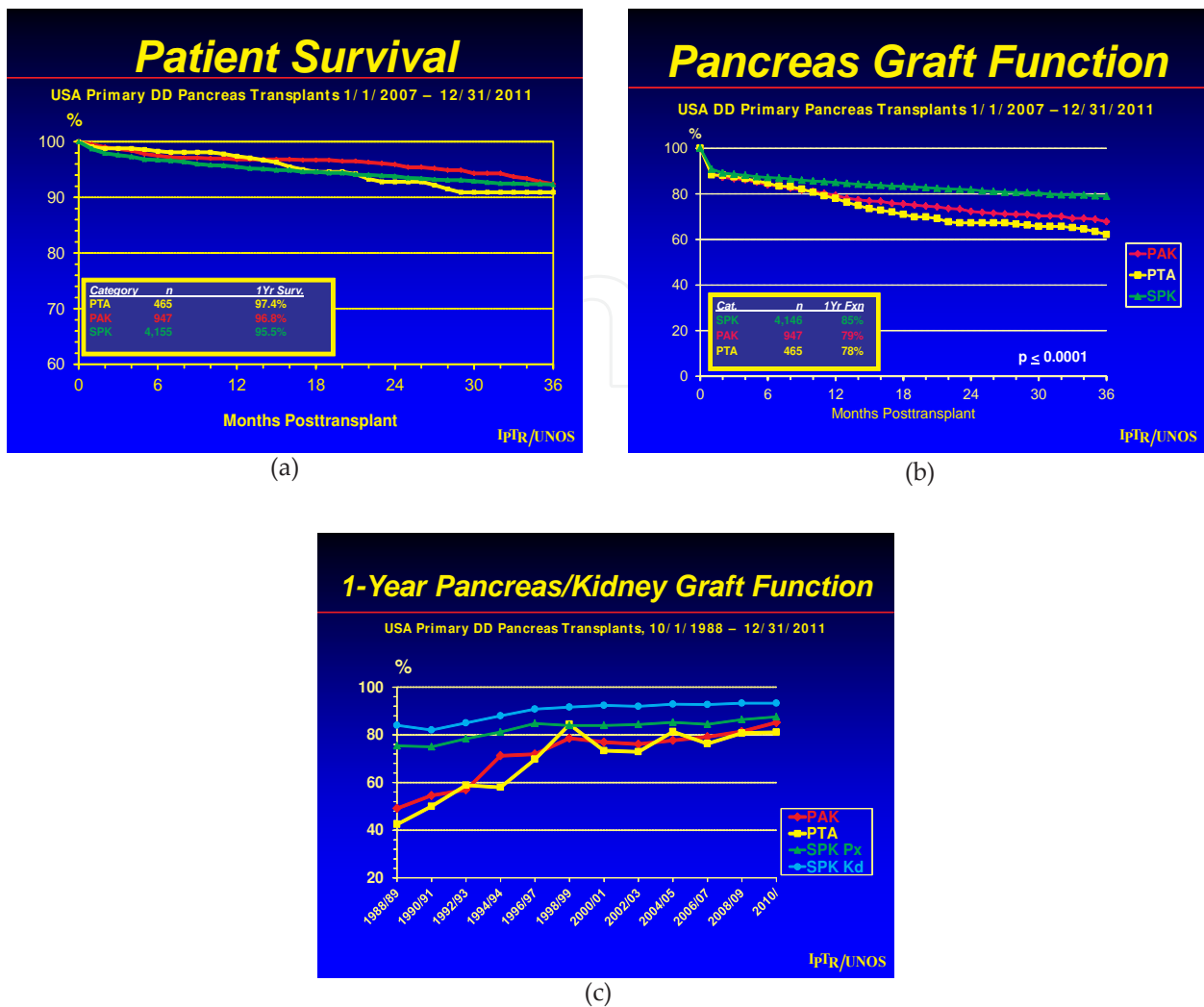
The current gold standard IS therapy for all three categories of pancreas transplantation includes induction with polyclonal antibodies and for the maintenance therapy, association of Tac with either MMF or Rapa, the last drug being less popular at least during the first postoperative period due to its possible side-effects (Fig 19).

Based on that potent IS therapy, functional results and patient survival rates of PT are coming closer to those currently achieved in kidney transplantation (Fig 20).

SPK transplantation remains the best therapeutic approach for type 1 diabetic recipients with (pre) end-stage renal failure (creatinine clearance $< 50\text{ml/min}$), up to 55 years of age, without any cardiovascular risk. They have three options: either waiting for the 2 grafts coming from the same -cadaver or live- donor, or one graft –usually the kidney – coming from a live donor who is in stand-by while waiting for the pancreas from a cadaver donor.

PAK can be offered to diabetic recipients who had the opportunity of having a live donor for kidney transplantation.

For other type 1 diabetic recipients, with (pre) end-stage renal failure, more than 55 years of age, with cardiovascular risk factors, they have 2 options: either receiving a kidney transplant alone (and eventually waiting for islet cells) or waiting for a simultaneous islet and kidney transplantation from the same cadaveric donor.



*By courtesy from A.E. Guessner
 Department of Surgery,
 University of Arizona, Tucson, USA.

Figure 20. International Pancreas Transplant Registry* Panel (a): Patient survival in US primary pancreas transplants between 1/1/2007 and 12/31/2011. Panel (b): Pancreas graft function in all 3 categories (SPK, PAK, PTA). Panel (c): One year pancreas and kidney graft function in US primary pancreas transplants, between 10/1/1988 and 12/31/2011.

PTA should be considered for selected type 1 diabetic candidate without nephropathy, with hypoglycemia unawareness syndrome, with proliferative retinopathy. These candidates could be also candidates for islet transplantation, knowing the fact that they will be submitted to the same IS therapy and its long term deleterious side-effects in both options, they might also know that, with islet insulin independence is not always achieved.

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