



History of Pancreas Transplantation

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The First Transplant of Pancreatic Tissue

On December 20, 1893, 3 years after von Mering and Minkowski had shown that total pancreatectomy in dogs resulted in diabetes mellitus [1], Dr. P. Watson Williams in Bristol, England, grafted three fragments of a pancreas obtained from a freshly slaughtered sheep into the subcutaneous tissue of a 15-year-old boy in extremis, 5 months after clinical onset of diabetes [2]. The recipient died 3 days later, not of complications from the unsuccessful transplant, but of unrelenting acidosis, a sequela of basically untreated diabetes. At autopsy, the recipient's own pancreas was shriveled, and sections showed little but fibrous stroma. According to Williams, the history and the postmortem examination left

little doubt that the patient had “pancreatic diabetes,” a case that “presented all the conditions that might lead one to hope for beneficial results from successful grafting of the pancreas, if anything can be hoped for in this direction at all.” He was not discouraged, and further stated that “failure was possibly due to obtaining the graft from a sheep that had been killed by bleeding If ever I felt justified again in resorting to pancreatic grafts in a similar case, I should obtain them from a living animal anesthetized or dispense with the anesthetic altogether.”

Williams' use of the term “pancreatic diabetes” reflected the prevailing attempts at classification by etiology and the concept that not all cases of diabetes are secondary to an abnormality of the pancreas. He mentions the canine pancreatic extirpation experiments of Minkowski (not naming von Mering) that resulted in diabetes (no citation, implying it was general knowledge) and the clinical cases of diabetes associated with severe pancreatic atrophy secondary to calcareous ductal obstruction reported by Freylan (Berl Klin Woch 1893;6). On the other hand, he cautions not to overlook the results of the investigations of the pancreas in cases of

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diabetes by Williamson (no citation, but probably R.T. Williamson, author of *Diabetes Mellitus and Its Treatment*. Edinburgh; 1878), which showed that in 50% the gland was normal in structure, “rendering it evident,” in Williams view, “that we must guard against attributing too important position to the pancreas as a factor in diabetes mellitus.”

Williams’ 1894 article conveys the prevalent confusion over the relation of the pancreas to diabetes. Before grafting the sheep pancreas, Williams gave extracts of sheep pancreas, first orally and then by injection (without effect, a failure that he noted duplicated that of others), actions that reflected the uncertainty over whether an external or internal pancreatic secretory product was crucial in maintaining glucose homeostasis.

The tone of Williams’ 1894 article suggests that his reference to Minkowski was to the 1890 publication coauthored with von Mering that dealt strictly with pancreas extirpation—and not to the canine pancreas autotransplant work Minkowski published in 1892 [3], which made an internal secretion the most tenable hypothesis.

Similarly, as also published in 1892 [4], Hedon did a partial pancreatectomy in dogs and transposed the pancreatic remnant (uncinate process)—totally disconnected from the duodenum but on a vascular pedicle—to the subcutaneous tissue with creation of a ductocutaneous fistula, so that reconnection to the intestine was impossible (thus addressing a criticism of earlier experiments). Diabetes did not ensue, proving that an internally secreted substance must exist [4].

In addition, in 1893 Laguesse named the nonacinar clusters of cells scattered throughout the pancreas the “islets of Langerhans” [5] after Paul Langerhans, who first described these formations (Zellhaufen) in his doctoral thesis at the University of Berlin in 1869 [6]. Undoubtedly, Williams was not aware of the post-1889 experiments of Minkowski in Strassburg (then in Germany) or of Hedon in Montpellier, nor of the suggestion of Laguesse that the islets were the source of the postulated internal secretion (indeed, Laguesse coined the term *endocrine secretion* [5] and later, in animal experiments, was one of the first to show that ligation of the pancreatic duct was followed by atrophy of the acinar cells, usually without destruction of the islets or without development of diabetes [7]).

Laguesse’s insight shifted the focus of correlating diabetes and pancreatic pathology from the gross and general to the microscopic and particular [8]. Several investigators, using advances in techniques leading to distinction of cell types (with the β -cell ultimately identified as the source of the internal secretion named insulin), clearly described islet lesions, or even the absence of islets in the face of no other abnormalities, in association with diabetes mellitus [9–14]. However, there were also cases of diabetes where no islet pathology was discerned, and there were examples of islet

pathology in the absence of diabetes [8]. Thus, the clinical-pathologic correlation of diabetes and the pancreas remained confusing at both microscopic and gross levels.

In Williams’ day, the clinical classification of diabetes was little more than a general recognition of mild and severe forms. The mild form was seen more commonly in adults and associated with obesity (*diabetes gras*); the severe form was more common in children and associated with leanness (*diabetes maigre*) [15].

However, at the end of the nineteenth century, it was clear that there was a form of diabetes that should be amenable to treatment by pancreatic extracts or transplants. Both extracts and transplants were successfully applied in the twentieth century [16, 17] and remain as treatments in the early part of the twenty-first century. The development of both these treatments—exogenous insulin and transplants (β -cell replacement)—depended on the persistent efforts of individuals who built on the cumulative knowledge and technical advances of preceding generations in multiple disciplines.

The Dual Nature of the Pancreas

It took centuries to understand that the pancreas is a nearly unique organ with dual components that function more or less independently: (1) the exocrine portion (98% of the gland), connected by a ductal system to the intestine, excretes lytic enzymes to aid in digestion; and (2) the endocrine portion, comprised of about one million separate cellular spheres scattered throughout the gland—called islets because of their appearance when sliced in histological section. The islets secrete hormones into the blood stream, of which one, insulin, is essential to sustain life by its promotion of carbohydrate metabolism in nearly all tissues of the body. End-stage disease can occur simultaneously in both components of the pancreas (endocrine or exocrine), but more often one component is affected and the other is not.

Given its dual nature, the entire pancreas can be transplanted as an immediately vascularized graft to correct endocrine deficiency alone (most common), exocrine deficiency alone (rare), or both. Or, the endocrine portion (islets) can be isolated and transplanted as a free graft to an ectopic site in a diabetic recipient, restoring autoregulated insulin secretion after neovascularization occurs. Within the islets, β -cells synthesize and secrete insulin. Insulin acts at the cell membrane level, facilitating entry of glucose into the cell for metabolism. The role of the β -cell is to maintain blood sugar levels within a narrow range. The brain does not require insulin to drive glucose into the cells but does require a sufficient level of glucose in the blood so that enough is constantly available for metabolism. Thus, β -cells are not only synthesizers and secreters, but also glucostats (analogous to mechanical thermostats or humidistats). They turn on to

secrete insulin when the blood sugar rises above the threshold level (about 83 mg/dL) and shut off when the blood sugar reaches or is below this level [18]. The β -cell is the ultimate in a close-looped insulin pump.

Discoveries About the Relationship Between the Pancreas and Diabetes Mellitus

The highlights of discoveries about pancreatic anatomy and physiology were described by Busnardo [19], by Child in his history of pancreatic surgery [20], and by Wellman and Volk in their historical review of the diabetic pancreas [8]. Landmarks in the evolution of our understanding of the nature of diabetes were summarized by Papaspyros [21] and Levine [22] and put in perspective by Gale [23].

In early English writings, the pancreas was called “sweetbread,” [24] and the term has persisted in the language of the abattoir. The pancreas was grossly described around 300 BC by Herophilus of Chalcedon who is considered to be the first anatomist in the Western world to systematically perform scientific dissections of deceased human. It took four more centuries before it was given its name (pan=all; creas=flesh), in the second century AD, by Ruphos of Ephesus, a follower of Hippocrates. Galen (ca. AD 130–201) referred to the pancreas in his writings, but without an understanding of its function [20].

However, even the exocrine function of the pancreas was not understood until Claude Bernard performed his experiments in the mid-nineteenth century [25]. The realization that the pancreas must have a dual nature, with both external and internal secretions, did not occur until the end of the nineteenth century [26]. Diabetes mellitus, as a syndrome with clinical characteristics, was described in ancient medical writings of several cultures [21]. Yet, it was centuries before an association with pancreas pathology was described—sketchily in the eighteenth century but not definitively until the nineteenth century [8].

From the time Galen described the pancreas as a cushion for the stomach, virtually no references to the organ were recorded until the Middle Ages [8, 19, 20]. The fact that the pancreas had a duct was mentioned by Luzzi in 1275. But, the first accurate description of the pancreas and its anatomic relations was not published until 1543, in the monumental *DeHumani Corporis Fabrica Libri Septem* by Vesalius and his student Fallopio.

In the seventeenth century, Thomas Wharton noticed the structural similarity of the pancreas and salivary glands. The main pancreatic duct was described by Wirsung in 1642, the accessory duct by Santorini in 1724, the termination of the main duct in a papilla by Vater in 1728, the vascular relationships by Walther in 1729, and the musculature surrounding the papilla by Oddi in 1887 [25]. The descriptions of anatomy were paralleled by physiologic studies [20].

The earliest experimental observations were by de Graf in 1664. He cannulated the pancreatic duct of a dog with a quill, collected secretions, and noted their corrosive action. However, it was nearly two more centuries before the function of the pancreatic secretions was described.

In the mid-nineteenth century, Claude Bernard, in Lyon, demonstrated that the secretions could emulsify fat, convert starch to sugars, and dissolve protein [25]. Bernard dismissed hints linking the pancreas to diabetes when the disease did not ensue in animals after atrophy of the pancreas was induced by duct injection of paraffin. In 1875, Heidenhain described the effect of vagal nerve stimulation on pancreatic secretions [27]. The very beginning of the twentieth century [28] was a fermentative period in the conceptualization of the hormonal and endocrine systems. The contemporary understanding of pancreatic exocrine secretions and their interaction with the gut via secretin was provided by Bayliss and Starling in 1902 [28].

The quest to understand the function of a specific organ, the pancreas, and the quest to understand diabetes were not fully joined until the serendipitous experiment of von Mering and Minkowski in 1889 [1]. This experiment, originally designed to study digestion [29, 30], definitively showed that total extirpation of the pancreas resulted in diabetes. Until then, the quests had been on different pathways that only on occasion been touched. But, after von Mering and Minkowski’s experiment, understanding the anatomy, function, and pathology of the endocrine pancreas became synonymous with understanding diabetes.

It is easiest to describe each pathway separately, with a comment on where they bumped together before joining.

Regarding the quest to understand diabetes, the pathway was tortuous, because there are so many forms of the disease. Today’s classification of diabetes is complex, according to etiology, pathogenesis, or treatment [31, 32] (see Chap. 1). The classification of the American Diabetes Association (ADA) distinguishes four types: type 1 (formerly called insulin-dependent) due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency; type 2 (formerly called non-insulin-dependent, but some patients will need exogenous insulin) due to a progressive loss of β -cell insulin secretion frequently on the background of insulin resistance; gestational diabetes mellitus (diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation); and specific types of diabetes due to a variety of causes including, but not limited to, monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis, pancreatitis, after pancreatectomy), drug- or chemical-induced diabetes (such as with glucocorticoid or calcineurin inhibitor use, in the treatment of HIV/AIDS), infection-related and immune-mediated diabetes, and extrapancreatic or endocrine diabetes (e.g., with hyperadrenalism).

The term *diabetes* was coined by the Greek physician Aretaeus of Cappadocia in the second century AD [21]. It means “to run through a siphon.” Aretaeus described the clinical syndrome of diabetes “as a melting down of flesh and limbs into urine.” However, at that time, the word diabetes was essentially synonymous with polyuria.

Polyuria has many causes. Polyuric syndromes are described in ancient literature, including the Egyptian papyrus *Ebers* from around 1500 BC. Japanese and Chinese physicians of the second and third centuries and Indian physicians of the sixth century describe cases of polyuria associated with a sweet taste to the urine, almost certainly diabetes mellitus as we know it today. Avicenna, the famous Arabic physician, also described around AD 1000 a syndrome consistent with diabetes that was associated with sweetness of urine.

Few European references to diabetes were recorded until Paracelsus described a case in the early sixteenth century [21]. Indeed, he evaporated urine from a diabetic patient and obtained a white powdery residue that he thought was salt. In the seventeenth century, Thomas Willis rediscovered the sweetness of the urine in some individuals with diabetes (polyuria) [33]. Willis even stated that sugar first appeared in the blood and then the urine. Dobson in the eighteenth century also linked glycosuria to elevated sugar in the blood [34]. In 1815, the French chemist Michel Chevreul (1787–1882) showed that the sugar in the urine of diabetics was not the sugar of the cane but of the grape (glucose) [35].

Willis makes clear that there are two forms of diabetes: with glycosuria and without [36]. The qualifying adjective *mellitus* (Latin for “sweetened with honey”) was added to diabetes (Ionic Greek) by William Cullen in 1787 to distinguish it from polyuria of other causes, or what he termed *diabetes insipidus* (urine with no taste, i.e., insipid) [37].

Attempts to classify diabetes mellitus into subtypes began in the nineteenth century, primarily as a guide to the only treatment available, dietary [38]. The class we recognize today as (insulin-dependent) type 1 diabetes would have been rapidly fatal then, no matter what the diet. Thus, most of the descriptions of success in the literature of the late eighteenth and nineteenth centuries probably reflect the response of individuals with type 2 diabetes [39, 40].

In 1887, Lancereaux first introduced the terms *diabetes maigre* (lean diabetes) and *diabetes gras* (obese diabetes) [15]. He [41], along with his contemporary Frerichs [42], also described diabetes associated with gross pancreatic pathology that they considered etiologic. But, they were not the first to note gross pancreatic pathology associated with diabetes mellitus. This honor belongs to Thomas Cawley in 1788 [43], but from his article it is apparent that he believed that the association was fortuitous and that it was the kidney that was diseased in diabetes mellitus, a logical assumption based on polyuria.

An understanding of the secondary nature of the polyuria of diabetes was provided by the nineteenth-century French physician Bouchardat [44], a prodigy of Chevreul. He developed reliable techniques for quantification of the sugar in blood and urine. Bouchardat was also one of the first physicians to demonstrate truly good results with dietary therapy. He observed that during the food shortage of the Franco-Prussian war of 1870 and 1871, his patients with diabetes improved [14]. Later, dietary therapy was carried to the extreme of starvation for patients with type 1 diabetes, juvenile onset, rapidly lethal severe diabetes [45].

In the nineteenth century, hints that the pancreas was involved in diabetes were dismissed by Claude Bernard and Moritz Schiff (in Italy) because of the results of experiments with injection of paraffin into the pancreatic duct of animals: despite the atrophy induced in the gland, diabetes did not appear [22, 25]. However, Bernard was a pioneer in understanding the action of pancreatic secretions as well as the physiology of carbohydrate metabolism (and thus diabetes) through his discovery of glycogen [25]. Others had studied pancreatic secretions, including Brunner in the seventeenth century (who also observed polyuria in pancreatectomized dogs but did not deduce that they were diabetic [19, 20]). However, Bernard was the first to quantify their action in breaking starch into sugar, emulsifying fat, and dissolving protein [25]. Indeed, Bernard began the modern studies of physiology of the exocrine pancreas.

Before Paul Langerhans described the clusters of pancreatic cells that bear his name, there was little reason for Bernard or anyone else to suspect that the pancreas was anything other than an exocrine organ. The significance of Langerhans’ findings was not appreciated until after the observations of von Mering and Minkowski [1]. Diabetes had rarely been associated with the gross or microscopic pathology induced by duct occlusion, as described by several groups during the nineteenth century (reviewed by Minkowski himself [29, 30]). But, with von Mering and Minkowski’s experiment [1], everything changed.

One of the first questions asked was how the absence of the pancreas induced diabetes. Minkowski proposed that the pancreas secreted a substance into the vascular system that lowered blood sugar (so-called *internal secretion*, although not a term he coined). In 1893, he published the results of an experiment in which he transposed a segment of the canine pancreas to the subcutaneous tissue on a vascular pedicle, did a completion pancreatectomy, and later severed the pedicle. Diabetes did not ensue, apparently prevented by neovascularization of the pancreatic fragment [3]. Hedon, in 1892, described a similar experiment. He did a partial pancreatectomy of the tail and body of the pancreas, while transposing the descending portion (equivalent to the uncinat process in humans, but basically a second tail in dogs) to the subcutaneous tissue on a vascular pedicle [4]. Diabetes did not ensue

until the pancreatic remnant was removed. With the exocrine secretions collected externally via a fistula, there could be no doubt that an internal secretion had to exist.

In 1893, Laguesse postulated that the clusters of pancreatic cells described by Langerhans were the organelles that secreted the substance that lowered blood glucose in the vascular system [5]. Laguesse (who coined the term islets of Langerhans 5 years after the discoverer's death) later showed (along with others) that duct ligation of animal pancreases induced exocrine atrophy while leaving the islets intact. Pathologists then swung into full gear. By the beginning of the twentieth century, Opie [12], among others, described hyalinization of islets in association with diabetes. The observations were not clean. Shortly thereafter pathologists also described hyalinization of islets in autopsy material in individuals who did not have diabetes, and cases of diabetes were also described in which no obvious pathology of the islets was present (referenced in Wellman and Volk [8]). Yet, histologic techniques were being refined. In 1907, Lane labelled the two types of islet cells as α and β [13]. In 1931, Δ -cells were described by Bloom [46].

Meanwhile, pancreatic duct ligation experiments continued. In 1902, Ssobolew [47] emphasized that the anatomic isolation of the islets by duct ligation “will permit the testing, in a rational way, of an organotherapy for diabetes.” MacCallum, in 1909 at Johns Hopkins University [48], confirmed that pancreatic duct ligation was followed by atrophy of the exocrine parenchyma with survival of the islets. He showed that diabetes occurred after removal of the duct-ligated pancreas, adding a nuance to the original observations of von Mering and Minkowski.

Discoveries About Insulin and Diabetes Classification

The new information fueled intense efforts to extract the internal secretion of the pancreas to use for exogenous therapy [49]. The name *insulin* was first given to this theoretical substance by DeMayer in 1909 [50] and was used by Sharpey-Schafer, of Edinburgh, in 1916 [51]; this name is what fellow Scotsman Richard Macleod, chairman of the Department of Physiology at the University of Toronto, insisted [21] be used for the internal pancreatic secretion isolated in his laboratory by Banting and Best in 1921 [52].

Banting's quest was sparked by reading the 1920 article by Moses Barron on pancreatic lithiasis. Barron described pancreatic atrophy with preservation of the islets of Langerhans [53]. The acid-alcohol extraction process was used by Banting and Best on duct-ligated canine pancreases. It was further refined by Collip, so it would work with normal pancreases without duct ligation, and was effective for insulin extraction from cow and pig as well as dog pancre-

ases [54]. Thus, the modern therapy for what is now called type 1 diabetes mellitus began.

A description of the history of classification of diabetes and the terms type 1 and type 2 was provided by Gale [23]. Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400–500 AD with type 1 associated with youth and type 2 with being overweight [55]. In modern times, it was not until 1936 that Harold Himsworth finally distinguished between the two types of diabetes and defined them as “insulin-sensitive” and “insulin-insensitive” [55]. The paradigm shift to view type 1 diabetes as an autoimmune disorder did not occur until the 1970s [23]. Nonetheless, islet inflammation was described as early as 1901 by Opie [12], and the term *insulinitis* was coined by von Meyenberg in 1940 [56]. The autoimmune nature of type 1 diabetes was further hinted at in the 1950s and 1960s by the pathologic observations of LeCompte [57] and Gepts [58]. Clinically, the twin pancreas transplant experience at the University of Minnesota, as described below, provided clear evidence of the autoimmune etiology of type 1 diabetes. Also in the 1970s, the demonstration of cell- [59] and humoral- [60] mediated autoimmunity, of an HLA association [61], and of spontaneous animal models [62, 63] made autoimmunity the most compelling hypothesis to explain the pathogenesis of type 1 diabetes. Autoimmunity must be overcome for clinical pancreas and islet transplants to succeed (see Chaps. 1–3) [64, 65].

Animal Models

Although Carrel transplanted several different organs in animal models in the early 1900s, the pancreas was not one of them (although he did mention that it should be done for functional studies) [66]. The first reported attempt at transplantation of the pancreas as an immediately vascularized graft was by Hedon in 1913 [67]. He placed an allograft in the neck of pancreatectomized dogs and did not observe even temporary correction of diabetes, probably a failure for technical reasons that he did not recognize. He also did somewhat complicated cross-circulation experiments [68] between normal and pancreatectomized dogs and temporarily corrected diabetes in the latter with both systemic and portal connections. He erroneously concluded that the innervation is necessary for proper function, even though that would have required reinnervation of the transposed neovascularized pancreatic segment autograft in his severed vascular pedicle experiments reported earlier and discussed by him until 1920 [69]. The vascular pedicled/delayed severed neovascularized canine segmental pancreatic autograft model with technical variations was described in detail in 1926 by Ivy at Northwestern University in Chicago [70],

with a hint that both exocrine and endocrine function were retained (removal of the rest of the pancreas was not described) and a promise that the details would be reported in later articles (the articles never appeared).

After Hedon [67] (and 5 years after the discovery of insulin), the next reported attempt of an immediately vascularized pancreas transplant was by Houssay and Molinelli in 1927 [71], also to the neck in pancreatectomized dogs and also without correction of diabetes, again probably for technical reasons and again leading to the erroneous conclusion that extrinsic innervation was necessary for the endocrine pancreas to function. That same year, Gayet and Guillaumie reported immediate correction of diabetes by pancreas allotransplantation to the neck of pancreatectomized dogs [72] and concluded that extrinsic innervation was not necessary for endocrine function of the pancreas and were certain that the experiments of Hedon [67] and Houssay [71] had failed for technical reasons. Houssay et al. then repeated their experiments [72, 73] and duplicated the results of Gayet and Guillaumie with correction of diabetes by a pancreas allograft to the neck of pancreatectomized dogs. They described in great detail the technical aspects of the operation [74] (they used the 1900 Payr vascular anastomosis technique, connecting vessels by eversion through and over a metal tube [75]) (ignoring Carrel). They also studied the effect of at least partial denervation of native pancreases in comparison to grafted pancreases on glucose tolerance and concluded the effect was minor [74, 76]. Gayet et al. [77–79] largely used the canine neck vascularized pancreas-duodenal transplant model to do physiologic studies of exocrine function and the role of extrinsic and intrinsic nervous function on the secretin response to various stimuli, concluding that the intestine does not need extrinsic innervation to perform its endocrine function any more than the pancreas.

Perhaps the most interesting pancreas transplant experiment in the series performed by the French investigators is that of Houssay et al. [80], in which multiple pancreases (four) were transplanted simultaneously into normal dogs, one to each side of the neck (carotid-jugular) and groin (femoral vessels). Hypoglycemia did not ensue despite five pancreases, showing to their satisfaction that glucose homeostasis was not a function of the islet mass, but of the regulation of insulin secretion by glucose itself, perhaps the first articulation of the concept that the β -cell acts as its own glucostat.

All the French groups doing pancreas transplants for physiologic studies used the Payr technique for their vascular anastomoses, but mention neither Payr nor Carrel. The only other article on pancreas transplants from this era, by Bottin of Liège in 1936 [81], does refer to both Carrel and Payr and flatly states that the Payr technique is better because the ischemia time is less. However, the world was not convinced and all subsequent descriptions of immediately revascularized pancreas transplants clearly use the Carrel

technique. However, after Bottin (who simply did allografts to the neck in non-pancreatectomized canine recipients and followed the unmodified course of the graft-death from the toxicity of rejection necrosis within 8 days), no articles appear on the topic until the 1950s.

After a 20-year hiatus, the first article on pancreas transplantation is a resurrection of the Hedon vascular-pediced transposition autograft, but is at least a confirmation that neovascularization occurs and even carries the experiment a step further by free-grafting the neovascularized tissue component [82]. Rundles and Swan, as reported in 1956 [82], transposed the splenic tail of the pancreas, based on the splenic vessels, to the subcutaneous tissue. In 6–8 weeks, a completion pancreatectomy was made of the remaining intra-abdominal pancreas, and the vascular pedicle to the transposed portion was ligated. Seven of the 15 dogs did not become diabetic, indicating that the autograft was neovascularized and producing insulin. Subsequently, the neovascularized graft was excised, minced, and then reimplanted intramuscularly. All recipients initially became hyperglycemic, but were treated with insulin for 1–2 months; insulin was then withdrawn and two of the dogs remained euglycemic. Following excision of the transplanted pancreatic fragments, the dogs again became diabetic. Thus, Rundles and Swan clearly showed the ability of pancreatic fragments to become neovascularized, confirming the outcomes reported by Hedon and Minkowski more than a half-century earlier. Brooks, in 1959 [83], published a brief description of similar experiments and cited Ivy (apparently unaware of the nineteenth-century experiments or the more recent ones of Rundles and Swan). He also excised the neovascularized fragment, but exchanged it between dogs (allograft) and observed no evidence of function or survival. Brooks also did vascularized pancreas allografts to nonpancreatectomized recipients; he described technical problems or allograft rejection in less than 1 week in all cases and was not able to perform functional studies. Interestingly, Brooks also described transplantation of human pancreas allografts using fragments of neonatal tissue, again without any evidence of success in the diabetic recipients [83].

The first description that can be found in the literature of an intra-abdominal immediately vascularized pancreas transplant is by Irving Lichtenstein (of hernia fame) and Richard Barschak (a veterinarian) in 1957 [84]. They placed pancreas allografts to the iliac vessels of nonpancreatectomized dogs, described the techniques in great detail, and simply killed the dogs at 6–8 weeks, finding no residual pancreatic tissue at the graft site. They seemed completely unaware of any preceding attempts, failing to reference the French work or the Rundles and Swan work, and obviously believed that they were the first to ever have done an immediately vascularized pancreas allograft in any model. They mentioned theoretical reasons for why an allograft might be successful in humans,

referring to successful kidney transplants between monozygotic twins (but not referencing the obvious source of this information—Murray and associates in Boston). They also mentioned that homografting of skin has been successful in patients with agammaglobulinemia (again not referencing the work by Varco et al.) in Minnesota [85], work that was cited by Rundies and Swan. However, the canine pancreas allograft technique described by Lichtenstein and Barschak [84] was modern and similar to that described in pancreatectomized recipients by the subsequent investigators in the 1960s who set the stage for clinical application, namely, Lucas et al. [86], DeJode and Howard [87], Reemtsma et al. [88], Bergan et al. [89], Teixeira et al. [90], Seddon and Howard [91], Ota et al. [92] and, most critically, in Kelly et al.'s [93] laboratory (segmental), Merkle et al. [94], and in Lillehei et al.'s [95] laboratory (whole pancreaticoduodenal), Largiader et al. [96], and Idezuki et al. [97], experiments well-summarized in the classic article by Lillehei et al. in 1970 [17].

The numerous pancreas transplant experiments in animal models from 1970 to the mid-1990s have been summarized in detail in previous reviews [98–103]. Those with particular significance for clinical application, including the earlier ones, are cited here.

The segmental pancreas allograft technique in dogs described by Merkle et al. [94, 104] was similar to that used in the first human [93]. Merkle, working in Kelly's laboratory, interposed the graft superior mesenteric–splenic–portal vein complex and the celiac–splenic artery complex to the iliac vein and artery of the recipient dog, to reduce the risk of thrombosis by maximizing the flow through the graft vessels. In the first clinical case, the vein complex was interposed (side-to-side with the intervening recipient iliac vein ligated, a departure from the dog model where the interposition was end-to-end) but the arterial complex was not [93]. The point of Merkle's experiment was to reduce exocrine function by irradiation [104], but the strategy was not effective, at least clinically [93].

Largiader et al. [96] were the first to describe completely orthotopic allotransplantation of the pancreas in dogs with exocrine drainage, via a Roux-en-Y duodenojejunostomy, which was the technique used for the sixth through 13th pancreas transplants in the early Minnesota series [17, 105]. The 14th transplant, the last done by Lillehei, was performed with only the papilla of Vater anastomosed to a Roux-en-Y limb of recipient jejunum, after the technique developed in Lillehei's laboratory by Acquino et al. [106].

Because of the perception that many of the early complications of pancreas transplantation were related to the duodenum, segmental transplantation was clinically popular from at least the mid-1970s to the mid-1980s [107]. Accordingly, segmental grafts were used in animal experiments to develop methods of duct management [99].

Gold, in 1972, reported on segmental pancreas transplants in dogs with ductoureterostomy [102], a technique applied clinically by his mentor, Marvin Gliedman, at Montefiore Hospital in New York beginning in the early 1970s [108]. Similarly, Cook, in 1983, reported on segmental pancreas transplants in dogs with ductocystostomy [109], a technique applied clinically by his mentor, Hans Sollinger, at the University of Wisconsin beginning in the early 1980s [110]. Gold et al. [111] and Cook et al. [109] both hinted that urine amylase might be a marker for rejection. Prieto et al., in canine experiments, and Gruessner et al., in porcine experiments, at the University of Minnesota in the mid/late-1980s [112, 113], formally showed that a decline in urine amylase preceded hyperglycemia as a manifestation of rejection of bladder-drained segmental pancreas allografts (see Chap. 6). Shortly thereafter, Marsh et al. at the Mayo Clinic demonstrated the utility of transcystoscopic biopsy for pathologic diagnosis in bladder-drained canine pancreaticoduodenal allografts [114], followed by clinical application there and at the University of Minnesota [115, 116].

Between the development of the two techniques of urinary drainage, and as an alternative to the hazardous enteric drainage of segmental grafts [117], Dubernard, in the mid-1970s in Lyon, applied the technique of duct injection with an occlusive and locally toxic polymer (his choice, neoprene) to suppress and induce fibrosis of the exocrine tissue of segmental pancreatic allografts in dogs and humans [118]. Dubernard refers to the use of acrylate glue for occlusion of the pancreatic duct of native canine and human pancreases by the American surgeon J.M. Little [119], but it is of interest to note that pancreatic duct injection began at Lyon in the nineteenth century in the experiments of Bernard (paraffin) [25] and Thiroloix (oil and lampblack) [120, 121] (as discussed by Hedon [122]). Following the publication of Dubernard's work, several groups used duct injection experimentally and clinically with a variety of polymers: prolamine by Land et al. at Munich [123]; polyisoprene by McMaster et al. at Cambridge [124]; and silicone at the University of Minnesota [125, 126].

The Dubernard experience at Lyon was a stimulus to resume pancreas transplants experimentally and clinically at the University of Minnesota. We did a series of segmental pancreas transplants in dogs and pigs, comparing the outcome with neoprene injection to that of simply leaving the duct open to drain freely into the peritoneal cavity [127–130]. To our surprise, the animals tolerated the open duct very well, absorbing the pancreatic secretions with only an occasional case of enzyme activation and chemical peritonitis. Although not as successful clinically as other methods of duct management [131], the open-duct technique was used routinely in our animal laboratory [132, 133] for a variety of investigations on the site of venous drainage (systemic vs. portal) [134–136], preservation [137–139], metabolism [140–142], and immunosuppression [143–145].

The metabolic effect of the site of pancreas venous drainage, systemic or portal, has been the subject of experiments since the initial attempts by Hedon [68]. Idezuki et al. [97] were the first to drain pancreas graft venous effluent into the portal system, but no formal metabolic studies were carried out. Ruiz et al. [146] were the first to do studies comparing glucose metabolism for systemic- vs. portal-drained canine pancreas transplants, and at least as far as glucose tolerance, no differences were discerned. Florak et al. [135] and Hanks [147], in segmental pancreas autograft experiments, found that both denervation and site contribute to the hyperinsulinism associated with systemic venous drainage. In canine pancreas allograft experiments, despite the theoretical reasons as to why the immune response should be dampened, rejection has been similar with systemic and portal drainage [136, 148]. (Clinically, less rejection with portal drainage of pancreas allografts has been reported at a single center [149].)

Large-animal experiments have been critical for the development of methods for *ex vivo* organ preservation prior to transplantation. Idezuki et al. [97] in 1968 first reported on pancreas preservation prior to transplantation and demonstrated function of canine allografts after 22 h of hyperbaric chamber storage in a 5% dextran-balanced salt solution. Westbroek et al. [150], in 1974, were the first to report on pulsatile pump machine preservation of pancreas grafts and were able to successfully preserve some for 24 h. Machine preservation longer than 24 h has not been achieved [139], but Florak et al. [138], in 1982, showed that canine pancreas grafts could be cold-stored for 48 h in a silica gel-filtered plasma solution, a solution that proved satisfactory to routinely preserve human pancreas allografts for >24 h at the University of Minnesota [151] until superseded by the non-biologic (thus eliminating the risk of disease transmission) hyperosmolar solution developed at the University of Wisconsin (UW) by Fred Belzer in the late 1980s [152]. The UW solution was first shown to be effective for preservation for up to 72 h by Wahlstrom in a canine pancreas transplant model [153]. In 1994, Kuroda in Kobe, Japan, showed that by using a two-layer method with UW solution and perfluorochemical, canine pancreas graft preservation could be extended beyond 72 h [154]. The two-layer technique was applied clinically for pancreas preservation beyond 30 h by Matsumoto et al. [155] Tanioka et al. [156] also showed that the two-layer technique allowed the canine pancreas to be stored significantly longer prior to islet isolation for transplantation.

Most of the clinically relevant experiments on pancreas transplant surgical techniques and preservation were in large animal models, including a pig model of en-bloc pancreas and kidney transplantation on one vascular pedicle by Gruessner et al. [157], modified techniques of which were later introduced clinically (see Chaps. 28–32). But the rat

model has been used as well to address certain questions of clinical interest. Pancreaticoduodenal transplants in rats were first reported by Lee et al. [158] from the University of California at San Diego in 1972, and the model was used by Orloff et al. [159] at the same institution to study the long-term (and favorable) effect of pancreas transplantation on secondary complications of diabetes. Metabolic problems have also been addressed in the rat model. For example, Schang et al. did bladder-drained pancreaticoduodenal transplants in rats and showed that the metabolic acidosis that ensued was mainly due to the duodenal secretions rather than the pancreatic secretions [160].

A technique for segmental pancreas transplantation in rats was developed by Squifflet et al. [161] and has been used to address several questions [133], e.g., the manifestation of rejection in relation to β -cell mass engrafted for pancreas vs. islet allografts [162].

Immunologic questions have been addressed in both the rat and large-animal models. For example, Lillehei was the first to suggest that a pancreas transplant alone (PTA) was more likely to stimulate a rejection response in an immunosuppressed host than a combined kidney and pancreas transplant alone [95]. One possible explanation was that uremia itself is immunosuppressive. We tested this hypothesis in both rat and pig models [163–168]. Nakai et al. [163] made rats uremic by removal of all of one and part of the remaining kidney or diabetic by streptozotocin or both, and then did simultaneous pancreas and kidney (SPK) transplants, kidney transplants alone (KTA), or PTA allografts in rats with one or the other or both afflictions. Uremia was found to delay pancreas graft rejection independent of whether the kidney and pancreas grafts were transplanted together or separately, but this was not the whole explanation for the greater rejection risk for PTA transplants: even without uremia, an SPK pancreas graft was less likely to be rejected. In nephrectomized, or pancreatectomized, or nephrectomized/pancreatectomized pigs (unlike the rat model, done at the time of the transplant, so they were not uremic prior to the transplant), the outcome was nearly the same as in the experiments in nonuremic rats: SPK pancreas grafts were rejected later than PTA grafts [164–168].

The original notion of Lillehei et al. [105] that there was a hierarchy of rejection susceptibility was confirmed in Gruessner et al.'s large series of porcine allograft experiments (using a reliable model of streptozotocin-induced diabetes mellitus) [165], with the pancreas being more susceptible to rejection than the kidney (Chap. 6) [164, 166]. Correlative pathology in this porcine allograft model by Nakhleh et al. [167] showed that rejection in the pancreas and kidney, pancreas and duodenum as well as kidney and duodenum is not always concordant, consistent with the clinical observations in dual same-donor transplants that rejection of one organ is not always associated with rejection of

the other organ [103]. Thus, the porcine studies conducted by Gruessner et al. in the late 1980s demonstrated a hierarchy of rejection not only according to recipient category (SPK, KTA > PTA), but also according to transplanted organ (kidney > exocrine pancreas > endocrine pancreas, duodenum) [164–168].

A historical review of experimental pancreas and islet transplantation in animal models, encompassing a period from the end of the nineteenth to the beginning of the twenty-first century, as one section in a single book chapter, cannot do justice to the unique contributions of so many investigators. A book itself would be required to capture the nuances of innovation.

General History of Clinical Pancreas Transplantation

Insulin independence in a type 1 diabetic was first achieved on December 17, 1966, when William Kelly and Richard Lillehei (Fig. 5.1) transplanted a duct-ligated segmental pancreas graft simultaneously with a kidney from a deceased donor into a 28-year-old uremic woman at the University of Minnesota [93] (Fig. 5.2). The pancreas segment (body and tail) was transplanted extraperitoneally to the left iliac fossa, with anastomosis of the graft celiac axis to the left common

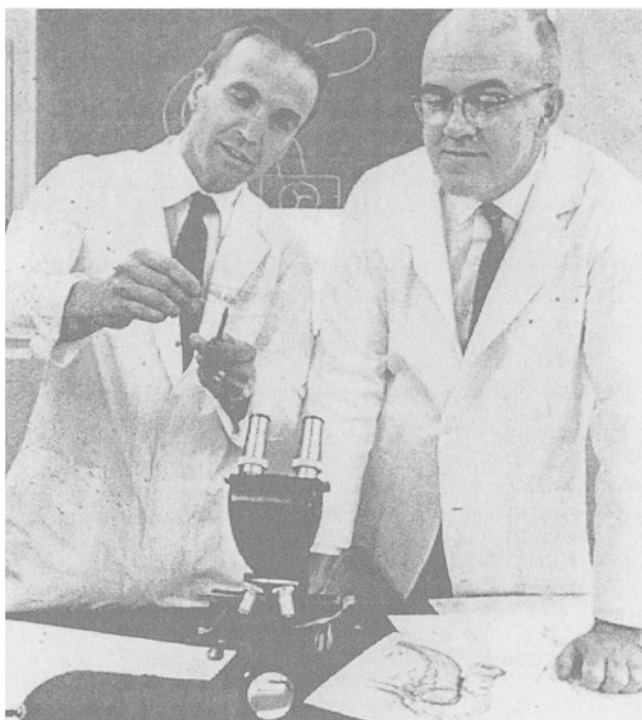


Fig. 5.1 Richard Lillehei, left, and William Kelly, right, discussing a pancreas graft histology report. On the desk, the schematic drawing of the second ever performed pancreas transplant (see text). On the board, a schematic drawing of the pancreaticoduodenal graft anatomy

Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy

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Fig. 5.2 First page of the original article on the first two pancreas transplants performed by William Kelly and Richard Lillehei at the University of Minnesota. Coauthors were Fred Merkel, who worked in Kelly's laboratory; Yasumo Idezuki, who worked in Lillehei's laboratory; and Frederick Goetz, head of the Division of Endocrinology at the University of Minnesota. (Reprinted with permission from Kelly et al. [93])

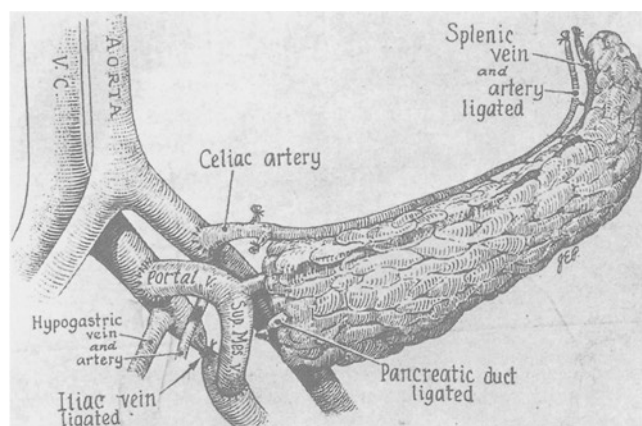


Fig. 5.3 Schematic drawing of the first pancreas transplant as published in *Surgery* (see text for operative details). (Reprinted with permission from Kelly et al. [93])

iliac artery. The graft splenic vein was left attached to its junction with the superior mesenteric and portal vein; each was anastomosed end-to-side to the recipient's iliac vein with ligation of the intervening segment, converting the donor venous conduit into a bypass graft (Fig. 5.3), a technique devised by Fred Merkel (also a member of the surgical team) in experiments in dogs to reduce the risk of thrombosis [104]. Posttransplant immunosuppression consisted of azathioprine (8 mg/kg/day tapered to 4 mg/kg/day by day 3) and prednisone slowly tapered from 150 mg/day. Cobalt [59] 950 rads (300, 200 and 150 rads on consecutive days) was administered to the pancreas graft in an attempt to suppress exocrine function, again based on the experiments of Merkel [104].

The objective of the irradiation was not achieved and the recipient's postoperative course was complicated by a pancreatic fistula requiring open drainage of amylase-rich peripancreatic fluid at 7 days posttransplant. At relaparotomy, the pancreas graft was swollen, and a graft biopsy was consistent with pancreatitis. The recipient was insulin-free for only 6 days and then needed increasing doses of insulin. On

February 14, 1967, the pancreas (along with the kidney) was removed. During graft removal, a longitudinal tear in the side of the iliac vein occurred that was repaired but resulted in narrowing of the vessel. Postoperative anticoagulation had to be discontinued because of bleeding but swelling of the leg improved progressively with bed rest and elevation. However, the recipient died from pulmonary embolism 13 days after pancreas graft removal. Histologically, the pancreas graft was noted to show a moderate mononuclear cell infiltrate between lobules of acinar tissue, on occasion within acinar (but not in islet) tissue. Islets also appeared normal in configuration. This first case exemplified many of the problems that were associated with pancreas transplantation over the following two decades: surgical complications, wound infections, and graft rejection.

In that first pancreas transplant, Kelly was the lead surgeon and Lillehei his assistant [93]. But, in the second pancreas transplant, on New Year's Eve 1966, Lillehei was the lead surgeon [93, 169]. In that 32-year-old recipient, the donor's whole pancreas and attached duodenum were transplanted extraperitoneally to the left iliac fossa. (As with the first transplant, the kidney was transplanted extraperitoneally to the recipient's right iliac fossa.) The donor's celiac axis and superior mesenteric artery on a small cuff of aorta were anastomosed end-to-side to the left common iliac artery, and the portal vein was anastomosed end-to-side to the left common iliac vein. The proximal duodenal end was closed blindly and the distal end (duodenum with the first portion of jejunum) was brought out as a cutaneous graft duodenostomy-jejunosomy (Fig. 5.4).

Immunosuppressive therapy for that December 31, 1966, recipient was with azathioprine and prednisone (as for the first recipient), but no posttransplant graft irradiation was

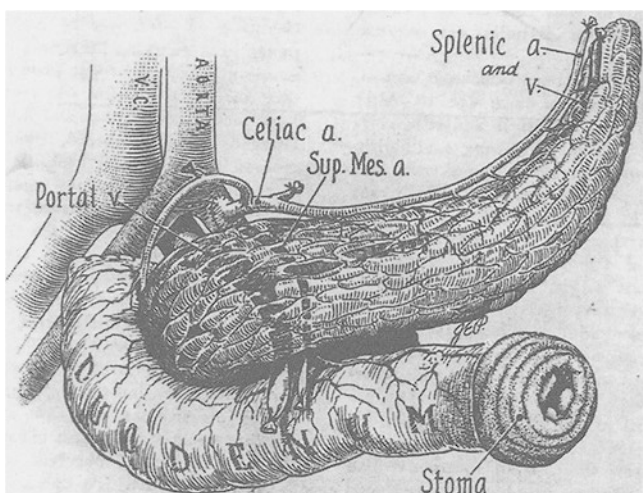


Fig. 5.4 Schematic drawing of the second-ever pancreas transplant (first-ever whole pancreaticoduodenal transplant) as published in *Surgery* (see text for operative details). (Reprinted with permission from Kelly et al. [93])

administered. The second time, a more prolonged state of pancreas graft function was achieved. But rejection treatment (consisting of prednisone boluses and graft irradiation) had to be instituted 3 and 8 weeks posttransplant. During both rejection episodes, the graft duodenum was affected: It showed superficial erosions, with some intermittent bleeding; histologically, the tips of the villi were sloughed, but they regrew with recovery from rejection. The recipient was on insulin when she died 4.5 months posttransplant from sepsis. Of interest, between the first and second transplants, significant changes in surgical technique had been made pertaining to graft size (segmental vs. whole organ) and duct management (duct ligation vs. cutaneous duodenostomy). In part, these changes were based on the experimental work conducted in Kelly's and Lillehei's laboratories at the time. Kelly was the senior author on the publication describing these two first recipients [93]. The second case (pancreaticoduodenal) was redescribed separately, with Lillehei as the lead author, in the next volume of the same journal within the context of pancreas and bowel transplantation [169].

Lillehei performed a total of 13 pancreas transplants [17, 105], the last on January 11, 1973 [105] (Figs 5.5 and 5.6). In publications on his personal series, he numbered his cases 1–13 and gave the number 0 to the first institutional case (done by Kelly). This first series addressed most aspects of pancreas transplantation that were discussed over the following decades, such as the management of the exocrine secretions and type of graft.

In his first four transplants, Lillehei managed the exocrine secretions with a cutaneous graft duodenostomy; in the next 8, with internal exocrine drainage using a Roux-en-Y duodenojejunosomy (Fig. 5.7); and in the 13th and last, with only the papilla of Vater retained for anastomosis to the recipient's bowel [105]. He initially chose external (over internal) drainage, to enable early detection of graft rejection (by direct observation of the duodenal mucosa and measurements of the volume of exocrine secretion) and to avoid the risk of an anastomotic leak. After experimental studies in his laboratory using the dog model showed that internal drainage could be done safely, he clinically introduced enteric drainage via a Roux-en-Y loop [17]. Regarding graft size, both Kelly and Lillehei thought that transplanting a segment (body and tail) was simpler and faster, but associated it with a higher risk of leakage of pancreatic juice and a reduction in the number of islets. Transplantation of the whole pancreas and duodenum was perceived as technically more difficult and associated with a higher output of exocrine secretions.

Other technical aspects of that first series of 13 pancreas transplants are still valid today. Lillehei anastomosed the whole pancreaticoduodenal allograft in the recipient's iliac fossa and restored the blood supply by anastomosing the

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Pancreatico-Duodenal Allograft Transplantation: Experimental and Clinical Experience

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The origin of an original work is always the pursuit of a fact which does not fit into accepted ideas—CLAUDE BERNARD

IN 1922 Banting and Best reported on the use of pancreatic extracts to treat diabetes mellitus in man* (Fig. 1). This advance seemed to herald the end of this scourge of man for all time. In the nearly half century since this discovery, diabetic acidosis nearly disappeared as a cause of death. Moreover, the juvenile-onset diabetic for the first time was able to look forward to reaching maturity, marrying and having children. Yet, at the same time, doubts have steadily increased that diabetes mellitus could be cured by giving insulin. For, despite careful control with insulin and diet, the premature deterioration of small arteries which characterizes diabetes seemed to proceed inexorably in

many patients. This arterial disease, which occurs all over the body is characterized initially by thickening of the basement membrane and has a predilection for the kidney and retina. As a result over three quarters of juvenile-onset diabetics have significant retinopathy or nephropathy by age 30 no matter how carefully they have been managed. These problems are becoming more common as more diabetics reach maturity and the absolute number of diabetics increases. This problem is less severe in adult-onset diabetes mellitus. Nevertheless, the principal cause of death in adult-onset diabetics is also associated with premature onset of vascular disease.

Diabetes mellitus is a genetically based disease, probably associated with a recessive gene of variable penetrance. This gene may occur in up to 20% of the population. Presently about 2.5–3%, or five million of the population in the United States have the disease in varying degrees of severity. At the present growth rates in the United States the population may reach 975,000,000 in 1975.

Presented at the Annual Meeting of the American Surgical Association, White Sulphur Springs, West Virginia, April 27–29, 1970.

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Fig. 5.5 First page of the original article on the first pancreas transplant series published by Richard Lillehei et al. (Reprinted with permission from Lillehei et al. [17])

donor aortic cuff (containing the celiac axis and superior mesenteric artery of the graft) to the side of the recipient's common or external iliac artery and anastomosing the end of the donor's portal vein to the recipient's common iliac vein.

Indeed, the technique he employed in his fifth through 12th cases is nearly identical to the contemporary methods of pancreaticoduodenal transplantation with enteric drainage described in Chap. 28–32.

Fig. 5.6 First page of the original article on Richard Lillehei's complete series of pancreas transplants. The title page has a photo of Paul Langerhans from 1873. (Reprinted with permission from Lillehei et al. [105])

Introduction

It is barely 100 years ago that Langerhans presented his inaugural thesis on the "Microscopic Anatomy of the Pancreas". In this dissertation he described the specific cells in the pancreas which were later shown to secrete insulin. These specific cells, of course, later bore his name and became the "islets of Langerhans", Fig. 1 and 2 (1).

Langerhans' thesis stimulated further studies of the pancreas by many other investigators. Several of these came close to unraveling the relationship between the islets of Langerhans and diabetes mellitus. None came closer than Moses Barron who wrote in 1920 "that the islets secrete a hormone directly into the lymph or blood streams (internal

Fig. 1.

Paul Langerhans



Regarding the recipient category, of those first 13 pancreas transplants, 9 were done with a simultaneous kidney transplant (SPK category); 4 (3 in non-uremic patients) were done without a kidney (PTA category). Interestingly, most complications were associated with the kidney graft: First, kidney rejection occurred in almost all SPK recipients without evidence of pancreas graft rejection. This issue of synchronous vs. dyssynchronous rejection episodes was later studied extensively, both experimentally and clinically [166, 169–173]. Yet, Lillehei had already proposed a "hierarchy" of rejection, according to which the pancreas was less antigenic than the kidney (correct) and also less antigenic than the duodenum (incorrect) [17]. Second, most of the recipient deaths in this series resulted from problems with the kidney graft; in only one recipient was the pancreaticoduodenal graft the cause of death.

Because most of the complications in the SPK group were associated with the kidney graft, Lillehei postulated correctly that doing PTA would greatly reduce morbidity and mortality. He further postulated that PTA would allow researchers to study whether or not a normally functioning pancreas can "influence the course of the characteristic vascular lesions of diabetes mellitus" [17].

None of the pancreas grafts in this early series functioned for more than 1 year and only three grafts functioned for 5–12 months. Kelly and Lillehei had proven the technical feasibility of the procedure. Insulin independence had been established and maintained for up to 1 year.

Worldwide, after those first four pancreas transplants at the University of Minnesota, the next four transplants (May through September 1968) were performed in South America [107, 174, 175]: three in Brazil (one at the University of Rio

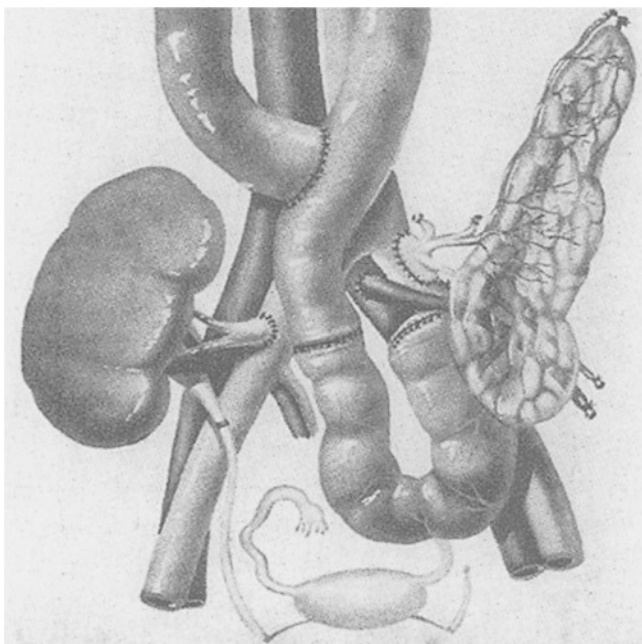


Fig. 5.7 Technique of whole-pancreaticoduodenal transplant with enteric drainage via Roux-en-Y loop as devised by Dr. Lillehei. This technique was used in his fifth pancreas transplant and then in all but his last transplant. (Reprinted with permission from Lillehei et al. [17])

de Janeiro, two at the University of Sao Paulo) and one in Argentina (Buenos Aires Hospital). Of those four South American solitary pancreas grafts, only one functioned for 4 months, but it was subsequently lost to rejection [107].

In 1969, two other US institutions performed one SPK transplant each: one at the University of Colorado (Merkel and Starzl) and one at the University of California, Irvine Medical Center (Connolly) [107, 176]. The first pancreas transplant in Europe (along with a kidney transplant) was performed in 1972 at Guys Hospital in London [107].

Until December 31, 1970, only 25 pancreas transplants had been performed at six institutions worldwide. Two thirds of those early pancreas transplant were done along with a simultaneous kidney transplant and one third (in non-uremic patients) without. Exocrine secretions had been handled by duct ligation, cutaneous duodenostomy, or enteric drainage using a Roux-en-Y loop. Of these 25 grafts, only 1 (from Lillehei's original series) functioned for almost 1 year, and none for more than 1 year. Of the 25 recipients (9 PTA, 16 SPK), only 6 (5 PTA, 1 SPK) survived for more than 1 year. Thus, morbidity was significantly higher for SPK recipients. During the 1970s, however, SPK mortality rates began to steadily decrease, but lower rates remained associated with the PTA (vs. SPK) category [177].

On November 24, 1971, the first pancreas transplant using urinary drainage via the native ureter was performed by Marvin Gliedman at Montefiore Hospital in New York. In 1973, Gliedman et al. published the results of four segmental

pancreas transplants in which the pancreatic duct had been anastomosed to the recipient's ipsilateral native ureter [108]. Gliedman introduced this technique "to avoid an intraperitoneal procedure, transplantation of the duodenum, a small-bowel anastomosis, or a continuing external pancreatic fistula." Gliedman and associates performed a total of 11 ureteral drained pancreas transplants in the early 1970s [178], 8 in uremic patients, 3 received SPK transplants, and in 5, the pancreas was grafted prior to a kidney transplant. Of this series, 1 graft functioned for 22 months, another for 50 months—until then, the longest pancreas graft survival recorded [178]. However, ureteral drainage did not find widespread application because of the tenuous leakage-prone duct-to-ureter anastomosis, leakage from the pancreas cut surface, and the need for ipsilateral native nephrectomy in some cases. Interestingly, Merkel et al. in 1973 reported a segmental PTA with end-to-side ductoureterostomy without the need to sacrifice the kidney in a non-uremic diabetic recipient [179].

By the mid-1970s, it was recognized that the management of exocrine pancreatic secretions with the drainage techniques of that time remained a major cause of graft failure from leakage. Thus, two new techniques were introduced in the mid and late 1970s: open drainage and duct injection. As with duct ligation, enteric drainage, and ureteral drainage before, the two new techniques had been extensively studied in large-animal models and appeared promising. Open-duct drainage (in contrast to duct ligation) preserves the function of exocrine pancreatic tissue, and pancreatic secretions are absorbed by the peritoneum if the enzymes are not activated (without opening the bowel there is no exposure to the main activating enzyme, enterokinase; although tissue thromboplastin is a weak activator, once activated the enzymes are autocatalytic). Key to a successful outcome is preventing intra-abdominal contamination at the time of the transplant. The first two open drained pancreas transplants were performed on February 3, 1976, by Bewick at Guys Hospital in London [107] and on July 25, 1978, at the University of Minnesota [128]. The latter recipient lived for 18 years until she was thrown off a horse and died with a functioning graft [180].

In 1978, Dubernard et al. [118] reported on a technique in which the pancreatic duct of the segmental pancreas graft was injected with neoprene, a synthetic polymer (Figs. 5.8 and 5.9). Various synonyms such as duct obstruction and duct occlusion have subsequently been used, but duct injection best describes the purpose of this technique. Before its clinical use, duct injection was studied in dogs: Progressive fibrosis of the pancreatic tissue was demonstrated, yet the islets usually remained vascularized and functioned for prolonged periods. The first transplant using duct injection was performed on October 22, 1976, fittingly in Lyon, the city of Claude Bernard, who more than a century earlier had injected

A new method of preparation of segmental pancreatic grafts for transplantation: Trials in dogs and in man

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A new method of eliminating the exocrine function of the pancreas by obstruction of pancreatic duct with neoprene was investigated in dogs and applied to three cases of human segmental pancreatic transplantation. Neoprene is a liquid synthetic rubber which flocculates with changes in pH. In animals, progressive fibrosis of the pancreatic tissue occurs after injection of neoprene in the main pancreatic duct, leaving islets well vascularized and functioning for prolonged periods. Using this technique, three severely diabetic patients received a cadaver segmental pancreatic allograft. Blood sugar returned to normal levels within the first hours or days after operation. All three grafts continue to function 1.5, 2, and 8 months, respectively, following transplantation. If these results are confirmed by further clinical experience, this method may be of considerable assistance in the treatment of severe diabetes by pancreatic transplantation.

From the Hospital E. Herriot, Lyon Cedex, France

THE PREVALENCE of diabetes mellitus and the severity of its degenerative complications which occur despite insulin control stress the need for new approaches in treatment. Investigations of pancreatic replacement for clinical use have progressed in three directions: (1) the artificial pancreas, (2) transplantation of isolated islets cells, (3) whole organ transplantation. The first two approaches are impractical as yet, while diversion of pancreatic juice has been the major technical difficulty in transplantation of the entire gland. If exocrine function or need for enteric anastomoses could be eliminated, extraperitoneal transplantation of the vascularized organ would be relatively uncomplicated.

MATERIAL AND METHODS

Neoprene is a liquid synthetic rubber which flocculates with changes in pH. As its natural pH is 12 to 14 and the pH of the pancreatic juice is 8 to 9, the material hardens when placed in the pancreatic duct, especially when small amounts of acid are added to the mixture. These chemical conditions allow no bacterial growth, and vials of neoprene can be sterilized in an autoclave.

Animal experiments. Twenty-seven mongrel dogs were used in these studies. The dogs were weighed before operation and baseline levels of blood sugar, electrolytes, urea, and amylase were obtained. The animals were fasted for 12 hours before operation

Fig. 5.8 First page of the original article by Jean-Michael Dubernard et al. on the use of duct injection for segmental pancreas grafts. (Reprinted with permission from Dubernard et al. [118])

paraffin into animal pancreases and showed that diabetes did not occur despite the glandular atrophy induced [25].

By the end of the 1970s and during the early 1980s, duct injection became the most common technique for drainage of exocrine secretions, in particular in Europe. Yet, the overall number of pancreas transplants remained small. By the time of the first report of the International Pancreas and Islet Transplant Registry at the Lyon meeting in March 1980, only 105 pancreas transplants had been performed worldwide: 53 in the United States and 52 outside the United States (mainly in Europe) [181]. The most active centers at that time in the United States were the University of Minnesota in

Minneapolis and Montefiore Hospital of the Albert Einstein College of Medicine in New York; in Europe, Huddinge Hospital in Stockholm, Sweden, and the Hospital Edouard Herriot in Lyon, France. After the Lyon meeting, pancreas transplant activity rapidly increased [107]. The ongoing debate on the optimal surgical technique for managing pancreatic exocrine secretions was exemplified by those institutions: In the late 1970s, the technique being used at the University of Minnesota was open drainage; at Montefiore Hospital, ureteral drainage; at Huddinge Hospital, enteric drainage; and at the Hospital Edouard Herriot, duct injection [107]. Clearly, the most suitable technique had not been

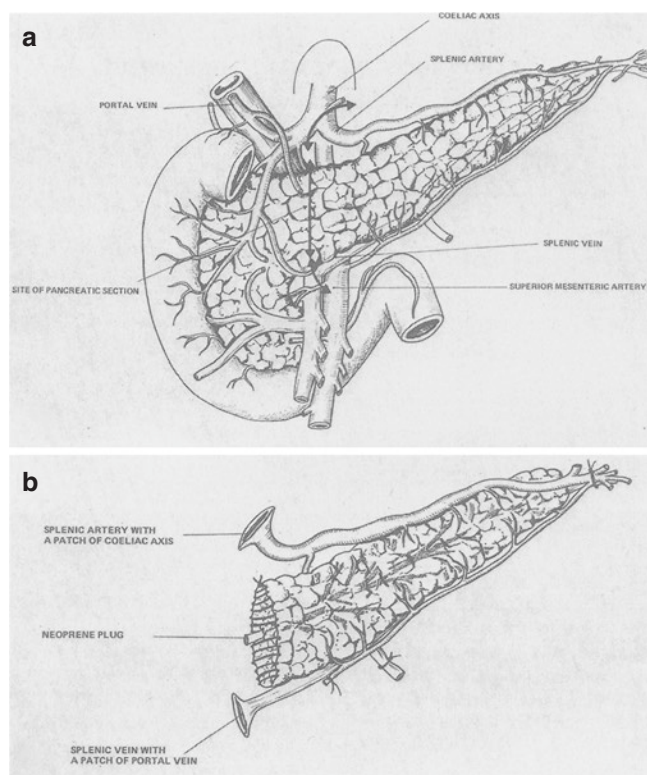


Fig. 5.9 Schematic drawings of the duct injection technique in the article by Dubernard et al. (a) cut line in the neck of the pancreas for removal of the distal pancreas and subsequent transplantation. (b) distal (segmental) pancreas with the splenic vessels as used for the purpose of transplantation. (Reprinted with permission from Dubernard et al. [118])

identified, and the quest for a less complication-prone technique continued. Segmental grafts were favored by most at the time, based on the perception that the complications Lillehei described were related to the duodenum, although a critical examination of his cases showed that the majority of complications were related to the kidney graft [105].

In 1983, Hans Sollinger at the University of Wisconsin reported on a technique that over the next decade in one variation or another was the most used method for managing pancreatic exocrine secretions: bladder drainage [182] (Fig. 5.10). In essence, it is an extension of the concept of urinary drainage originally introduced by Gliedman [108], but using the bladder for direct anastomosis of a segmental graft was technically easier [182]. After developing the technique in dogs [109], Sollinger et al. reported an initial series of ten bladder-drained pancreas transplants (9 SPK) in 1984 [110]. The first clinical pancreatico-cystostomy was performed at the University of Wisconsin June 30, 1982 (according to IPTR data, the 225th documented pancreas transplant) [177]. Sollinger and others later incorporated the modification of Nghiem and Corry [183] of whole pancreaticoduodenal transplantation with a secure duodenocystostomy. Sollinger et al. rapidly accumulated a large experience and in 1988 reported an extremely low incidence of surgical

complications (in particular a low leak rate) with bladder drainage [184]. In the initial clinical publication on the technique in 1984, Sollinger et al. stated that “a significant decrease in urinary amylase might be a sensitive indicator for early pancreatic rejection,” [110] and Prieto et al. later showed his hypothesis to be correct [185].

Urinary drainage began with segmental pancreas transplants, first to the ureter [108] and then to the bladder [110], and was further modified for whole-pancreas transplants. In 1985, Gil-Vernet et al., from Barcelona, described a urinary drainage technique in which the papilla of Vater of a whole-organ graft was anastomosed to the recipient’s ipsilateral ureter (pancreaticoureterostomy) [186], preparing the graft as described by Lillehei for his last clinical case (enteric drained) [105]. The technique did not become popular, probably for the same reasons that Gliedman’s ureteral drainage had not been adopted as a routine by other transplant centers (see above). In 1987, Nghiem and Corry [183] at the University of Iowa described the technique of bladder drainage via a graft-to-recipient duodenocystostomy for whole pancreaticoduodenal grafts (Fig. 5.11), preparing the donor organ as described by Lillehei for his first 12 cases [17, 105]. They pointed out that the “anastomosis from the duodenum to the bladder is safer than the duodenojejunostomy, since the leak can easily be controlled by reoperation, whereas a gastrointestinal leak would be catastrophic.” [183] They also noted that the use of the duodenum (instead of the duct of Wirsung) for anastomosis would avoid stenosis. Bladder drainage via the graft duodenum was quickly adopted by most US centers; it was the predominant surgical technique for managing pancreatic exocrine secretions well into the mid-1990s, as documented by annual IPTR reports [187]. For SPK transplants, the dominant reason to use bladder drainage was for safety, since rejection could be monitored by serum creatinine. But, for solitary pancreas transplants, bladder drainage had the advantage of urine amylase monitoring for rejection. The IPTR analyses consistently showed a significantly lower graft loss from rejection for bladder-than nonbladder-drained solitary pancreas transplants in the late 1980s and early 1990s (see Chap. 50) [187].

In Europe, duct injection and enteric drainage remained the predominant surgical techniques in the late 1980s, in part because nearly all transplants were SPK and the surgical techniques were refined. The Stockholm group reported that for segmental grafts, using a Roux-en-Y loop for the pancreaticoenteric anastomosis and a pancreatic duct catheter for temporary protection, the complication rate was lowered [188, 189]. Nevertheless, a pancreatic ductoenterostomy is an inherently complication-prone procedure, and every surgeon recognizes that an enteroenterostomy is technically easier and more secure. Thus, in 1984, Starzl et al. [190] reintroduced the technique of enteric-drained whole-organ pancreaticoduodenal transplants as originally described by Lillehei [17].

Fig. 5.10 First page of the original article by Hans W. Sollinger on exocrine pancreatic drainage for segmental grafts. (Reprinted with permission from Sollinger et al. [110])

Clinical and Experimental Experience With Pancreaticocystostomy for Exocrine Pancreatic Drainage in Pancreas Transplantation

H. W. Sollinger, K. Cook, D. Kamps, N. R. Glass, and F. O. Belzer

THE MAJOR technical problem in segmental pancreas transplantation is the management of exocrine secretions. Graft failure, increased morbidity, and mortality have been associated with the failure to establish adequate and safe exocrine drainage. Since the first pancreas transplant performed in humans in 1966 by Kelly and associates, a variety of drainage procedures has been ascites may necessitate removal of the pancreatic graft. Duct ligation was used in nine patients, and none of these grafts are functioning. Gliedman et al reported the use of ductoureterostomy in an early series with good long-term follow-up.¹ The disadvantage of this method is that a nephrectomy has to be performed at the time of pancreas transplantation to use the ureter as a drainage conduit.

Nearly everyone was convinced that whole-organ pancreaticoduodenal transplants were preferable for transplants from deceased donors, and methods for reconstructing the vasculature to both organs after liver and pancreas procurement were devised by the community of transplant surgeons [191–193]. The Stockholm group continued to do enteric drainage but by direct duodenoenterostomy [194].

The Lyon group also adopted the whole-organ pancreaticoduodenal technique [195], comparing bladder drainage as described by Nghiem and Corry with enteric drainage as described by Lillehei and Starzl. At the University of Minnesota, whole pancreaticoduodenal transplants were also resumed after the Starzl report [196], with bladder drainage preferred for solitary and enteric drainage for SPK transplants [180, 197].

From the mid-1980s to the mid-1990s, bladder drainage became the most common technique worldwide, for SPK transplants because of its safety, for PTA for this reason and because a decrease in urine amylase activity could be used as a sensitive, if nonspecific, marker of rejection that preceded hyperglycemia by several days [198–200]. In the early days, IPTR analyses consistently showed higher survival rates or a lower incidence of rejection failure for bladder than for enteric-drained solitary pancreas transplants [187]. The late 1990s then saw a shift again from bladder to enteric drainage [187], in particular for SPK transplants. In the new millennium, enteric drainage became the most commonly used technique in all three recipient categories [201–203]. Enteric drainage is a more physiologic way to drain pancreatic exocrine secretions, and improvements in antimicrobial and immunosuppressive therapy reduced the risks of complications as well as rejection. In addition, the chronic complications of bladder drainage (e.g., urinary tract infections, hematuria, acidosis, dehydration) led to the need for enteric conversion in 10–30% of bladder-drained recipients [187, 201–203]. The first successful conversion from bladder to enteric drainage was reported by Tom et al. [204] from the University of Cincinnati in 1987.

Enteric drainage is now done for about 90% of all pancreas transplants; bladder drainage accounts for less than 10% (see Chaps. 29 and 66) [201–203]. The other techniques whose historical account is given above—in order applied, duct ligation, graft duodenostomy, ureteral drainage, duct injection, and open-duct drainage—are virtually never used unless for salvage of a technical situation (e.g., duct injection might be used to manage a leak). Other techniques that were used in only a few cases should also be mentioned: gastric drainage as described by Calne et al. [205] in 1984 and used in a few cases by Tyden et al. [206]; and drainage via the recipient gallbladder as reported by Helmut Wolfe from Berlin in the 1980s (personal communication).

In regard to venous drainage of pancreas grafts, portal would be the most physiological but from the first cases of Kelly and Lillehei [93] until Calne reported using the recipient splenic vein as the outflow for a gastric-duct-drained segmental pancreas graft venous effluent in 1984 [205], the systemic venous system was accessed. Following Calne's case [205], other groups drained segmental grafts into the portal system, specifically the superior mesenteric vein in Stockholm [206], the splenic vein in Barcelona [186], and the inferior mesenteric vein at the University of Minnesota [207].

The first whole-organ pancreaticoduodenal transplant drained via the portal circulation was reported by Mühlbacher from the University of Vienna, Austria, in 1989 [208] (see Chap. 29). He described a unique technical modification in which the distal end of the donor splenic vein was anastomosed to the recipient portal vein. Using the distal end of the donor's splenic vein allowed drainage of the pancreas via the duodenum into the bladder. Like many other creative surgical modifications in pancreas transplantation, the combination of portal venous and bladder drainage never found widespread application.

In 1992, Rosenlof et al. from the University of Virginia [209] and Shokou-Amri et al. from the University of Tennessee [210] described the use of portal drainage at the junction of the recipient's superior and splenic veins in recip-

HOW I DO IT

Technique of Simultaneous Renal Pancreatoduodenal Transplantation With Urinary Drainage of Pancreatic Secretion

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Duct-drained pancreases have been shown to maintain their long-term functional integrity and architecture better than those with ductal occlusion [1]. In this regard, drainage of the pancreatic exocrine secretion into a hollow viscus appears to be the most physiologic drainage in pancreatic transplantation [2]. Anastomosing the duct to the gastrointestinal tract, specifically the jejunum or the stomach, is associated with infection from gastrointestinal organisms [3,4]. Recently, the use of the bladder as an alternative to drain pancreatic exocrine secretion has gained more acceptance [5–8]. Encouraged by these reports and by our series of 20 consecutive renal pancreatic transplantations performed from March 1984 to August 1985 [4], we have drained the pancreatic exocrine secretion into the urinary bladder through a duodenocystostomy in nine patients. This report describes the technique used.

Technique

The pancreatoduodenal graft is removed and prepared according to a technique described previously [4]. It is vascularized by both celiac and superior mesenteric arteries arising from a common aortic patch and drained by the portal vein. The pancreatic transplant operation is performed through a right lower quadrant incision (Figure 1). A portal vein of adequate length is anastomosed end-to-side to the right iliac vein. The anastomosis is positioned very low on the iliac vein about 3 cm above the inguinal ligament. The aortic patch is joined to the right external iliac artery approximately 5 cm cephalad to the venous anastomosis. Both anastomoses are performed using continuous fine nonabsorbable monofilament sutures. The 5 cm duodenal segment is closed at both ends by staples, turned in by Lembert sutures, and anastomosed side-to-side to the bladder using a 2 cm duodeno-

tomy and cystotomy. This anastomosis is constructed in two layers, the inner full-thickness layer with absorbable sutures and the outer seromuscular layer with fine nonabsorbable sutures. The transplant is positioned intraperitoneally. A drain is inserted into the right iliac fossa before closure and kept in place for 24 to 48 hours. The abdomen is then prepared again and redraped, and the

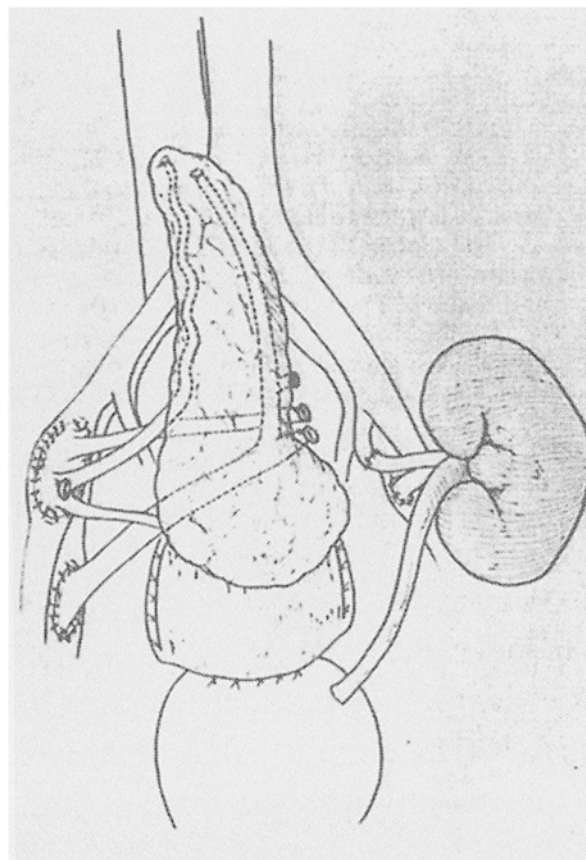


Figure 1. Renal and pancreatic anastomoses in the simultaneous procedure.

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Fig. 5.11 First page of the original article of pancreatic exocrine secretion via the bladder for pancreatoduodenal grafts as described by D.D. Nghiem and R.J. Corry. (Reprinted with permission from Nghiem and Corry [183].)

ients of enteric-drained whole-organ pancreaticoduodenal transplants. Subsequently, Gaber et al. reported on a large series of cases from the University of Tennessee [211], touting its metabolic and possible immunologic advantages, features also noted at the University of Maryland, another large program that at the time converted to doing portal drainage almost exclusively [149]. By the end of the 1990s, about 20% of pancreas transplants in the United States were being done with portal drainage, but the proportion did not increase nearly as much as the proportion of pancreas grafts that are enteric drained, to over 50% for solitary and over 70% for SPK transplants [212] (see Chap. 42).

Since the beginning of the new millennium, portal drainage has seen a further decline. According to IPTR data, only 11% of all pancreas transplants are nowadays portal-drained (see Chap. 66) [213]. This comes despite the introduction of new surgical techniques such as duodenal drainage which allows for drainage of the exocrine secretions into the recipient duodenum and engraftment in an anatomical position that favors portal drainage (see Chap. 30). Reasons why portal drainage has fallen out of favor include the failure to convincingly show lower rejection rates and the risk of a higher thrombosis rate by creating a venous anastomosis between a low flow donor organ and the low flow mesenteric system of the recipient [213].

The issue of whether to use a segmental or a whole-organ pancreas graft has also evolved over time. Most transplants in the late 1960s and early 1970s were whole-organ grafts. Segmental transplants became more common in the late 1970s and early 1980s. Since the mid-1980s, whole-organ transplants with a duodenal segment (rather than a duodenal button or patch) have been standard. Segmental transplants have not completely disappeared, but are primarily used with living donors (LDs). Pancreas transplants with LDs began at the University of Minnesota in the late 1970s [214] and have been done in all three recipient categories [126, 214]. The first LD pancreas after kidney (PAK) transplant was performed on June 20, 1979, the first LD PTA on May 14, 1980, and the first LD SPK transplant on March 10, 1994 [215]. All three firsts were at the University of Minnesota, the same institution where LD laparoscopic distal pancreatectomy was introduced in 2001 by Gruessner [215, 216].

As an aside, recurrence of autoimmune isletitis in pancreas grafts with selective destruction of β -cells in the absence of rejection was first described at the University of Minnesota in 1984 for segmental transplants from LDs [217], either from an HLA-identical sibling to a minimally immunosuppressed recipient or from an identical twin to a nonimmunosuppressed recipient [218] (see Chap. 39). In subsequent identical twin segmental pancreas transplants, isletitis was prevented by immunosuppression [219]. The level of immunosuppression to prevent autoimmune recurrence of disease is probably less than that necessary to pre-

vent rejection in most pancreas allograft recipients, but not in all, as demonstrated by the occurrence of selective total loss of β -cells in two allografts removed by Tyden et al. in Stockholm, long after recurrence of diabetes [220]. Most likely, isletitis had been present but resolved once the antigenic stimulant (the β -cells) had been eliminated. When it becomes possible to induce specific immune tolerance to donor alloantigens and eliminate immunosuppression to prevent rejection, it may still be necessary to immunosuppress to prevent recurrence of disease, unless the strategy to induce allotolerance also restores self-tolerance.

Over the past decade, seminal contributions to recurrence of type 1 diabetes (T1DR) in SPK recipients have been made by Burke et al. from the University of Miami (see Chap. 56). In their series the incidence of T1DR was about 5% and T1DR appeared to occur in association with autoantibody conversion and in the presence of autoreactive, memory CD4+ and CD8+ T cells [221] (see Chap. 56).

Another technical modification that relies on transplanting segmental grafts is the split pancreas procedure. In 1988, a deceased pancreas graft was split into two segments (head and body-tail) and successfully transplanted in two recipients with negative cross-matches to the donor despite high panel reactive alloantibody levels [222].

Besides the use of LDs for SPK transplants to facilitate achievement of insulin independence as well as a dialysis-free state in a nephropathic diabetic, for recipients whose LD can or is willing only to give a kidney, an SPK transplant can still be done. Each organ would come from different donors, either fortuitously having a deceased pancreas available at the time of a scheduled LD kidney transplant, as was first done at the University of Minnesota in the 1980s [197], or with the LD kidney donor oncall to come in when a deceased pancreas becomes available for the recipient. A relatively large series in the latter category was reported by Farney et al. from the University of Maryland in 2000 [223].

Factors Contributing to Improvements in Outcome

Refinements in surgical techniques have been critical not only to the development of pancreas transplantation, but also to improved outcome. Unlike in kidney transplantation, discussion of surgical techniques in pancreas transplantation dominated the seminars organized to forward the field in the first decades that followed the first case (see below). Also critical to progress in the field was the development of multiorgan donor procurement (see Chap. 14 for details), improvements in the diagnosis and treatment of rejection, advances in immunosuppressive protocols for induction and maintenance therapy, and antimicrobial prophylaxis and treatment, all of which evolved over time.

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. In SPK same-donor transplants, serum creatinine could be used as a marker, because rejection usually (there were exceptions [224]) involved both organs and usually manifested in the kidney first (see Chap. 50). For solitary pancreas transplants, rejection was more difficult to diagnose because hyperglycemia was such a late event, occurring only after a substantial proportion of β -cells were destroyed. Clinical parameters in pancreas rejection (e.g., fever, graft tenderness) were no more specific or likely to occur than in kidney rejection, where many rejection episodes are silent and manifested solely biochemically until advanced. The ordinary laboratory tests were either late indicators of rejection (e.g., plasma glucose) or nonspecific and not always manifest (e.g., serum amylase and lipase). The introduction of bladder drainage resulted in a better marker for rejection: urine amylase. Both experimental and clinical models showed that hypoamylasuria preceded hyperglycemia by several days, thus creating a therapeutic window to successfully reverse the rejection episode [103, 185]. As for other solid-organ transplants, graft biopsy has been the gold standard for diagnosing rejection right from the beginning. But, in pancreas transplantation, graft biopsies when they began to be done at the University of Minnesota in the early 1980s were by laparotomy [225], a deterrent to an aggressive pursuit of tissue sampling.

The use of imaging techniques and other maneuvers largely eliminated the need for laparotomy to obtain pancreas graft tissue. In 1990, James Perkins from the Mayo Clinic described a cystoscopic transduodenal biopsy technique [115]. In 1991, Richard Allen from Westmead Hospital, Sydney, Australia, described an ultrasound-guided percutaneous biopsy technique for bladder-drained pancreas transplants [226]. In 1992, Osama Gaber at the University of Tennessee described computed tomography (CT)-guided percutaneous biopsy for bladder- or enteric-drained pancreas transplants [227], a procedure now used routinely [228]. On occasion, these maneuvers fail. Thus, in 1996 a laparoscopic pancreas graft biopsy technique was described at the University of Minnesota [116, 228]. Percutaneous ultrasound or CT-guided biopsies have now become the gold standard for tissue diagnosis in pancreas transplantation. Both the cystoscopic approach (limited to bladder-drained transplants and now rarely done) and the laparoscopic approach require general (or regional) anesthesia and short-term hospitalization and are rarely done nowadays.

Advances in immunosuppressive protocols and the introduction of new immunosuppressants have had a major impact on improved outcome after pancreas transplants (see Chaps. 48 and 49). The introduction of the calcineurin inhibitors (cyclosporine in the 1980s and tacrolimus in the 1990)

significantly increased the number of pancreas transplants. In 1979, Calne et al. first reported the successful use of cyclosporine in two pancreas recipients (one simultaneously received a kidney and one a liver) [229]. In the early 1980s, maintenance immunosuppressive regimens were shifted from dual (azathioprine and steroids) to triple (cyclosporine-based) drug therapy (see Chap. 49) [230]. Triple-drug therapy was the most common according to IPTR analyses until tacrolimus and mycophenolated mofetil were Food and Drug Administration (FDA) licensed in the mid-1990s [187]. Starzl et al. first reported the use of tacrolimus in pancreas allograft recipients during the investigative period in 1989 [231]. After FDA approval, the first report on the use of tacrolimus for pancreas transplantation was by Shaffer et al., successfully reversing ongoing acute rejection in two SPK recipients [221]. The advantageous combined use of tacrolimus and mycophenolate mofetil in pancreas transplant recipients was shown by our group in the early 1990s and almost completely substituted the use of azathioprine and cyclosporine [232–237]. Perceived as having greater potency and better absorption in diabetic recipients, tacrolimus has been the predominant calcineurin inhibitor used in pancreas transplants [232–235]. Since the late 1990s, over 90% of all pancreas recipients worldwide were on tacrolimus-based maintenance immunosuppressive regimens [187, 213]. Likewise, since the mid-1990s mycophenolate mofetil almost completely replaced azathioprine (the mainstay immunosuppressant or co-immunosuppressant for more than three decades) [236–238]. The combination of tacrolimus and mycophenolate mofetil remains the most popular maintenance therapy regimen for pancreas transplant recipients [201–203, 239], despite the introduction of the less diabetogenic immunosuppressive drug sirolimus [240, 241]. Although being used in pancreas recipients quite frequently shortly after its introduction, sirolimus now accounts as a maintenance immunosuppressant in only about 1% of all pancreas transplants according to IPTR data (see Chaps. 49 and 66) [203, 213, 239].

Induction therapy with anti-T-cell preparations to prevent early pancreas graft rejection was used in some of the first cases according to information in the IPTR database (see Chaps. 48 and 66) [167]. Polyclonal antibodies were first used for US pancreas recipients in 1970 and outside the United States (Argentina) in 1968. Monoclonal antibody therapy (Muromonab-CD3; OKT3) was first used for US pancreas recipients in 1985 until discontinuation and outside the United States (Czechoslovakia) in 1983. After the advent of cyclosporine, quadruple immunosuppression (induction therapy plus three drug maintenance) quickly became popular worldwide [167] (see Chap. 15). In the late 1990s, the spectrum of antibody induction therapy for pancreas recipients was expanded to those directed against the interleukin-2 receptor (basiliximab, daclizumab) and the CD 52

antigen marker (alemtuzumab) (see Chap. 48). Based on I PTR data (see Chap. 66), depleting polyclonal antibodies are nowadays greatly favored over non-depleting antibodies and both interleukin-2 receptor (non-depleting antibody) and the CD 52 antigen marker (depleting monoclonal antibody) are used in about 11% of all pancreas transplants [203, 239].

The history of pancreas transplantation is also intertwined with the study of secondary complications of diabetes (see Chaps. 58–64). Before the Diabetes Control and Complications Trial (DCCT) was completed [242], a favorable impact of successful pancreas transplantation (euglycemia) on diabetic complications was shown, including on neuropathy [243–248], to a lesser extent retinopathy [249], nephropathy in both transplanted [250–252] and native [253] kidneys, microcirculatory disorders [254], and atherosclerotic risk factors [255, 256]. Several groups found that the addition of a pancreas improves survival probabilities of uremic diabetics over and above that of transplanting a kidney alone [257–260], and a successful pancreas transplant alone was also associated with improved survival probabilities in neuropathic diabetics [246, 261]. Studies in the 1980s showed that pancreas recipients perceived the quality of their lives to be better when nondiabetic on immunosuppression than when they were nonimmunosuppressed but diabetic [262, 263].

History of β -Cell Replacement Therapy at the University of Minnesota

The first clinical (human) transplant as an immediately vascularized pancreas allograft and the first clinical transplant of isolated adult allogenic pancreatic islets were done at the University of Minnesota in 1966 [93] and 1974 [264], respectively.

The clinical pancreas transplant program at the University of Minnesota remains one of the largest in the world. Since 1966, it has performed more pancreas transplants than any other institution [213]. Although there are several unique facets of the β -cell replacement program at the University of Minnesota, the program has readily adopted techniques devised by others [197]. The interactions between programs are part of the overall story.

The clinical β -cell replacement program has largely been driven by physicians who had one foot at the bedside and one foot in the laboratory, cross-fertilized by interactions with basic scientists [197].

The major players in the development of islet isolation and transplantation in the Department of Anatomy, independently as well as in collaboration with the Department of Surgery, were Arnold Lindall, Michael Steffes, Rouf Younoszai, Robert Leonard, Orion Hegre, and Robert McEvoy [265–269].

Arnold Lindall was the first to use Ficoll gradients to separate islets from the ductal and exocrine tissue of collagenase

digested adult pancreases [265]. The technique of collagenase digestion for dissociation of pancreatic tissue had been introduced by Moskalewski in Poland in 1965 [270]. Lacy et al. at Washington University in St. Louis in 1967 [271] reported a modification of the Moskalewski technique in which the exocrine tissue of a rat pancreas was first disrupted by retrograde perfusion fluid into the pancreatic duct under pressure; the pancreas was then minced, the exocrine and endocrine tissue dissociated by collagenase digestion, and the islets handpicked under a dissecting microscope, a tedious procedure. Islets are physically less dense than other pancreatic components, and Lindall found they could be cleanly isolated by density gradient centrifugation in Ficoll, a sucrose polymer. The Ficoll gradient islet isolation technique has been the standard in the field since the publication by Lindall et al. in 1969 [265].

Michael Steffes used the Ficoll gradient technique to isolate islets from rat pancreases for physiologic studies of islet cells [266]. He was acutely aware of the potential of islet transplantation and later became a major player, but it was another graduate student, Rouf Younoszai, who did the world's first transplant of isolated adult islets [267].

Younoszai presented his work at the 1970 American Diabetes Association meeting [267]. Rats with alloxan-induced diabetes became normoglycemic for several days after intraperitoneal transplantation of allogenic adult rat islets isolated by the collagenase digestion-Ficoll gradient technique. Recurrence of hyperglycemia was attributed to rejection, although no posttransplant histologic studies were done.

The publication by Younoszai et al. [267] preceded by 2 years the oft-cited publication of Ballinger and Lacy from St. Louis on partial amelioration of diabetes by intraperitoneal transplantation of syngeneic, isolated islets in rats [272]. The latter article is commonly regarded as the beginning of the modern era of experimental islet transplantation. The early events of this era have been described in detail [98, 99, 269].

Clinical kidney transplantation began at the University of Minnesota in 1962 [273]. Kelly had an interest in immunology [274] and was appointed by the chairman, Owen Wangenstein, as the surgical director of the clinical transplant program, but several surgeons, including Lillehei, were involved. Both Kelly and Lillehei saw the diabetic patient as a challenge, in particular the uremic diabetic, and believed pancreas transplantation would be a necessary addition for kidney transplantation to succeed. Their laboratories were completely independent of one another. Both had residents or fellows working on the problems to be solved for clinical application. Frederick Merkel, in Kelly's laboratory, did segmental pancreas transplants in dogs [94, 104]. Felix Largiader, from Zurich, and Yasuo Idezuki, from Tokyo, working in Lillehei's laboratory, did whole pancreaticoduodenal transplants [96, 97]. Merkel attempted to reduce graft exocrine function by irradiation [104]. He also attempted to

prevent graft thrombosis by interposing the donor portal vein into the iliac vein of the recipient [94], as was done in the first clinical cases (Fig. 5.3) [93].

John S. Najarian, who did the first kidney transplant at the University of California in 1962, became the chairman of the Department of Surgery at the University of Minnesota in July 1967. He assumed directorship of the transplant program, and shortly thereafter, Kelly left the University to enter private practice.

Lillehei, with the assistance of surgical fellows recruited from around the world, continued his clinical and investigational work on the technical aspects of pancreas transplantation [105]. One human pancreas allograft functioned for nearly 1 year (SPK transplant with enteric drainage via a Roux-en-Y duodenojejunostomy)—case 5 in his series (case 6 overall); 4 of his 12 pancreaticoduodenal grafts failed from perforation or necrosis of the duodenum. So for his last whole-organ transplant, he retained only the papilla of Vater for anastomosis to the recipient, as devised by Acquino in his laboratory [106]. The last case was technically successful, but the graft was rejected 3 months later.

Najarian participated in some of the pancreas transplant operations with Lillehei and saw firsthand the complications. The experience convinced him to pursue a less invasive approach to endocrine replacement therapy in diabetic patients. He recruited a surgeon, Richard Simmons, and a nephrologist, Carl Kjellstrand, to develop a large-volume kidney transplant program with a focus on diabetes mellitus. They challenged the concept that correction of diabetes was necessary for a kidney transplant to succeed and began doing KTAs in the uremic diabetics [275].

Lillehei, however, did not give up and continued to do pancreas transplants, but with a new emphasis on the non-uremic, labile diabetic [105]. Now, instead of surgical complications, he had rejection [276].

Najarian did not wait to beg in a new approach. In 1970, Steffes, then a graduate student in the Department of Anatomy, told Edward Etheredge, a senior resident working in Najarian's laboratory on immune monitoring, of the work with islet isolation in the Department of Anatomy. The potential to apply islet transplantation clinically was obvious, and a program of basic and applied islet transplant research using animal and human pancreases (from deceased donors) was initiated in the Department of Surgery with the assistance of Steffes. Etheredge left the laboratory for the clinic in 1971, while one of us (D.E.R.S.) entered the laboratory for a 2-year period devoted solely to transplant research, with special emphasis on islet isolation and transplantation in large- and small-animal models and with an aim to clinical trials. Islet isolation was done from all local deceased donor pancreases [277] except the few that Lillehei used for transplantation. Although the yields of pure human islets were usually low, at least some were viable in that they secreted insulin and glucagon *in vitro* in response to physiologic stim-

uli, studies done in collaboration with Steffes and Brian Noe, another graduate student in the Department of Anatomy [278].

We also had been able to ameliorate diabetes by islet transplantation in animal models [277, 279] and hoped that the human islet preparations would be adequate for transplantation [280]. On February 8, 1974, we did our first purified human islet transplant intraperitoneally in a recipient of a previous kidney allograft, the first in a series of 10 done over the next year [281]. The last five were done intraportally, based on the animal studies by Kemp et al. [282] at St. Louis showing the intrahepatic site to be the most favorable for engraftment. We also found the intraportal site to be best in rodents [283], but none of our human recipients became insulin-independent [281]. We were not sure if the failure was from rejection or insufficient β -cell mass and viability.

Given animal experiments showing that islet purification was not necessary [284], we did a second series of 10 human islet allografts with unpurified tissue from 1977 to 1981 [285, 286], including 2 from living donors. Half of the recipients became C-peptide positive, and one (islets from a living donor) was insulin-independent the third posttransplant week, but the results were still disappointing [197]. To test whether the problem with the allografts related to our human islet preparation technique, we did intraportal islet autografts in patients undergoing total pancreatectomy to treat chronic pancreatitis [287, 288]. Our first islet autograft recipient, done in 1977, was insulin-independent after the operation [289], a state that was sustained until she died 6 years later of vascular disease [290]. Although islet autotransplantation was not successful in all pancreatectomized recipients, there was direct correlation of success with yield [290]. We concluded that either it was difficult to get a sufficient yield of viable islets from deceased pancreases with the preservation techniques available in the 1970s or that islets were highly sensitive to allorejection [285].

In the experimental laboratory, we used islet transplants for a variety of experiments with a stream of collaborative investigators [197]. For example, diabetic nephropathy could be reversed in rats by islet transplantation [291]. However, based on our initial clinical attempts at islet allotransplantation [285], by the late 1970s we became convinced that, to meet the immediate desires of our patients for β -cell replacement therapy, we would have to resume clinical pancreas transplantation [197]. We continued with islet transplant experiments in the laboratory [125] and never stopped doing clinical islet allografts, ultimately achieving some success [292].

Few pancreas transplants were being performed anywhere by the late 1970s. In the United States, an occasional transplant was being performed at Montefiore Hospital in New York City [293]. In Europe, the only activity was in Stockholm [294] and Lyon [295]. In 1977, we heard a pre-

sensation by Dubernard of Lyon at the European Surgical Research Society meeting in Warsaw on the duct injection technique in animals and man. In his animal experiments, he had no controls to compare complications in recipients of noninjected and injected grafts. Shortly thereafter, we did the experiments at the University of Minnesota, and to our surprise, the dogs [127] and pigs [296] tolerated intraperitoneal open-duct pancreas grafts with virtually no complications; they were able to absorb the graft secretions in the absence of enzyme activation.

Although leakage from pancreatic anastomosis in humans was associated with a high level of morbidity, we reasoned a pure open-duct graft would be different, with no exposure to enterokinase. It seemed reasonable to test clinically.

By this time, we had many diabetic patients who had undergone KTAs [297] and were candidates for PAK transplants. Thus, in July 1978, we initiated a series of deceased segmental open-duct PAK transplants [128] and did 12 in a 2-year period. Two of the 12 grafts thrombosed. Of the other 10, 3 functioned from 4 to 17 years, 4 were rejected within 4 months, and 3 had to be removed because of peritonitis or ascites, a much higher incidence than we had observed in our animal models [129]. Thus, we abandoned the open-duct technique and, over the next 20 years as detailed in our publications [180, 197], went on to sequentially do duct injection, enteric drainage, a comparative study of duct injection vs. enteric drainage, bladder drainage, a comparative study of bladder vs. enteric drainage, and, in the 1990s, ending our studies of duct management and using techniques selectively, largely enteric drainage initially for SPK transplants and eventually also for solitary pancreas transplants.

We began in 1978 with PAK transplants in diabetic patients who had already received kidney transplants. We liked the simplicity of placing one organ at a time; for the uremic diabetic advocated placement of an LD kidney first, followed by either a deceased pancreas or a segmental graft from the same (practically ensuring a low rate of rejection) or another LD [298]. Nearly all other programs in the world focused on SPK transplants from deceased donors, but because the rejection rate was high in the pre-cyclosporine era, we placed great emphasis on LD PAK and PTA transplants to minimize the rejection risk. Once cyclosporine became available in the mid-1980s, we began doing SPK transplants, at first from deceased donors [196] and later from LDs as well [299]. Our philosophy was to do pancreas transplants in all categories of diabetic patients, with no more emphasis on one than the other [187].

Beginning in the early 1980s, we did a series of segmental pancreas transplants from nondiabetic identical twins to their diabetic counterparts [217–219] (see Chap. 38). When one twin becomes diabetic, the other one does so only 30% of the time, almost always within 10 years of the onset of diabetes in the proband reference. All our cases had been discordant for more than 10 years and thus we felt the risk in the donor

was low. Although we were aware of the work by Naji et al [64] in the BB rat model of autoimmune diabetes where an islet graft could be affected, we thought the clinical situation would be different so many years after onset of the original disease. Thus, in our first cases, we did not immunosuppress the recipients because rejection could not occur. All the twin recipients became insulin-independent initially. The first identical-twin graft, done in 1980, was duct-injected and in 6 weeks hyperglycemia recurred, which we initially attributed to the duct injection-induced fibrosis [131]. In 1982, we saw recurrence of hyperglycemia without rejection in an HLA-identical sibling segmental allograft in which β -cells were absent in the graft islets at the time we did the biopsy [131], similar to the histology described by Tyden et al. [220] in two deceased grafts biopsied late after recurrence of diabetes. Although we recognized that the diabetes had recurred in the absence of rejection, we missed the immunologic nature of the failure because of the absence of isletitis. In retrospect, the isletitis disappeared once the β -cells were destroyed, but it took the second and third identical-twin transplants, done only a few weeks apart in 1983, to tip us to the reality of autoimmune recurrence of disease [217]. The second and third identical-twin transplants were done with enteric drainage. At 6 and 12 weeks, almost at the same time, each became hyperglycemic: graft biopsies clearly showed isletitis with selective β -cell destruction. In some lobules the β -cells were absent, and there was no isletitis (late phase), while in other lobules islets still had β -cells surrounded by inflammatory cells with no other pathology [218]. The other two cases of recurrence of diabetes in which the biopsy had not shown rejection were reexamined. In the HLA-identical sibling case, on resectioning the biopsy, a few islets with β -cells still present were found and these, and only these, had isletitis. The first identical-twin recipient had a fibrotic gland from the duct injection, but the islets were not fibrotic, only inflamed. To pathologist, Richard Sibley, must go the credit for recognizing the recurrent nature of the disease, recapitulating the natural history of autoimmune isletitis in type 1 diabetes as described in the native pancreas by Foulis [300].

We did not stop doing identical-twin donor segmental pancreas transplants [219]. We simply gave the recipients of identical-twin grafts maintenance immunosuppression, and recurrence of disease was prevented [219], with follow-up of over 14 years [180]. We know from our HLA-identical sibling case [131], the Stockholm and now the Miami cases [220, 301] that autoimmunity can manifest in the presence of immunosuppression sufficient to prevent rejection [302]. The main historical point is that we demonstrated through pancreas transplantation that the recurrence of disease with isletitis and selective β -cell destruction in non-immunosuppressed recipients (of a pancreas graft from an identical-twin donor) left no doubt that classic type 1 diabetes is an autoimmune disease.

Apart from the identical-twin transplants, our immunosuppressive strategies evolved over time [180]. As new

immunosuppressants were developed in other programs (cyclosporine at Cambridge, tacrolimus at Pittsburgh, mycophenolate mofetil at Wisconsin), we incorporated them into our protocols [233, 236, 237]. Anti-T-cell antibody therapy has always been an integral part of our protocol and became even more so after the introduction of ganciclovir for cytomegalovirus (CMV) prophylaxis, leading us to a steroid-free protocol for SPK and PAK recipients [303]. For PTA recipients, we have used pretransplant immunosuppression and occasionally pretransplant blood transfusions, with graft survival rates almost reaching those of the other categories [304].

The pancreas transplant program at the University of Minnesota has always been interdisciplinary and a product of inter- as well as intrainstitutional interactions [180, 197]. It has not necessarily been unique in any aspect because nearly every feature of our program can be found in some other, but it has been comprehensive. We have formally documented the effect of pancreas transplantation on metabolism and on secondary complications of diabetes and quality of life. We have used LDs routinely until the 1990s and pulled only back when pancreas and kidney allocation policies allowed a greater number of diabetic patients to undergo a combined pancreas and kidney transplant. The pancreas transplant program at the University of Minnesota continues to do pancreas transplants as it does kidney transplants, as an alternative to what for some diabetics is simply onerous—daily blood sugar monitoring and exogenous insulin injections. And pancreas and islet transplantation have been integrated into a program of β -cell replacement therapy. The philosophy of offering an insulin-free life to diabetics remains unwavering at the University of Minnesota despite changes in clinical leadership.

The Minnesota pancreas transplant team published the first edition of this comprehensive textbook on “Pancreas Transplantation” in 2004 [305]. The majority of the contributors included former or current transplant faculty and fellows. As this field has evolved over the past two decades, this second edition still includes authorships of many Minnesota-trained surgeons and physicians, but also comprises the contributions of many other clinical leaders from around the world who have made pancreas transplantation the focus of their professional careers and have made seminal contributions to this field.

Conferences, Workshops, Meetings, and Societies in the Evolution of Pancreas Transplantation

Advances in the clinical application of pancreas and islet transplantation were greatly facilitated in the 1970s and early 1980s by the interactions between the clinicians and investigators developing the field. Besides workshops, the annual or semiannual meetings of the transplant societies were

forums for exchange. The exchanges can be captured only in part from the published proceedings of the meetings. The unpublished portion, half of the body of scientific knowledge, is oral history, some of which will be related here.

In regard to published proceedings, The Transplantation Society has a nearly complete record from its semiannual meetings in *Transplantation Proceedings* beginning in 1968 and extending into the early new millennium. The first meeting is devoid of discussions on β -cell replacement therapy, but from 1970 on an ever-increasing proportion of articles appeared on the topic, several of which are cited in this chapter.

The American Society of Transplant Surgeons (ASTS) first met in 1975 and their first 20 years (the period where pancreas transplantation matured) were captured in a volume that summarizes the advances in each of the organs that were of interest, including the pancreas [306]. From 1975 through 1993, 851 articles were presented at meetings, of which 93 (11%) were on pancreas (8 clinical, 13 experimental) or islet (32 clinical, 36 experimental) transplantation. Of these, 62 (67%) were published in the official journal (*Transplantation*) and another 21% in other journals, bringing to 88% the total of articles presented that were published or in press in peer-reviewed journals. Many of these articles are also cited in this chapter. In 2000, the ASTS held the first American Transplant Congress (ATC) in conjunction with the American Society of Transplantation (AST, formerly known as American Society of Transplant Physicians [ASTP]) in Chicago. Since then, abstracts on pancreas and islet transplantation presented at the annual meetings have primarily been published in the *American Journal of Transplantation*.

The *Surgical Forum*, sponsored by the American College of Surgeons at its annual meetings, is well represented by citations in this chapter, in particular the experimental work going on at the time clinical applications began. The proceedings of the European Societies for Organ Transplantation are also represented by citations in this chapter.

Only a few examples of the interactions between the players in the field can be given. One that is personal (D.E.R.S.) occurred at the meeting of the European Society for Surgical Research in Warsaw in 1977 [307]. There were only a few articles on pancreas or islet transplantation on the program. However, the highlight of the pancreas and islet transplant session was an ad hoc presentation by Dubernard on the Lyon experience with duct-injected segmental pancreas allografts in humans, then with 1-year follow-up of his first cases. Dubernard presented to a packed hallway on both the clinical experience and the experiments in dogs, illustrating the exocrine atrophy with islet survival in the canine grafts. The obvious safety of this technique was one of the stimulants to resume clinical pancreas transplantation at the University of Minnesota. Because he had not compared complications in dogs with injected and noninjected pancreas grafts, we did so and found that open-duct grafts were well-tolerated and functioned better than duct-injected grafts

[296]. Shortly thereafter, the technique was used clinically but with a higher complication rate than in the animal model [128]. Nevertheless, it was the beginning of a clinical program that can trace its start to a meeting designed to foster scientific exchange on the personal level.

One of the most important workshops facilitating the development of pancreas and islet transplantation was held in Lyon in March 1980 (Fig. 5.12).

The workshop was organized by Max Dubernard and Jules Traeger [308], and virtually every pancreas or islet transplant done to date was scrutinized. It was also the beginning of the International Pancreas and Islet Transplant Registry (see Chap. 66 for more details on the history). There was a tremendous excitement in the air, with all the participants realizing that the tools were available to advance the field. Roy Calne had introduced cyclosporine, the duct injection technique was safe, and it was just a matter of time, probably a short time, for widespread application to occur. The 1-year graft survival rate for pancreas transplants at that time was 20%, but 7 years later the Pancreas Transplant Registry analyses showed 1-year graft survival rates of ~70% for SPK and ~50% for solitary pancreas transplant [187].

Another important series of workshops were those organized by Walter Land from the University of Munich and held at the ski haven in Spitzingsee, Germany, beginning in 1982. The proceedings of the first three workshops were published [309–311], but the nonpublished aspects of the meetings, the interactive portions, are just as important. At the first Spitzingsee meeting, Hans Sollinger was skeptical of all the methods presented on pancreas graft duct management. The second evening of the meeting, after an afternoon of skiing, the participants with energy to spare gamed at the lodge bowling alley. During a bowl, Hans Sollinger stopped in midstride, drew back his ball, and said, “I’ve got it.” Everyone wanted to know what he had gotten. He said, “I’m not telling; you’ll find out later.” He then went back to the UW, Madison, and developed the bladder drainage technique. By the time of the next Spitzingsee meeting, as documented by the Registry report [312], bladder drainage was the dominant technique.

The International Pancreas and Islet Transplantation Association (IPITA) was incorporated in 1993, formed as the result of successive congresses held in Stockholm in 1988 [313], Minneapolis in 1989 [314], and Lyon in 1991 [315]. The proceedings of the IPITA meetings and their predeces-



Fig. 5.12 Participants of the historic 1980 pancreas transplant workshop in Lyon, France: Sir Roy Calne (far left), Jules Traeger (third from left), David Sutherland (center, fifth from left), Paul McMaster (fourth

from right), and Jean-Michel “Max” Dubernard (second from right) and Robert Corry (far right)

sors chronicle the progress that has been made in β -cell replacement therapy. In 2011, IPITA established the Richard C. Lillehei Memorial Lecture to commemorate his fundamental contributions to pancreas transplantation. This biennial award is given to an outstanding clinician and/or scientist for their substantial contributions towards advancing the field of pancreas transplantation. The inaugural recipient in 2011 was David Sutherland, followed by Max Dubernard (2013), Hans Sollinger (2015), Raimund Margreiter (2017), Angelika and Rainer Gruessner (2019), and Robert Stratta (2021).

Pancreas Transplantation in the New Millennium

Pancreas transplants continue to be performed worldwide. Since the first pancreas transplant in 1966 and through 2020, over 65,000 pancreas transplants have been reported to the IPTR [213] and over 35,000 transplants in the United States alone (see Chap. 66). In the new millennium, the number of pancreas transplants has substantially increased in South America and Asia, the United States saw a temporary decrease from 2004 to 2013 [316–319]. The number of patients who have remained insulin-free for more than 10 or 20 years continues to grow (see Chap. 73) [316].

With the beginning of the new millennium, a new era in pancreas transplantation was ushered in. Many of the first generation of pancreas transplant surgeons retired and new programs opened up. The torch has been passed to a new generation of pancreas transplant surgeons whose foremost task is to expand on what was built by the generation before them. What has not changed since the first pancreas transplant in 1966 is that long-term insulin-independence can still only be achieved consistently in diabetics through pancreas transplantation, albeit in the presence of life-long immunosuppressive therapy. Avoidance or safe discontinuation of all immunosuppression and avoidance of recurrence of diabetes in the absence of immunosuppression will be the biggest challenges for the next generation of transplant scientists.

Surgical techniques and immunosuppressive regimens are now widely standardized, progress in antimicrobial prophylaxis and therapy, more stringent donor selection criteria, and better recipient work-up have all resulted in significantly improved outcomes [316]. The most recent IPTR data show that since the beginning of the new millennium, enteric with systemic venous drainage is the most commonly used surgical technique. Portal venous drainage is now performed in about 10–20% of all transplants and bladder drainage and segmental transplants have become rare procedures [201–203, 239, 316]. Duodenal and gastric drainage for the management of exocrine secretions have been introduced and are refined tools in the technical armamentarium (see Chaps. 30–32). They allow direct access to

the donor duodenum and pancreas for endoscopic surveillance, biopsy, ultrasound, and ERCP and have been successfully performed with both systemic and portal venous drainage. Retroperitoneal placement of the pancreas with portal-enteric/duodenal/gastric drainage may result in a more fixed position with yet to be defined advantages (see Chaps. 29–32).

HLA typing has lost its importance and most pancreas transplants are actually performed without HLA consideration with the exception of cases with donor-specific antibodies (see Chaps. 50 and 66) [201–203, 239, 316]. The concept of quadruple immunosuppression for induction therapy and triple immunosuppression for maintenance therapy has not changed since the introduction of tacrolimus and mycophenolate mofetil [201–203, 239, 316]. The initial excitement about using steroid-free protocols and the use of sirolimus has waned; and calcineurin-free protocols remain elusive (Chap. 49) [201–203].

Over the past two decades, pancreas transplants are increasingly performed in uremic Type 2 diabetic patients (see Chap. 71) [239, 320]. Pancreas transplantation is no longer limited to Type 1 diabetic patients only. Of note, there is no difference in outcome between type 1 and type 2 diabetic patients (see Chap. 66) [201–203, 239, 316]. The number of pancreas transplants in racial minorities continues to increase (see Chaps. 66 and 71) [213, 238]. Substantial progress has also been made in the classification of pancreas graft rejection through definition of standardized histopathological guidelines based on the BANFF criteria (see Chap. 51) [321, 322].

Except for a relatively small number of transplants in selected patients who have become insulin-independent, the results of islet transplantation still continue to trail those of pancreas transplantation (see Chap. 84) [239, 323]. However, pancreas and islet transplantation should not be considered competing, but rather complementary treatment options for diabetic patients. In some countries such as Canada and the United Kingdom, transplant candidates are listed on a common list for pancreas and islet transplants (see Chaps. 18–20). At the time of this writing, the largest insurance companies in the United States including Medicare and Medicaid still do not approve coverage for islet transplantation. The complementary nature of the two procedures is also shown by the fact that pancreas transplants have been successfully performed with excellent long-term outcome after failed islet transplants (see Chap. 85) [324]. In addition, pancreas transplantation is also an option for patients with surgically induced diabetes after total pancreatectomy for chronic pancreatitis to cure both endocrine and exocrine deficiency (see Chaps. 80–83) [325].

If we can learn from the history of this field, a paradigm shift toward solitary pancreas transplants in non-uremic and post-uremic patients is necessary (Chap. 21–24). This would prevent the development or progression of secondary dia-

betic complications and the need for a kidney transplant (PTA) and recurrence of diabetes in a previously transplanted kidney (PAK) and alleviate the shortage of kidney donor organs (SPK). It has been shown that long-term outcome after solitary pancreas transplants has markedly improved as shown by their survival benefits (Chap. 66) [239, 326–328].

Pancreas transplantation remains both a steady and evolving field. In 2006, the 40th anniversary (Fig. 5.13) of the first pancreas transplant in 1966, and in 2017, the 50th anniversary were commemorated at the University of Minnesota with many of the first generation of pancreas transplant surgeons in attendance (Fig. 5.14). In 2018, a consensus report on defining outcomes for β -cell replacement therapy in the treatment of diabetes was published (Chap. 65) [329]. And in 2019, the First World Consensus Conference on Pancreas Transplantation was held in Pisa Italy to further advance the case for pancreas transplantation



Fig. 5.13 Organizers of the 40th Anniversary of the First Pancreas Transplant in Minneapolis, Minnesota, in 2006. From left to right: David E.R. Sutherland, Rainer W.G. Gruessner, and John S. Najarian



Fig. 5.14 Participants of the 50th Anniversary of the First Pancreas Transplant in Minneapolis, Minnesota May 2017). From left to right: Jean-Michel “Max” Dubernard, Frederick Merkel (member of the surgical team of the first pancreas transplant), David Sutherland, and Hans Sollinger

(Chap. 86) [330, 331]. The impact of new, unforeseen challenges on pancreas transplantation such as the COVID-19 pandemic need to be fully investigated with all their consequences (Chaps. 66 and 91), but we predict that even with new challenges and in the absence of long-term insulin-independent alternatives, pancreas transplantation is here to stay for the foreseeable future.

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