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3 The History of Pancreas Transplantation

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More than 115 years ago, it was demonstrated by Von Mering and Minkowski that pancreatectomy produced diabetes mellitus in dogs (1). Nearly four decades passed before attempts were made to restore glucose homeostasis by pancreas transplantation with surgical vascular anastomoses, but only for physiologic experiments (2,3). An additional three decades went by before preclinical studies for the potential purpose of ameliorating diabetes were undertaken in the late 1950s by Brooks and Gifford (4) and DeJode and Howard (5). After surgical technical problems were worked out in the canine model (summarized in Ref. 6), the first attempt to treat human diabetes mellitus with pancreas transplantation was carried out on December 17, 1966, by William Kelly and Richard Lillehei (7) at the University of Minnesota. The patient died after two months. The same Minneapolis team recorded the first success on June 3, 1969 (8). "Success" during this pioneer period came to be defined as patient and functional graft survival for at least one year.

Thus, the pancreas became the fourth kind of organ allograft to be successfully transplanted over a 10-year period (1959–1969) in which the feasibility of kidney (9,10), liver (11), and heart (12) already had been demonstrated (Table 1) (8–13). It was a stunning "proof of principle" development that was at first considered not credible by knowledgeable authorities who had viewed such efforts with distain. Hopes for organ transplantation had been based previously on experiments in neonatal mice (14) and in irradiated adult mice (15) in which it was shown that the development of donor-specific tolerance was associated with the donor leukocyte chimerism produced by splenic or bone marrow cell infusion. In an extrapolation of the mouse findings, the production of donor leukocyte chimerism by bone marrow infusion prior to or at the time of organ transplantation was expected to play an essential role in achieving organ engraftment. However, efforts to apply this strategy in animals were uniformly unsuccessful, in part because a good histocompatibility match was a prerequisite for avoidance of graft versus host disease. When discovery of the human leukocyte antigens made tissue matching feasible, human bone marrow transplantation was finally accomplished, but this was not until 1968 (13).

In the meanwhile, two unexplained qualities of the alloimmune response had made it feasible to forge ahead precociously with organ transplantation under drug immunosuppression (16). The first observation was that kidney allograft rejection that developed under azathioprine was regularly reversible by adding large doses of prednisone. The second finding was that organ allografts under the nonspecific immunosuppression of azathioprine and prednisone appeared to self-induce variable donor-specific tolerance. Tolerance was inferred from the rapidly declining need for immunosuppression after rejection reversal. However, because of the ostensible absence of donor leukocyte chimerism in these recipients, organ engraftment, including that of the pancreas, was attributed to different mechanisms than those of bone marrow cell engraftment. This chimerism-exclusionary dogma was not challenged until low-level (micro-) chimerism was discovered in 1992 in the blood and tissues of long-surviving organ recipients (17,18). Then it was obvious that alloengraftment was a form of partial tolerance that resulted from "... responses of co-existing donor and recipient cells, each to the other, causing reciprocal clonal exhaustion, followed by peripheral clonal deletion" (Fig. 1) (17,18). Successfully treated organ recipients and bone marrow recipients were mirror image versions of leukocyte chimerism, differing in the proportion of donor and recipient leukocytes (Fig. 2).

THE DOMINANT ROLE OF DRUG IMMUNOSUPPRESSION

Without the foregoing insight into the chimerism-dependent mechanisms of organ engraftment, further progress hinged almost exclusively on the development of stronger

Table 1 First Successful Transplantation of Human Allografts (Survival ≥1 Year)

Organ	City (Ref.)	Date	Physician/surgeon
Kidney	Boston (9,10)	1/24/59	Merrill/Murray
Liver	Denver (11)	7/23/67	Starzl/Groth
Heart	Cape Town (12)	1/2/68	Barnard
Bone marrow	Minneapolis (13)	8/24/68	Gatti/Good
Pancreas[a]	Minneapolis (8)	6/3/69	Lillehei/Kelly

[a]Kidney and pancreas allografts in uremic patient.

immunosuppression. The combined use of azathioprine and prednisone had been a critical step in the clinical development of kidney and other kinds of organ transplantation. But because allografts were being lost to acute rejections that could not be reversed, a worldwide policy drift occurred in which large doses of prednisone were administered from the time of operation, rather than in response to rejection. The addition in 1966 of a short course of post-transplant antilymphocyte globulin (ALG) to azathioprine and prednisone (the "triple drug cocktail") substantially reduced steroid needs (19,20) and was used for the first successful non-renal organ transplantations (8,11,12). Nevertheless, the heavy mortality, and particularly the devastating morbidity caused by long-term prednisone dependence, made organ transplantation (even of kidneys) as much a disease as a treatment in the view of critics. Widespread transplantation of the nonrenal organs (including the pancreas) was forestalled until the advent of cyclosporine (21,22) and tacrolimus (23).

As the more potent drugs became available, they were simply folded into the modified formula of heavy prophylactic immunosuppression that had been inherited from the 1960s and 1970s. Used in this way, the multiple drug cocktails fueled the golden age of transplantation of the 1980s and early 1990s. The dose ceilings of the individual primary and secondary drugs were imposed by drug toxicity, while the dose floors were revealed by breakthrough rejection. For example, the upper limit of azathioprine dosage [or comparably used substitutes such as cyclosphosphamide (24) or mycophenolate mofetil (MMF) (25)] was dictated by myelotoxicity that could be monitored conveniently by serial white blood counts. The more complex limiting side effects of the calcineurin inhibitors (cyclosporine and tacrolimus) are shown in Table 2. Of specific interest in the context of pancreas transplantation, both cyclosporine and tacrolimus are diabetogenic, in addition to their nephrotoxicity and neurotoxicity (26). The other T-cell directed agent, sirolimus, has its own distinctive panoply of dose-limiting side effects (27).

By using these agents in different combinations, it was possible with the various drug cocktails to reduce acute rejection to almost a non-problem during the last two decades. The unresolved issues now became the drug-specific side effects, chronic rejection, and the

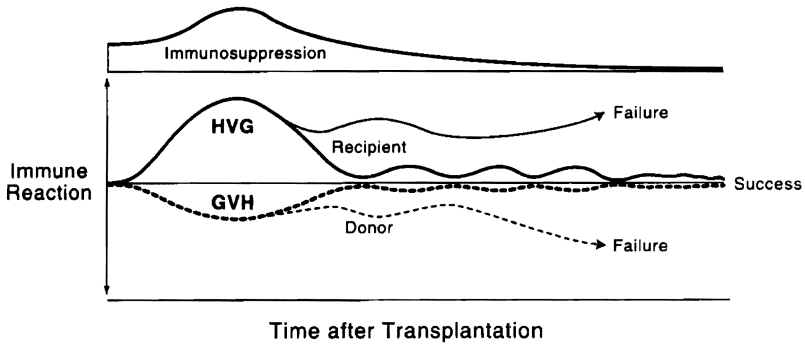

Figure 1 Contemporaneous host versus graft (HVG) (*upright curves*) and graft versus host (GVH) (*inverted curves*) responses after organ transplantation. If some degree of reciprocal clonal exhaustion is not induced and maintained (usually requiring protective immune suppression), one cell population will destroy the other. In contrast to the usually dominant HVG reaction of organ transplantation (shown here), the GVH reaction usually is dominant in the cytoablated bone marrow recipient. Therapeutic failure with either type of transplantation implies the inability to control one, the other, or both of the responses.

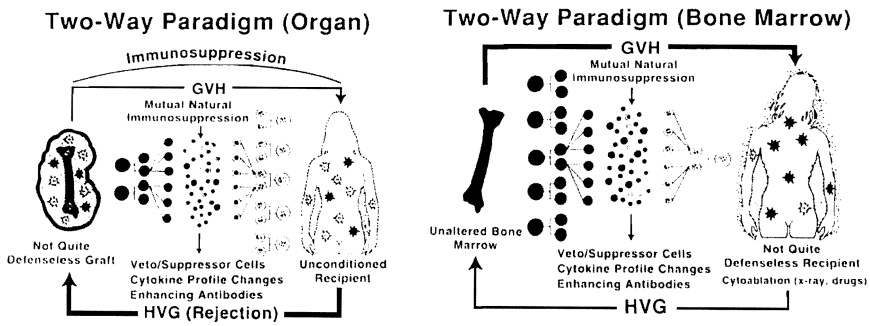

Figure 2 Two-way paradigm in which transplantation is seen as a bidirectional and mutually canceling immune reaction that is predominantly host versus graft with whole organ grafts (*left*) and predominantly graft versus host with bone marrow grafts (*right*).

risks of long-term immunodepression. The list of complications from protracted immunodepression per se was a long one, which could be divided into two broad categories: susceptibility to infections and the development of de novo malignancies.

PANCREAS TRANSPLANT PROCEDURES VS. IMMUNOSUPPRESSION ERA

Neither the development nor the merits of the different pancreas transplant operations could be discussed intelligently without parallel consideration of the immunosuppression that was available at the time these procedures were introduced. The point can be most easily made by perusing the 1988 textbook, *Pancreatic Transplantation*, prepared by Carl G. Groth (Huddinge Hospital, Huddinge, Sweden) (28) after it was apparent that cyclosporine had upgraded the prospects for a range of organ transplant procedures. In addition to the contributions by the Stockholm team members, Groth's book contains chapters from the seminal Minneapolis pancreas program and from programs in Cambridge (England), Iowa City, Lyon, Munich, and Pittsburgh. Because it provides a snapshot of pancreas transplantation in transition, the book is a historical treasure. In its pages, opinions about surgical technique, pancreas procurement and preservation, and other issues were discussed (circa 1987) by team leaders who continued to influence pancreas transplantation for the next dozen years and beyond.

Azathioprine Era

The first attempts at clinical pancreas transplantation were plagued by inadequate control of rejection despite the administration of frequently myelotoxic doses of azathioprine, large

Table 2 Nonimmunologic Profile of Calcineurin Inhibitors (Four + Worst): All Dose Related

	Tacrolimus	Cyclosporine
Nephrotoxicity	++[a]	++
Neurotoxicity	+	+
Diabetogenicity	+	+
Growth effects		
Hirsutism	0	+++
Gingival hyperplasia	0	++
Facial brutalization	0	+
Hepatotropic effects	++++	+++
Gynecomastia	0	+
Other metabolic effects		
Cholesterol increase	0	++
Uric acid increase	+?	++

[a]Less hypertension.
Source: From Ref. 26.

amounts of prednisone, and "induction" ALG. In addition to being diabetogenic, steroids were inimical to wound healing. The technical aspects of the pancreas transplant procedures developed during this period reflected efforts to work around these inadequacies of immunosuppression. In their first human operation at the University of Minnesota (7) on December 17, 1966, Kelly and Lillehei transplanted the head and tail of a cadaveric pancreas to the left iliac fossa of a uremic recipient after removing the graft duodenum and ligating the pancreatic duct. A kidney from the same donor was placed in the right iliac fossa. The recipient immediately became insulin independent, but died at two months from a combination of rejection and sepsis.

By 1973, Lillehei and associates had implanted 13 more whole human pancreas grafts, 10 in combination with cadaver kidneys from the same donor and the final three alone (8,29). In cases 2 to 6 pancreatic secretions of the allograft were exteriorized (cutaneous graft duodenostomy), while in cases 7 to 13 the exocrine drainage was directed via the graft duodenum into the host jejunum, using a Roux-en Y technique (8). In patient 14, a patch of graft duodenum containing the ampulla of Vater was anastomosed to recipient bowel. The only recipient (the sixth) in this pioneer series of 14 cases to achieve long-lasting insulin independence beginning on the day of operation (June 3, 1969) died shortly after reaching the one-year milestone with a functioning pancreas after losing the kidney graft and returning to dialysis. The 13 other pancreas graft losses resulted from technical complications including vascular thrombosis, death with a functioning graft, and, most commonly, lethal complications associated with exocrine pancreatic drainage. Similar discouraging results with pancreas transplantation during the early 1970s in Sao Paulo (Brazil), Chicago (Illinois), Irvine (California), Zurich (Switzerland), and in mostly unreported cases elsewhere caused abandonment of whole organ pancreas transplantation for more than a decade.

The grim early experience continued to influence surgical policies worldwide until the end of the 20th century. With the premise that the Achilles heel of the operation was the need for exocrine drainage, new strategies emerged to avoid entry into the host bowel, to eliminate the graft duodenum from the graft or to prevent or reduce the volume of the graft exocrine secretions. In 1973, Gliedman et al. (30) reported excision of the graft duodenum and the adjacent pancreatic head with transplantation of the rest of the pancreas; the segmental pancreatic duct was anastomosed to the recipient ureter. When two of these recipients lived insulin free for two and four years (31), momentum shifted for the next dozen years to the essentially exclusive use of distal pancreas grafts. Rather than exocrine diversion into the urinary tract or bowel, however, most surgeons either drained exocrine secretions from the pancreatic segment into the free peritoneal cavity or blocked the segmental duct by ligation (29) or by injection of a polymer (32). Only Groth and Tydén in Stockholm systematically resisted the trend by anastomosing the duct (or the draining segmental surface) to the bowel (33).

Cyclosporine Era

With better control of rejection and less steroid dependence made possible by cyclosporine, there was a resurgence of interest in pancreas transplantation as well as modifications of the surgical operation. Use of segmental cadaveric allografts continued until well into the 1980s, and remains an option today when live pancreas donors are used. In early 1982, we re-examined the reasons for abandonment of whole pancreas transplantation, and undertook reassessment of the procedure in dogs (34). Our conclusion was that the most logical operation of whole organ transplantation described by Lillehei and Kelly had been discontinued in favor of the inferior option of segmental pancreas transplantation. Consequently, a limited clinical trial of whole organ pancreas transplantation was begun in Pittsburgh in March 1983 (35). In a crucial modification of the original Lillehei procedure, we developed a technique for draining the allograft exocrine secretions into the host jejunum through a "bubble" of graft duodenum into which the ampulla of Vater emptied. The duodenal bubble was anastomosed to the side of the host jejunum (Fig. 3) (35,36).

Although the number of cases was small, the influence of the trial was amplified by the presence in Pittsburgh at the time of fellows or visitors who had come to observe the burgeoning liver transplant program and who also saw how easy and successful was the whole organ pancreas transplantation. One such fellow (1981–1983), Dr. Munci Kalayoglu, subsequently joined a team at the University of Wisconsin headed by Dr. Hans Sollinger, which had

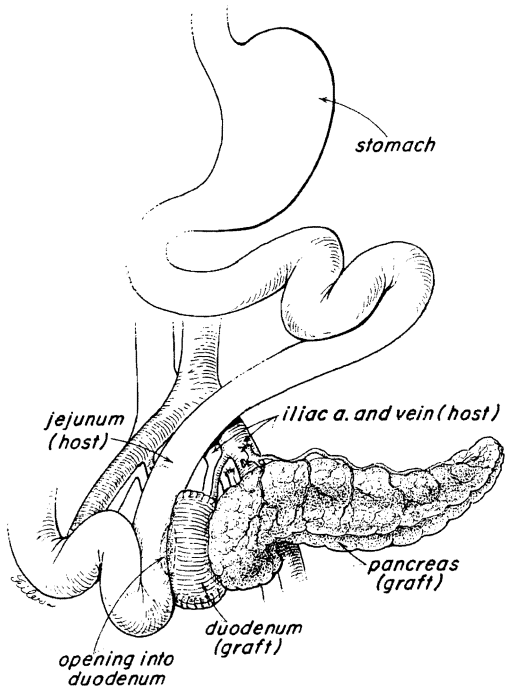

Figure 3 Use of donor "duodenal bubble" for exocrine pancreatic drainage introduced in Pittsburgh in 1983.

previously compiled a series of segmental transplantations with exocrine drainage into the bladder. After Kalayoglu's arrival in Madison, Sollinger and Kalayoglu changed from segmental to whole organ transplantation. Similarly, Dr. Robert Corry of the University of Iowa was persuaded during a sabbatical leave in Pittsburgh in late 1983 and early 1984 to adopt the whole pancreas transplantation procedure (37).

At their home institutions, Corry and Sollinger initially drained the graft duodenal bubble into the host jejunum. However, both teams soon advocated anastomosis of the bubble to the anterolateral wall of the host bladder (Fig. 4) (38,39). Bladder drainage was adopted soon thereafter for most cases at the University of Minnesota (39). With the enthusiastic endorsement from these three centers [reflected in separate chapters in Groth's book (40–42)] the bladder drainage technique was widely accepted. Serial measurement of urine amylase concentration became a means of immune surveillance, i.e., a drop in urine amylase signaled rejection. Complications from the bladder drainage were initially viewed as acceptable. However, digestion of the urethra by activated pancreatic enzymes, less serious but common examples of cystitis, uncorrectable metabolic acidosis caused by the continuous loss of bicarbonate, and a myriad of other problems necessitating conversion to enteric drainage began to diminish enthusiasm for bladder drainage by the mid 1990s. By this time, Corry (now at the University of Pittsburgh) had switched back to enteric drainage via the duodenal bubble. After the advent of tacrolimus, this became the reconstruction of choice at almost all centers (43–45).

Tacrolimus Era

Despite Corry's enthusiastic advocacy of tacrolimus, the drug was not widely used for pancreas transplantation until the mid 1990s because of its dose-related diabetogenicity. This view changed dramatically when a multicenter collection of cases demonstrated the ability of the new drug to rescue most of the treatment failures that were occurring under cyclosporine-based immunosuppression (46). Moreover, the superior control of rejection with minimal dependence on prednisone using tacrolimus-based immunosuppression from the outset has further eroded the arguments for exocrine diversion to the bladder. It also became possible with the simplified tacrolimus-based regimens to eliminate the perioperative induction

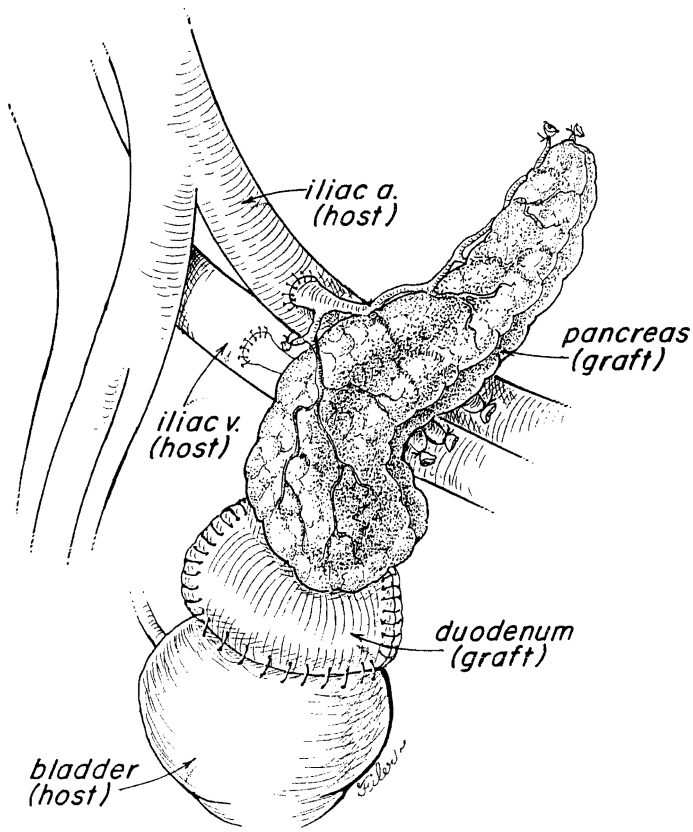

Figure 4 Drainage of pancreas exocrine secretions into the recipient bladder. This was the most commonly used procedure from 1985 until the mid or late 1990s.

therapy with ALG that had become a standard component of cyclosporine-based immunosuppression during the mid 1980s. Since 1995, general agreement about the superiority of tacrolimus-based immunosuppression was finally reached (33,43–45,47–49).

A New Era?

The long-term efficacy of pancreas transplantation is not yet clear. Only 16 recipients in the world are known to have functioning pancreas allografts that were transplanted before 1986 and none who were treated before 1981 (50). With the improvements that occurred since the 1980s, there have been many reports indicating that the survival of diabetic kidney transplant recipients is improved by cotransplantation of a pancreas (43–49). However, there has been at least one United Network for Organ Sharing-based analysis suggesting that the risk of death from staged kidney–pancreas transplantation has been greater, even in recent times, than in kidney-alone recipients who had been listed for a pancreas but failed to get one (51) (see also counter-arguments in Chapter 1). Apart from pancreas graft-related complications or functional failures, late recipient deaths have continued from cardiac, infectious, and peripheral vascular disease, and from de novo malignancies. Many, if not most, of these late complications can be traced to, or are aggravated by, the need for chronic immunosuppression.

The ideal solution would be to make organ recipients more tolerant and thereby less immunosuppression-dependent. This objective became realistic with the elucidation of the donor leukocyte chimerism-associated mechanisms of acquired tolerance (17,18) and

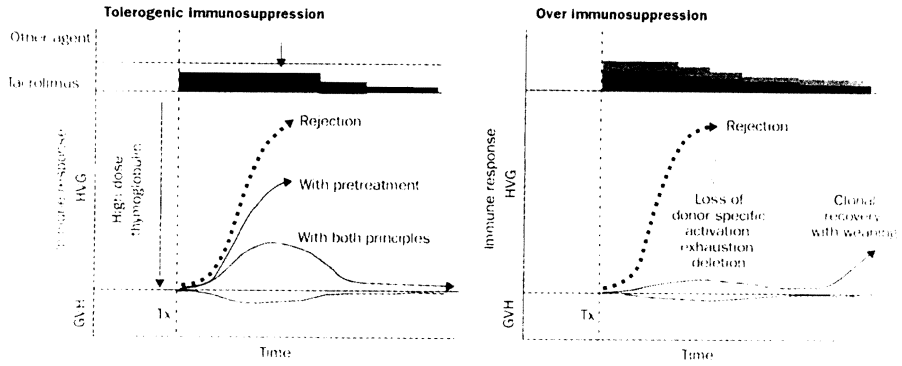

Figure 5 Mechanisms of immunosuppression. (*Left*): Conversion of rejection (*thick dashed arrow*) to an immune response that can be exhausted and deleted by combination of pretreatment and minimalistic posttransplant immunosuppression. (*Right*): If the clonal response is eliminated by excessive posttransplant immunosuppression, exhaustion–deletion shown on the left is precluded, and subsequent graft survival is permanently dependent on immunosuppression. *Abbreviations*: GVH, graft versus host; HVG, host versus graft; Tx, transplantation.

the recognition that organ engraftment is a form of partial tolerance (52,53). With this insight, it was obvious that the seminal mechanism of alloengraftment and acquired tolerance (i.e., clonal exhaustion–deletion) can be subverted by the "conventional" use of heavy prophylactic immunosuppression (Fig. 5, right) (53). In 2001, it was proposed that this undesired consequence could be prevented by observance of two therapeutic principles: recipient pretreatment and the use of minimal posttransplant immunosuppression (Fig. 5, left) (53).

Between July and December 2001, the late Robb Corry carried out a pilot trial based on these principles in 10 recipients of simultaneous pancreas and kidney allografts and four recipients of pancreas transplants alone. All of the donors were human leukocyte antigen-mismatched, heart-beating cadavers with the same ABO types as the recipients. The patients were infused prior to organ revascularization with approximately 5 mg/kg rabbit antithymocyte globulin (Thymoglobulin®) and were coinfused with 1–2 g methylprednisolone to prevent cytokine reactions (54). On the first postoperative day, twice-daily tacrolimus monotherapy was begun with a target 12-hour trough level of 10 ng/mL. After four to six months, patients who had been on stable tacrolimus monotherapy for at least two months had extension of the interval of tacrolimus doses ("spaced weaning") to once a day, every other day, or longer if this was compatible with stable graft function (Fig. 6).

A short-term follow-up of the patients was reported in 2003 (54). The results at three years and the current results are summarized in Table 3 for each case. Eleven (78%) of the 14 recipients remained insulin free for three years, but in two of these patients, hyperglycemia recurred after 36 months. Thus, nine (64.2%) still are insulin free after 43 to 49 months. Eight of the nine insulin-free patients are on treatment with a single drug and four are on spaced doses of tacrolimus (Figs. 6 and 7). Importantly, seven of the 10 patients who also received kidneys had life-supporting renal function at three years with serum creatinine concentrations $\leq$2 mg/dL in six. After Corry was killed in a motor vehicular accident in February 2002, the trial was placed on hold.

By the time of his death, Corry was aware that the management principles under evaluation were sound and required only fine-tuning. First, the initial step of weaning to every other day would have to be taken more cautiously. Second, weaning of monotherapy to intervals greater than every other day should be delayed until at least one year unless evidence of drug-specific side effects (e.g., nephrotoxicity, neurotoxicity, or diabetogenicity) called for earlier action. In 2003, the policy of tolerogenic immunosuppression was reinstituted with these foregoing modifications. In addition, lymphoid depletion was done with the broadly reacting antilymphoid monoclonal antibody, alemtuzumab (Campath®) rather than with Thymoglobulin. The superior early results with this management are described in Chapter 1. The chapter, along with the rest of this book, has been dedicated to Corry's memory. A Robb Corry Professorship has been established at the University of Pittsburgh, the inaugural occupant of which is Ron Shapiro.

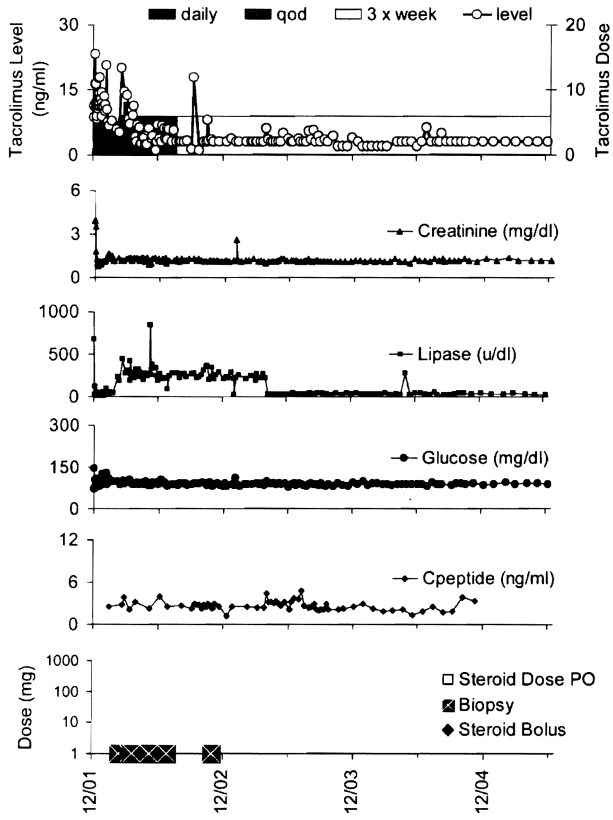

Figure 6 The course of a simultaneous pancreas–kidney recipient pretreated with antithymocyte globulin. The dose frequency of daily monotherapy was reduced to every other day at four months and to three times a week at eight months after transplant (*top panel*). Creatinine, lipase, glucose, and C-peptide (*middle panels*), have been stable throughout. This patient did not receive any steroids or other additional treatment and was biopsied five times with no evidence of damaging acute rejection.

Table 3 Tolerogenic Immunosuppression for Pancreas Recipients (Corry, 2001): Results at Three Years

Number	TX	Monotherapy (dose frequency)	Creatinine (mg/dL)	Fasting glucose (mg/dL)
Simultaneous pancreas–kidney				
1	7/01	Daily	2.0	80–90
2	8/01	Daily	1.3	80–100
3	8/01	Once/wk	1.0	70–80[a]
4	9/01	—	Failed 22 mo	Failed 5 mo
5	9/01	Daily	4	90–100
6	10/01	—	Failed 22 mo	90–140[b]
7	11/01	Thrice/wk	1.0	80–100
8	11/01	Daily	1.7	80–110
9	12/01	—	Failed 13 mo	Failed 7 mo
10	12/01	Thrice/wk	1.3	80–90
Pancreas alone				
1	7/01	Thrice/wk	1.7[c]	70–100
2	9/01	Daily multidrug	1.2[c]	90–140[b]
3	10/01	—	1.0[c]	Failed 5 mo
4	12/01	Daily	1.6[c]	70–90

Monotherapy: all tacrolimus except Case 1 (rapamycin).
—, Not applicable because of graft loss(s) and drug discontinuance.
[a]After three years, the patient developed disseminated metastases from breast cancer, and died insulin-free at 43 months.
[b]Became insulin-dependent after three years.
[c]Native kidney.
Note: Pancreas grafts functioning at three years: 11/14 (78.5%), currently 9/14 (64%); kidney grafts functioning at three years and now: 7/10 (70%).
Abbreviation: TX, transplantation.

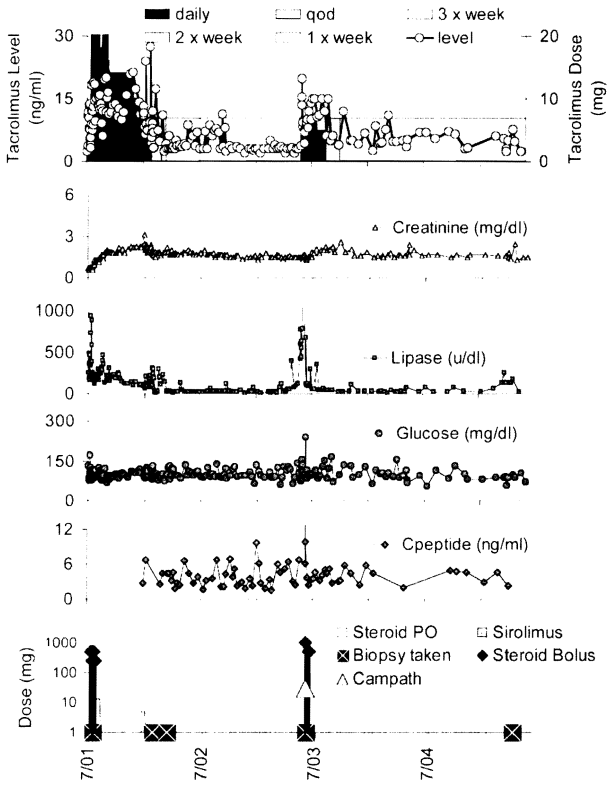

Figure 7 The course of the first pancreas recipient pretreated with antithymocyte globulin. The dose frequency for this pancreas-alone recipient was reduced quickly after six months reaching a minimum of one dose per week at one year. A biochemically indicated, pathology-confirmed rejection at 23 months was reversed with steroids, a dose of alemtuzumab (*lower panel*), and the temporary resumption of daily tacrolimus that subsequently was re-weaned to three times a week. The benefit of reduced exposure to tacrolimus is apparent in the creatinine levels depicted in the second panel; i.e., the patient's kidney functioned better with less treatment and worse with more treatment. Other than during the rejection episode, graft function, as reflected in the lipase, glucose, and C-peptide levels, has been stable throughout. Later patients (Fig. 6) were weaned less aggressively.

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