Pancreas transplantation, when successful, is a reproducibly effective method to normalize glycemia without the use of exogenous insulin treatment in patients with diabetes mellitus. Success rates for combined pancreas and kidney transplantation are ~70%, and patient survival rates are ~90% 1 yr postoperatively. Metabolic benefits of this procedure include normalization of levels of fasting plasma glucose and HbA1c. Glucose-induced insulin secretion and intravenous glucose tolerance are normalized. Improvements are also observed in glucose recovery after insulin-induced hypoglycemia and in glucagon secretion during hypoglycemia. Pancreas transplantation is also associated with normalization of kidney structure and both motor and sensory nerve function. However, no benefits have been observed with regard to pancreatic polypeptide secretion, kidney function, and the retinal pathology of diabetes mellitus. Pancreas transplantation has reached a point in its history where the operative technique and its ancillary medical therapy have been optimized. Improvement in the rates of success, morbidity, and mortality will probably depend on improvement in immunosuppressive drugs and the physical condition of the recipients themselves. The time is at hand when we need to carefully consider whether it is ethical and advisable to make pancreas transplantation available to individuals who have fewer chronic complications of diabetes mellitus. Future studies of pancreas transplantation must incorporate more rigid experimental controls than have been used in the past to better assess the relative merits of this procedure. Diabetes 40:1085–89, 1991

Extraordinary efforts are expended daily by patients with diabetes mellitus and their health-care providers to regulate abnormally high levels of glycemia. Pursuit of this goal carries with it the keen anticipation that normalization of glucose homeostasis will stabilize or prevent the chronic complications of diabetes mellitus. However, the reality of the situation is that few patients are able to establish normal levels of circulating glucose throughout the day and maintain normal levels of HbA1c. Among the experimental forms of treatment that have been developed to improve control of glycemia, none is more effective or controversial than pancreas transplantation. In this perspective, I provide a brief history of the operative procedure, the known metabolic benefits it provides, its impact on the chronic complications of diabetes, and a consideration of the future of pancreas transplantation.

Brief Overview of Pancreas Transplantation
Pancreas transplantation as therapy for patients with diabetes mellitus was ushered into the medical arena at the University of Minnesota in December 1966, when two diabetic patients with advanced complications received combined pancreas/kidney allografts (1). The first patient developed postoperative complications necessitating removal of the pancreas and kidney grafts; she died soon thereafter of pulmonary embolism. The second patient fared much better. She became normoglycemic within 6 days of pancreas transplantation and at the time of this report, 4 mo after the operation, remained normoglycemic. The subsequent successes and failures of this operative procedure at the University of Minnesota have been meticulously chronicled by Sutherland et al. (2). Since 1966, many changes have been made in operative techniques, types of immunosuppressive drugs and their use, and strategies of graft surveillance to monitor for rejection episodes. However, perhaps the most important change contributing to the markedly improved graft and patient survival rates is that today’s recipients are a great deal healthier than those who received transplants in 1966.

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Currently, patients undergoing pancreas transplantation receive 1–2 days of immunosuppression before the procedure. The source of the pancreas is usually a recently deceased individual, i.e., a cadaveric graft, or, less commonly, a 50% pancreas segment from a living, related donor. These procedures are performed with or without simultaneous kidney transplantation at the University of Minnesota, but the combined procedure is the more common approach elsewhere (3). The drug regimen used to establish chronic immunosuppression is universally the same and consists of cyclosporine given at doses to reach a serum trough level of 100 ng/ml, 2.5 mg · kg\(^{-1}\) · day\(^{-1}\) azathioprine, and prednisone tapered to 0.2 mg · kg\(^{-1}\) · day\(^{-1}\) by 1 yr. Since the initial experience in 1966 at the University of Minnesota, both graft and patient survival rates have improved considerably. Over the past 4 yr, the graft survival rate has been ~60% (Fig. 1), and the patient survival rate has been ~90% (Fig. 2) 1 yr postoperatively. Graft survival increases to 70% success if solitary pancreas transplants are excluded so that only simultaneous pancreas and kidney transplants are considered. Many institutions report an ~50% graft survival rate 4–5 yr postoperatively (4). The patient survival rate has also improved greatly since 1966. This is more difficult to assess in absolute terms because the patients undergoing pancreas transplantation are usually self-selected, and among their complications, autonomic neuropathy is common, a condition that itself is associated with earlier mortality (5–8). Only a trial incorporating a strictly randomized design for assignment of patients to either pancreas transplantation or optimal medical treatment would ascertain how much the operation itself contributes to the 15% mortality rate observed 5 yr postoperatively. Such a trial has never been performed. In any event, it appears that the major research efforts of the surgery surrounding pancreas transplantation have reached

![Graph](https://example.com/graph1.png)

**Fig. 1.** Graft survival rates for pancreas transplantation at the University of Minnesota. Data are presented by eras and show progressive improvement in graft survival rates. Data include both solitary pancreas transplantation and simultaneous pancreas and kidney transplantation. When combined pancreas and kidney transplantation alone is considered, graft survival rate is ~70% 1 yr postoperatively. Tx, transplantation. From data provided by International Pancreas Transplantation Registry, University of Minnesota, Minneapolis.

![Graph](https://example.com/graph2.png)

**Fig. 2.** Patient survival rates at University of Minnesota during eras depicted in Fig. 1. Notable improvement in patient survival after 1st era was due to selection of fewer ill patients, improvements in operative techniques, and more effective immunosuppressive regimens. Tx, transplantation. From data provided by International Pancreas Transplantation Registry, University of Minnesota, Minneapolis.
the point of diminishing returns, because graft and patient survival rates are virtually indistinguishable among the major institutions performing pancreas transplantation worldwide (4). Future improvements in this procedure will probably grow out of development of more effective and less toxic immunosuppressive drugs and agents capable of inducing immune tolerance. In addition, provision of pancreas transplantation to patients with shorter durations of disease and fewer complications would doubtless improve graft and patient survival rates. In this respect, this point in the history of pancreas transplantation is similar to that observed in the development of many successful surgical operations, i.e., the point at which the operative technique and ancillary medical therapy have been optimized and the early poor clinical results and severe mortality rates are no longer observed. At this point, the question arises whether patients who are compromised to a much less extent by the disease process should be accepted for the procedure.

**METABOLIC CONSEQUENCES OF SUCCESSFUL PANCREAS TRANSPLANTATION**

Patients who have undergone successful pancreas transplantation are capable of maintaining normal fasting plasma glucose levels without the use of exogenous insulin treatment. They maintain nearly normal glucose levels over 24-h periods, during which they exercise and eat normally and maintain HbA1c levels that are within the normal range (Table 1).

Several groups have reported that recipients of successful pancreas allografts have normal phasic β-cell function during intravenous challenge with various secretagogues (9,10). This was first reported by Diem et al. (9), who found elevated levels of basal insulin accompanied by two- to threefold exaggerated first- and second-phase insulin responses to glucose and to arginine. Steroid therapy was considered to be part of the explanation for the elevated levels of basal insulin, a speculation shown to be valid by the valuable studies by Luza et al. (11), who used euglycemic hyperinsulinemic clamps in pancreas recipients to demonstrate steroid-induced insulin resistance. This possibility was evaluated by comparing insulin and C-peptide responses during intravenous glucose or arginine challenge in pancreas recipients and in nondiabetic recipients of kidney transplantation who were treated with prednisone, azathioprine, and cyclosporine. Both groups had elevated basal levels of C-peptide, but neither group had exaggerated C-peptide responses during glucose or arginine stimulation (9). It was thus concluded that the drugs alone were not primarily responsible for the exaggerated insulin levels during glucose or arginine stimulation. An alternative explanation seemed more likely, i.e., that pancreas allografts have systemic venous drainage, whereas insulin from the native pancreas normally drains into the portal vein for delivery to the liver to undergo >50% degradation before reaching the systemic circulation. In support of this idea were findings from two patients who received pancreas allografts with portal rather than systemic venous drainage; they had glucose-stimulated insulin responses that were within the normal range (9). Thus, it was concluded that the major factor responsible for hyperinsulinemia during β-cell stimulation was systemic venous drainage of the allograft. More recently, Secchi et al. (12) and Robertson et al. (13) have reported both cross-sectional and prospective data from patients studied sequentially before and after successful pancreas transplantation. These patients retained remarkably stable responses of insulin and C-peptide to intravenous stimulation with glucose or arginine for several years.

**Pancreatic islet α-cell function and counterregulation of hypoglycemia have also been examined in recipients of successful pancreas transplantation.** Diem et al. (14) reported that most insulin-dependent (type I) diabetic patients awaiting pancreas transplantation at the University of Minnesota were deficient in their ability to counterregulate insulin-induced hypoglycemia. This defect was accompanied by virtual absence of glucagon secretion during hypoglycemia. After successful pancreas transplantation, patients had a twofold increase in basal glucagon levels and had significant improvement in their ability to recover from insulin-induced hypoglycemia. This was accompanied by a parallel improvement in glucagon secretion during hypoglycemia. Although it cannot be stated with certitude that the improved response in glucagon was completely responsible for the improved glucose recovery, it seems reasonable to assume that this normonal response played an important role. An additional consideration is the possibility of improved glucagon secretion from the native pancreas after normalization of glucose levels by the allograft pancreas. This consideration is important because the transplanted allograft is a denervated organ, and islet neural input is felt to play a role in counterregulation of hypoglycemia (15). Diem et al. (14) also reported that catecholamine responses during insulin-induced hypoglycemia were indistinguishable when comparisons were made among the nondiabetic, transplanted diabetic, and nontransplanted diabetic groups.

Diem et al. (14) reported that pancreatic polypeptide responses during insulin-induced hypoglycemia were significantly lower in type I diabetic patients awaiting pancreas transplantation compared with nondiabetic control subjects. Pancreatic polypeptide responses were not improved after successful pancreas transplantation (Table 1). It is not surprising that the denervated transplanted allograft would not contribute directly to pancreatic polypeptide secretion, because it has been established that pancreatic polypeptide secretion during insulin-induced hypoglycemia is dependent on intact CNS input. Diem et al. (14) also found that secretin-induced pancreatic polypeptide secretion was not increased after successful pancreas transplantation. A positive aspect of these negative results is that monitoring pancreatic polypeptide secretion could prove to be a valuable marker for

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**TABLE 1**

Summary of consequences of successful pancreas transplantation

<table>
<thead>
<tr>
<th>Normal</th>
<th>Improved</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>Glucose recovery ITT</td>
<td>PP secretion</td>
</tr>
<tr>
<td>Glucose kinetics</td>
<td>Glucagon secretion ITT</td>
<td>Kidney function</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Kidney structure</td>
<td>Retina</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>Nerve function</td>
<td></td>
</tr>
</tbody>
</table>

ITT, insulin tolerance test; PP, pancreatic polypeptide.
eventual innervation of the transplanted allograft should it occur.

A description of the metabolic consequences of successful pancreas transplantation would not be complete without a brief notation of the metabolic consequences of hemipancreatectomy in nondiabetic pancreas donors. Individuals who elected to donate half of their pancreas to related diabetic recipients have been studied in sequential fashion and reported by Kendall et al. (16). They noted that glucose levels during oral glucose tolerance tests at ~1 hr posthemipancreatectomy were higher than those observed in the donors preoperatively. Moreover, insulin responses during oral glucose tolerance tests were diminished in the same subjects compared with their preoperative control data. Roughly 25% of this group developed abnormal glucose tolerance curves that were diagnostic for diabetes mellitus. Seaquist et al. (17) reported that donors have markedly attenuated acute insulin responses to intravenous glucose. Nonetheless, despite these abnormalities, these individuals maintained nearly normal glucose levels over 24-h periods, during which they ate and exercised. Obviously, continual follow-up of these patients is mandatory given their proclivity toward developing diabetes mellitus. In addition, further study of these individuals may provide valuable insights into the importance of deficient pancreatic β-cell mass in the pathogenesis of non-insulin-dependent (type II) diabetes mellitus. In this respect, note that, given the nature of the operative procedure, these subjects are also deficient in α-cell mass, which may relate to their ability to maintain relatively normal glucose homeostasis despite loss of half of their β-cell mass.

**IMPACT OF SUCCESSFUL PANCREAS TRANSPLANTATION ON DIABETIC COMPLICATIONS**

The organs whose function is adversely affected by diabetes mellitus that have been studied most intensively in patients undergoing pancreas transplantation are the eyes, kidneys, and nerves. Ramsay et al. (18) compared 5-yr follow-up data from retinal examinations in a group of 22 patients who had successfully received transplants and from 16 subjects who had received transplants but failed to maintain a functioning pancreas graft. Disappointingly, no differences in the stability of retinopathy were observed during the first 3 yr, and both groups demonstrated continual progression of retinal disease. By the 4th and 5th yr, it appeared as though the patients who had successfully received transplants had acquired stability in retinal damage, whereas the group who failed successful transplantation continued to deteriorate; however, these differences were not statistically significant. Bilous et al. (19) reported that both glomerular volume and mesangial volume in 7 patients significantly decreased by 2 yr posttransplantation. The same group also reported prospective data indicating that patients with diabetes undergoing combined pancreas and kidney transplantation underwent less mesangial and glomerular volume expansion in the transplanted kidney than a cohort of patients with diabetes undergoing kidney transplantation alone (20), thus confirming an earlier report by Bohman et al. (21), who studied this issue cross-sectionally. However, in these reports, kidney function was significantly compromised by treatment with cyclosporine, a drug known to decrease glomerular filtration rate. Kennedy et al. (22) reported studies from 11 patients who had successfully undergone pancreas transplantation and noted an improvement in both motor and sensory nerve function compared with continued deterioration in nerve function in 12 patients who had been transplanted with pancreas allografts but failed to maintain the graft. Navarro et al. (8) reported that 152 patients with motor nerve conduction defects and/or autonomic nerve dysfunction had decreased survival rates compared with 57 diabetic patients without measurable defects. Their patients with abnormalities in either motor nerve conduction or autonomic nerve function who successfully received transplants had an improved survival rate compared with nontransplanted patients. A most provocative finding was that the group of patients with autonomic nerve dysfunction who received a transplant pancreas but failed to maintain the graft had a greater mortality rate than patients with autonomic nerve dysfunction who did not receive transplants. On the other hand, the group of patients with autonomic nerve dysfunction who successfully received transplants had a lower mortality rate than the nontransplanted cohort. Interpretation of these data is extremely difficult because this was not a randomized study. It might be concluded from these data that patients with autonomic dysfunction should not receive transplants because they run a substantially increased risk of dying should their transplant fail. Alternatively, it is possible that the patients who elected to undergo the operative procedure were more adversely affected by autonomic nervous dysfunction and hence ran a greater risk of dying. If so, these patients could be more likely to benefit from successful pancreas transplantation, because the individuals in this group who were successfully transplanted had a notably improved survival rate. If nothing else, these results underscore the need for a randomized trial of pancreas transplantation for accurate interpretation of benefits and risks.

**THE FUTURE OF PANCREAS TRANSPLANTATION—PROS AND CONS**

It is easy to understand the controversies that surround the notion of pancreas transplantation as a therapy for patients with diabetes mellitus. The morbidity after pancreas transplantation, successful or not, is great. This procedure is a major surgical challenge in patients who have complications from a major systemic illness. Superimposed on this are the adverse consequences of immunosuppression and the more specific adverse affects of cyclosporine and prednisone. However, the latter problem is lessened in cases where patients are destined to receive immunosuppression anyway because of the need for kidney transplantation. Importantly, it is not clear to what degree the sobering mortality rates after pancreas transplantation are due to the operative intervention, or whether a substantial part of the mortality rate is due to the advanced state of disease in most of these patients. In any event, the cost for the procedure runs into the tens of thousands of dollars, which, considering the alternative of insulin therapy, seems overwhelming. Finally, the ethical issue of obtaining informed consent is very complex. Although every attempt is made to educate the patients
about the impressive complications and costs of the surgery and immunosuppressive drugs, these patients are clearly self-selected for this operative procedure and usually see it in a better light than is portrayed by the medical staff. On the positive side of pancreas transplantation, it must be acknowledged that this operative procedure is the only means available of normalizing glucose levels without the need for insulin treatment in free-living human diabetic patients. This is an extremely attractive feature for patients who have spent the better part of their lives unsuccessfully attempting to achieve normal glucose levels. Before transplantation, many patients who receive transplants at the University of Minnesota relate impressive stories of profound problems with daily living and inability to maintain employment due to the brittleness of their diabetes. The issue of neuropathic complications of diabetes mellitus and its impact on survival is very important. It has been reported that patients with advanced neuropathy are at increased risk of dying (5–8). Judging from the published data of Navarro et al. (8), a randomized trial is needed to determine whether such patients may enjoy longer survival if they can be successfully transplanted with a pancreas allograft. Obviously, issues such as these are not only medical but ethical in nature. However, not only health-care professionals but patients themselves should have a hand in judging the ethics of this operative procedure. Often patients see advantages where we see only risks.

It is difficult to foretell the future for pancreas transplantation. Certainly, successful transplantation of pancreatic islets is more attractive should this alternative come to pass because of the lower surgical risk inherent in islet as opposed to organ transplantation. However, both interventions will require the same degree of immunosuppression unless a means is found to render pancreatic islets less immunogenic by pretransplantation manipulation or by use of immunoprivileged sites. It seems evident that the operative procedure of pancreas transplantation itself has reached its peak in terms of technology. Improvement in rates of success, morbidity, and mortality will probably depend on the two other variables, namely the type of immunosuppressive drugs being used and the physical condition of the recipients themselves. In this regard, we need to carefully consider whether it is ethical and advisable to make pancreas transplantation available to individuals who have fewer chronic complications of diabetes mellitus. These patients may be better able to undergo this procedure and more likely to benefit from normalization of glucose levels before the onset of complications rather than after they have been fully established. In any event, future studies of pancreas transplantation must incorporate more rigid experimental controls than have been used in the past if we are to gain more accurate information about the relative merits of this important procedure that, when successful, stands alone as a method that essentially normalizes glycermia without the need for insulin treatment in patients with diabetes.

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