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Starzl et al. evaluate the place of cadaveric pancreas transplants in diabetics with and without kidney transplants. A remarkable five of eight pancreas grafts were functioning 2.5–19 months posttransplant. It is proposed that the spleen be engrafted with the pancreas both to improve graft blood supply and to induce tolerance. With the most active transplant groups in the United States now exploring pancreas allografting, we may anticipate a "go" or "no go" answer to their utility within the next three years.

A Resurgence of Interest in Whole Pancreas Transplantation

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ABSTRACT

Eight patients have undergone whole pancreas transplantation for the treatment of diabetes mellitus at this center. Six of the recipients had previously been given cadaver kidneys, one was given a kidney from the pancreas donor, and the other patient received a pancreas alone. One of the pancreatic grafts failed from thrombosis, but the other seven provided prolonged function. Five of the grafts are still functioning from 2.5 to 19 months later, a sixth functioned perfectly for 14 months and then failed, necessitating return to insulin therapy, and a seventh is undergoing rejection after 4 months, for which monoclonal antilymphocyte globulin (ALG) therapy is being given. Exocrine drainage of whole-organ pancreatic grafts has been achieved conveniently by retaining a graft duodenal bubble through which exocrine pancreatic secretions are directed into the intestinal tract. A case has been made for transplanting the spleen with the pancreas for the purpose of improving the graft blood supply and with the possible objective of inducing graft acceptance.

DIABETIC RENAL-RETINAL SYNDROME, 3
ISBN 0-8089-1741-2

INTRODUCTION

The pancreas transplantations performed since the first attempt by Kelly and Lillihei, et al. in 1966[1] have been recorded by Sutherland and Kendall in an international registry.[2] By the end of June, 1984, a total of nearly 500 cases had been contributed from more than 50 institutions at a rapidly increasing accrual rate. The results from these efforts have remained discouraging. Even in 1983 and 1984, only about one-third of the transplants, including segmental grafts from relative donors, have functioned for as long as a year. During these recent times, the one-year patient mortality has remained at the disturbingly high level of almost 25 percent.[2]

The graft failures, patient morbidity, and patient mortality have been due partly to technical imperfections in the procedure itself and partly to the limitations of conventional immunosuppression. Consequently, this group has re-examined the technical aspects of pancreas transplantation. After preliminary work in dogs,[3] a procedure was developed that has yielded encouraging results in human recipients treated with cyclosporine and steroids.[4]

METHODS

Surgical Technique

The entire pancreas is removed along with the duodenum, proximal jejunum, and spleen. The arterial blood supply of the composite graft is based upon a Carrel patch of the anterior aortic wall, which includes the origin of the celiac axis and the superior mesenteric artery. The outflow from the graft is through the portal vein. The specimen is cooled with a chilled preservation (Collins) fluid. The arterial Carrel patch is anastomosed to the recipient common or external iliac artery, either intraperitoneally or in the left extraperitoneal space (Fig. 1). If necessary, the graft can be placed on the right side, although this requires rotation of the specimen (Fig. 2), as described elsewhere.[4]

The spleen usually is left with the graft. Graft splenectomy has been performed in only one of our 8 cases before transplantation. The jejunum, and as much proximal and distal duodenum as possible, is excised, leaving a "bubble" of duodenum into which the ampulla of Vater empties (Fig. 1). The proximal and distal ends of the bubble are closed and the duodenum is anastomosed to the side of the proximal jejunum.

Tissue Typing

The pancreas grafts were from heart-beating cadaver donors. In 7 of the 8 cases, the ABO groups of the donor and recipient were the same. In the eighth, the donor was blood type O and the recipient was A.

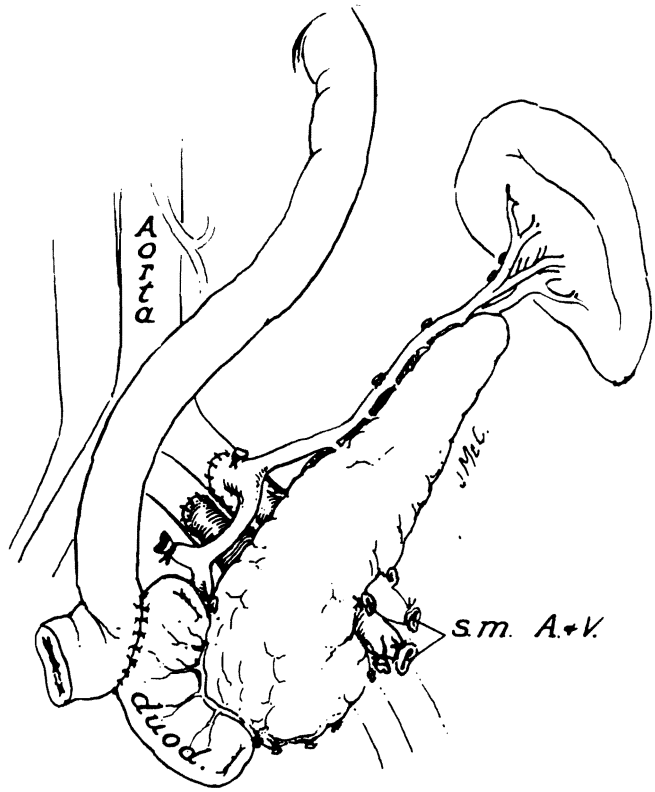

Fig. 1. Completed pancreatic transplantation. Note inclusion of spleen and removal of as much duodenum as possible.

Tissue matching was random, and because of this, there were no matches of the 4 possible antigens at the A and B histocompatibility loci in 6 of the patients. There was a one-antigen match in one case and a 2-antigen match in the other.

At the D_R locus, 6 of the 8 recipients had the 3,4 combination of antigens which has been associated with diabetes mellitus.[5] The 2 other patients had either a D_R3 or 4 antigen, but not both. Two of the donors had a D_R4, and no donor had both. In 2 of the 8 cases, a single D_R antigen was matched. No D_R antigens were matched in the other six.

Case Material

All 8 of the recipients were Type I diabetics. Their ages were 24–42 years (mean 31.2) and they had been insulin-dependent for 18–29 years. Seven were men and one was a woman.

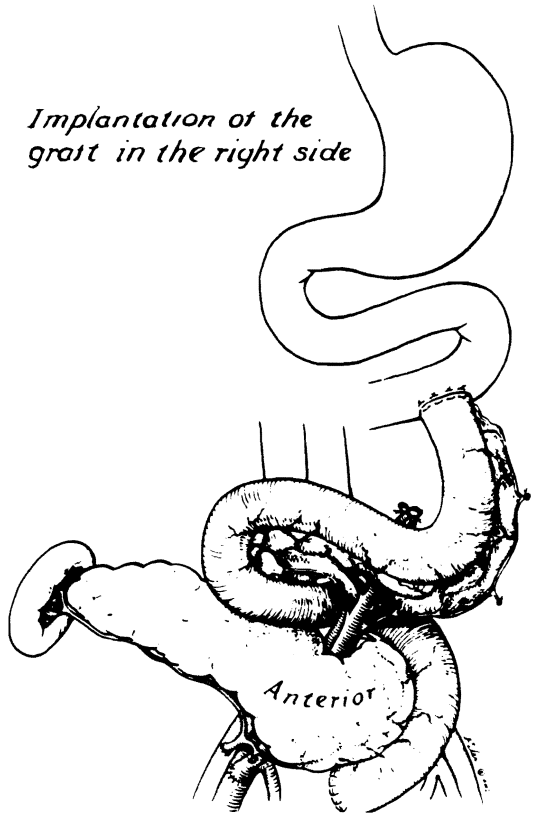

Fig. 2. Pancreatico-duodeno-splenic graft used in the first 2 patients. The intestinal segment developed mucosal slough and a protein-losing enteropathy which caused intractible diarrhea. At reoperation, the small bowel was trimmed to the proportions shown in Figure 1.

Six of the 8 pancreas recipients had been given a cadaver kidney from a few weeks to 8.5 months previously. A seventh patient was provided with a kidney from the same donor as the pancreas and one patient was given a pancreas alone.

The 6 patients who had been given cadaveric kidneys at an earlier time were already being treated with cyclosporine and steroids. At the time of the pancreatic transplantation, this immunosuppression was intensified, as described in detail elsewhere.[4] Patients undergoing pancreas transplantation alone, or in combination with kidney transplantation from the same donor, were treated by the techniques previously developed for cadaveric kidney[6] and hepatic[7] transplantation. Intravenous cyclosporine was given postoperatively until it was ascertained by pharmacologic

monitoring that the oral dosage was being well tolerated. Subsequently, the cyclosporine and steroid doses were gradually reduced. Cyclosporine doses were monitored by frequent measurements of the venous blood concentration of the drug.

RESULTS

Mortality

All eight of the pancreas recipients are still alive after follow-ups of 2.5–19 months. The patient who received only a pancreas had several serious bouts of insulin induced hypoglycemia preoperatively, leaving him with central neurologic deficits. Five weeks postoperatively he had a respiratory arrest. Despite prompt resuscitation, he has been left with further neurologic invalidism and is hospital-bound. The other 7 patients live at home.

Pancreatic Graft Function

One pancreatic graft was lost to vascular thrombosis within a few hours and was removed. The other 7 pancreases functioned promptly and permitted the patients to live completely free of insulin. One graft failed 14 months after transplantation, a few weeks after completely normal glucose tolerance tests had been obtained during testing in the Clinical Research Center. Insulin therapy was resumed, although at about half the dosage previously required.

The other 6 patients remained insulin-free 2.5–19 months postoperatively. The patient who received a pancreas alone 4 months ago had a rejection after 3.5 postoperative months, necessitating a return to insulin therapy. The rejection is being treated with a course of monoclonal OKT3 antibody, with at least partial restoration of pancreatic function.

The other 5 patients are insulin-free after 2.5, 4.5, 6, 11, and 19 months. All five have had normal glucose tolerance tests and have undergone significant social and/or vocational rehabilitation.

The patients who had had previous cadaveric kidney transplantation (6 cases) or a concomitant kidney transplantation (one case) have stable function of their renal grafts.

Complications of the Spleen

The spleen was transplanted as part of the graft in 7 of our first 8 cases. Splenectomy was performed in 3 of these 7 recipients at 6.5, 18, and 20 days postoperatively. In the patient with type A blood who had been given

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a type O spleen, the spleen was shown to have produced anti-A isoagglutins in sufficient quantities to cause severe hemolysis of the recipient's red blood cells.[4] This complication was relieved promptly by splenectomy. The other splenectomies (after 18 and 20 days) were because of thrombocytopenia and leukopenia (one case each). In the 3 patients who underwent graft splenectomy, the procedure was extremely easy. The lateral end of the wounds were reopened and each splenectomy was performed within a few minutes and with virtually no blood loss.

Four patients still have their grafted spleens in place after 2.5, 4.5, and 19 months.

Complications of the Duodenum and Jejunum

The first 2 patients developed intractible diarrhea several weeks postoperatively, as well as vague, cramping abdominal pain. In these patients, a long jejunal segment had been left for anastomoses to the recipient jejunum (Fig. 2). In one patient, the graft jejunum was detached and brought to the skin as a jejunostomy, where it was shown to elaborate from one to 3 liters of protein-rich, plasma-like fluid.[4] It was concluded that the jejunum was the site of a protein-losing enteropathy.[4] Eventually, the jejunum and most of the duodenum were removed, leaving a duodenal bubble such as that shown in Figure 1.

In patient 5, in whom the intent was to perform the duodenal bubble procedure, too much of the C-loop of the duodenum was left in place (Fig. 3). One month postoperatively, the patient was readmitted with uncontrollable diarrhea. The C-loop was trimmed back to the small bubble (Fig. 1) and the patient recovered with no further complaints.

Neuropathy, Blindness, and Gangrene

The patient whose graft thrombosed acutely, and the recipient with preexisting and subsequent neurologic invalidism have had no benefit from their transplantations. The other six have had variable reversal of peripheral neuropathy and evidence of reversal of the autonomic neuropathy that is common in end-stage diabetes.[7-9] They have redeveloped the capacity to adjust their heart rates to need, have had restoration of impaired gastrointestinal tract motility, and have had improved bladder function. The patient whose graft functioned for 14 months before failing resumed sexual function 6 months postoperatively, after more than 5 years of impotence.

All of the patients had had problems with retinopathy before transplantation, with an invariable history of multiple laser treatments. One patient was legally blind and another was completely blind in one eye. The preexisting situation was stabilized in each instance, but not reversed.

Fig. 3. A homograft C-loop (marked) which was responsible for diarrhea and which required resection.

One patient with bilateral Charcot ankle joints, complete distal anesthesia from his knees, and peripheral vascular insufficiency has undergone bilateral below-knee amputations. There was a partial reversal of the neuropathy, but this was incomplete and occurred too late to permit salvage of the legs.

DISCUSSION

The subtle but cumulatively dramatic benefits of successful pancreatic transplantation have been illustrated by the 6 patients who achieved long-term graft function in this experience. During the insulin-free state, the reversal of neuropathy and the stabilization of small-vessel disease and eye complaints were striking. The transplantation procedures necessary to achieve these effects were relatively simple and, except for thrombosis of the graft blood supply in one case, devoid of acute complications.

The inclusion of the extrapancreatic organs was nevertheless responsible for morbidity and in these studies, and the liabilities specific to both the spleen and the small intestine were defined. The spleen was responsible for isolated examples of hemolytic anemia, thrombocytopenia, and

leukopenia, complications of splenic transplantation which were recognized 2 decades ago in dogs[10] and in humans.[12]

In spite of these complications, this center has continued to include the spleen with total pancreatic grafts, with the proviso that there be donor-recipient ABO identity. One justification has been the provision of a high-flow blood supply to the graft. The other justification has been that mitigation or delay of the rejection of the kidney,[10] skin[14] and pancreas[16] has been described in such diverse species as the dog, rat, and guinea pig when the spleen is transplanted as a companion organ.

In contrast, this center has eliminated as much intestine as possible from all pancreatic grafts after the second one in this series, leaving only enough duodenum at the level of the ampulla of Vater for a side-to-side anastomosis to recipient jejunum (Fig. 1). Even in one of the later patients, in whom an excessive amount of the duodenal C-loop was retained (Fig. 3), severe diarrhea occurred which could not be relieved without excision of the superfluous duodenal tissue.

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