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World's Longest Surviving Liver-Pancreas Recipient

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In July 1988, the liver and pancreas of a cadaveric donor were transplanted separately into a man with type 1 diabetes with end-stage chronic hepatitis B virus. Two features of the operation may help explain the patient's current status as the longest-lived liver-pancreas recipient. One was enteric drainage of pancreatic exocrine secretions. The other was delivery of the pancreas venous effluent to the host portal system and then directly to the hepatic allograft. ***Liver Transpl 12:000-000, 2007.*** © 2007 AASLD.

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Kidney and pancreas transplants from the same deceased donor are frequently used to treat patients with renal failure caused by diabetic nephropathy. In contrast, combined transplantation of the liver and pancreas has been limited almost exclusively to nondiabetic recipients of abdominal multivisceral grafts. Here, we report simultaneous pancreas and liver transplantation to a patient with type 1 diabetes mellitus whose unrelated end-stage hepatic disease was chronic hepatitis B virus (HBV)-associated cirrhosis. The patient is noteworthy because he is the longest surviving liver-pancreas recipient in the world.[1] The case illustrates some aspects of pancreas transplantation and their relation to liver health that have not been fully clarified to the present day.

CASE REPORT

In 1963, a 15-year-old patient developed acute HBV hepatitis after the incomplete open heart repair of an atrioventricular (AV) defect in his native Poland. At the age of 29 years (and now in New York), he developed type 1 insulin-dependent diabetes mellitus that required treatment for the next 11 years with approximately 70 U of insulin per day in divided doses. Ongoing liver disease was not apparent until 1982. Analysis of a liver biopsy sample showed chronic active hepatitis and macro- and micronodular cirrhosis. Esophageal variceal hemorrhages in November 1986 and February 1987 were associated with ascites and hepatic encephalopathy. In May 1988, he had an episode of vibrio vulnificus bacteremia/cellulitis, followed by bacterial peritonitis from a gram-positive coccus. Further variceal hemorrhages led to his referral to the University of Pittsburgh Medical Center on June 29, 1988, for urgent consideration of liver transplantation.

Two days later, hepatic replacement with the liver of a 6-HLA-antigen-mismatched 12-year-old cadaveric donor was carried out by means of conventional techniques. The pancreas from the same donor was then transplanted below the transverse mesocolon and arterialized with a Carrel patch that encompassed the donor celiac axis and superior mesenteric artery origins. The Carrel patch was anastomosed to the recipient's infrarenal aorta. Venous outflow from the pancreas was directed into the recipient's superior mesenteric vein via a short interposition graft of donor iliac vein. Exocrine pancreatic secretions were drained into the recipient upper gastrointestinal tract through 2 end-to-side anastomoses: duodeno-duodenostomy at the second

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Abbreviations: HBV, hepatitis B virus; AV, atrioventricular.

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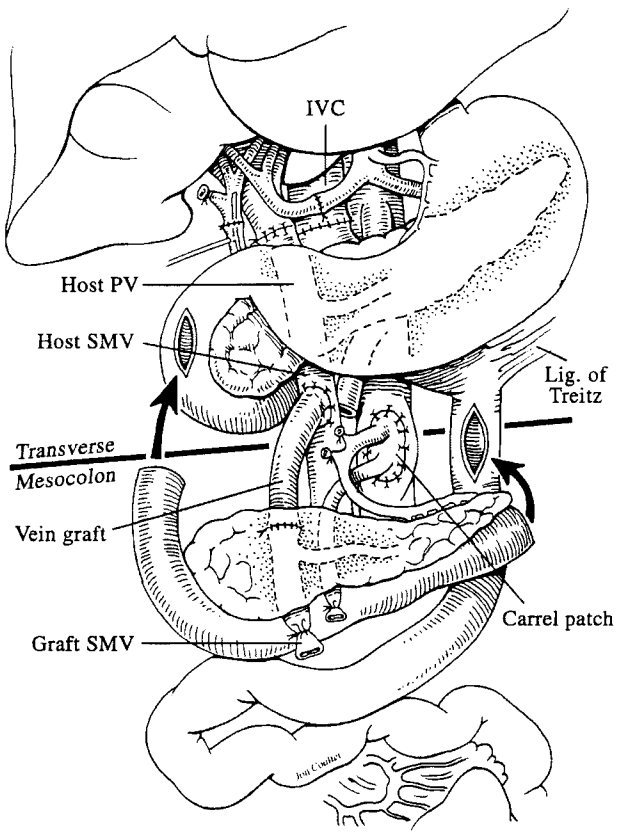

Figure 1. Liver-pancreas transplant operation performed on July 1, 1988. Key features included the interposition of the transverse mesocolon between the 2 separately revascularized organs, delivery of the pancreas graft venous outflow into the host superior mesenteric vein (SMV), and the method of enteric drainage of pancreatic exocrine secretions. With slight modifications (e.g., double exocrine drainage is not necessary), the pancreas engraftment technique could be used to test the value of portal pancreatic venous drainage in pancreas-alone or pancreas-kidney recipients. PV, portal vein; IVC, interior vena cava.

part of the host duodenum, and duodeno-jejunostomy near the host ligament of Treitz (Fig. 1).

Immunosuppression was with cyclosporine, azathioprine, and prednisone to which a 14-day course of basiliximab and muromonab was added to treat an early rejection. Thirteen weeks after transplantation, an increase in serum bilirubin (peak 7.1 mg/dL) and transaminase concentrations (serum glutamic-oxaloacetic transferase peak 400 IU) occurred that were first ascribed to rejection, then to recurrent HBV hepatitis. A stable functional state was achieved after 7-8 months. Since then, he has had mild to moderate increases of serum transaminases (usually less than twice normal) but with normal liver synthetic functions and bilirubin concentrations despite slowly worsening biopsy evidence of hepatic fibrosis (last sample 2003). He was found to be infected with hepatitis C in 1994 and was unsuccessfully treated with interferon alfa. He was treated with lamivudine between 1997 and 2004. His current medications include 25 mg cyclosporine twice a day (trough levels frequently undetectable), 5 mg/d prednisone, 10 mg/d adefovir dipivoxil, 2 antihypertensive drugs, and antacids. Serum creatinine concentrations are normal.

He has required no insulin therapy since his double organ transplant. His principal medical problems since 1990 have been cardiovascular, for the most part related the incomplete closure of the AV defect at age 15. In 1995, a permanent pacemaker was inserted for the treatment of heart block. Small strokes began in 1997 and were attributed to emboli passing through the incompletely closed AV defect. He then developed progressive congestive heart failure, and a second major cardiac procedure was undertaken in 2001. The operation included definitive repair of the AV septal defect, tricuspid valve annuloplasty, porcine mitral valve replacement, and a single-vessel coronary artery bypass graft. Glucose homeostasis has been excellent throughout. Current liver functions include a normal bilirubin (0.5 g/dL), aspartate aminotransferase (38 IU), serum albumin (4.1 g/dL), and international normalization ratio (1.2). The patient has been able to work, continues to demonstrate a sharp and ironic wit, and remains an avid reader of history books.

DISCUSSION

When the operation for this patient was planned in 1988, liver transplantation under cyclosporine-based immunosuppression had become a widely accepted form of treatment.[2] In contrast, pancreas transplantation faced an uncertain future because of its excessive morbidity and mortality.[3] One problem was that neither the whole organ pancreas transplantation originally described by Lillehei et al.,[4] nor the then more popular option of partial (segmental) pancreatic transplantation, were standardized operations. The principal lethal risks with both kinds of procedure were associated with enteric drainage of the graft exocrine secretions. Consequently, the strategy with almost all pancreas transplantations from the early 1970s to the mid-1980s was to divert the secretions to extra-alimentary destinations (e.g., the host urinary tract or free peritoneal cavity) or to eliminate the secretions by blocking the ducts of segmental pancreas grafts (e.g., with polymer injection).[3,5] In opposition to these trends, we had urged the use of the whole pancreas with enteral drainage of its exocrine secretions via the graft duodenum.[6] Both of these recommendations were carried out in our 1988 liver-pancreas recipient with diabetes (Fig. 1).

A second technical question was where to direct the venous outflow of the pancreas allograft. With the pelvic implantation site that remains in common use today for patients with diabetes who do not have liver disease, the pancreatic venous effluent usually is directed into the host systemic circulation by anastomosis to an iliac vein or to the inferior vena cava. This practice has potentially important undesirable implications. Glucose homeostasis is maintained by the liver, where insulin is almost completely removed from the blood with a single transhepatic passage. However, the insulin binding has

many other consequences for the liver. In the 1970s, it was shown that the first pass-exposure of the liver to endogenous or portally infused insulin is critical for normal maintenance of hepatic size, ultrastructure, function, and the capacity for regeneration.[7-11] To confer the hepatotrophic benefits of insulin and other molecules from the pancreas on the cotransplanted liver of our 1988 recipient, the venous effluent of the pancreas graft was drained into the host superior mesenteric vein.

Thus, the operation carried out in 1988 differed greatly from the only previous liver-pancreas transplantation into a patient with diabetes. In the earlier case (October 3, 1979), Calne et al.[12] implanted a segmental pancreas graft (body and tail) from the same donor in the pelvis of a liver recipient after polymer injection of the duct system. Venous outflow was directed into the iliac vein. Glucose homeostasis was promptly normalized. The recipient required resumption of insulin after 1 year, but survived for 6.1 years. AQ: 2 No other diabetic liver recipients are known to have undergone the double organ transplantation until the 1988 patient reported here.

However, an en bloc allograft of the liver and pancreas (with the attached duodenum) was being used in Pittsburgh throughout the 1988-89 period as replacement for the resected native upper abdominal organs of patients without diabetes with hepatic, pancreatic, or duodenal malignancies that had metastasized regionally.[13] A total of 21 patients received these composite ("cluster") allografts. Despite a high rate of tumor recurrence, the 3- to 5-year survival was >30%. All of the 21 recipients became insulin independent and remained so up to the time of death or to the 3- to 5-year follow-up.[14] However, graft pancreatitis was a frequent early complication and caused one death.[13,14]

Because of the possibility that pancreas complications could jeopardize the liver graft, the 2 organs were separated and transplanted individually in our 1988 patient with diabetes, above and below the host transverse mesocolon. This concern notwithstanding, recent reports of pancreas transplantation in 3 liver recipients with diabetes, 2 in Brussels[15] and 1 in Leeds,[16] have revitalized interest in the original en bloc transplant operation. Both groups emphasized the advantages (including the safety) of the en bloc procedure while noting the scarcity of liver recipients with diabetes who had undergone simultaneous pancreas transplantation of any kind (<10 reported). In view of the small number of reported cases, it is possible that pancreas transplantation is being underused in liver recipients with diabetes.

Our policy when pancreas transplantation is used in a liver recipient, whether simultaneously or later, has been to route the pancreas venous drainage through the hepatic allograft because this provides an ideal metabolic environment for the new liver.[17] In turn, survival of the pancreas may be aided by the well-known immune protective effect of the liver.[18] The persistence for 18 years of the still well-functioning liver allograft reported here was of particular interest in view of its prompt infection by HBV, and later hepatitis C virus. Although the HBV infection was treated with hyperimmunoglobulin, this therapy was not standardized in 1988, and effective antiviral drugs were not yet available. Consequently, the prognosis for disease recurrence was so dismal that HBV was considered at the time to be a relative contraindication for liver transplantation by most insurance carriers and an absolute one by all government agencies that funded this procedure. This patient beat the odds because of new HBV therapeutic developments that have continued to the present time.

Although the foregoing anatomic/metabolic considerations have been focused on the welfare of the hepatic allografts, they could be relevant to the health of native livers of recipients with diabetes in whom the allograft pancreas has been transplanted alone or in combination with the kidney or other nonhepatic organs. More than 90% of such pancreas grafts have their venous effluent diverted into the systemic circulation (i.e., around the liver).[5] The nonphysiologic drainage results in systemic hyperinsulinemia and has been associated with dyslipidemia, accelerated atherosclerosis, and insulin resistance.[19] In turn, insulin resistance is of particular concern to hepatologists because it is thought to be a seminal factor in pre- and posttransplantation nonalcoholic steatohepatitis syndromes.[20]

Formal comparisons of portal vs. systemic venous drainage in pancreas alone and kidney-pancreas recipients[19,21,22] have not included assessment of the effects on the liver. At the 40th anniversary celebration of the first human pancreas transplantation held at the University of Minnesota during December 6-8, 2006, interest was expressed in carrying out studies that would bring this important question to closure.

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