Chapter 118
Liver Transplantation

Carl G. Greer and Thomas E. Starzl

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Since the first transplantation of the human liver was attempted in 1963, close to 180 patients have now been treated with such an operation. Although the procedure at present is still experimental, a significant number of patients have benefited though at least temporary return to a normal life. With better selection of patients, increased experience with surgical techniques and improved methods of immunosuppressive preparations, the results can be expected to improve further in the near future.

PATIENT SELECTION

Recipients

In principle, all patients with life-threatening liver disease fit for which no curative therapy is available should be considered as potential candidates for hepatic transplantation. Practically, however, several limiting criteria must be taken into account. The existence of any active extrahepatic disease constitutes a potential contraindication. Psychosis or other severe psychiatric abnormalities, including uncontrolled alcoholism, are likewise potential contraindications. Ongoing infections are highly undesirable, since they are always necessary to complicate the patient's immunologic response after transplantation and because they may be life-threatening. Finally, patients with a history of cryoglobulinemia or lupus should probably not be considered for this kind of treatment because the ability of their plasma to induce immunosuppression has been found to be markedly reduced with advancing years.

The presence of a nonresectable, malignant liver tumor was initially believed to be an important indication for such liver replacement. Great care was exercised before proceeding with transplantation in patients with primary hepatic malignancy to exclude the existence of extraperitoneal metastases. (Nonetheless), disseminated tumor spread occurred after transplantation in a majority of these cases, whether the original tumor consisted of hepatoma, lymphoma, cholangiocarcinoma, or adenocarcinoma, and the transplantation of patients with hepatic malignancy failed.

Because of its inevitable course, nonresectable, malignant extrahepatic biliary atresia is presently the most definite indication for liver transplantation. However, transplantation for intrahepatic biliary atresia is hampered by the fact that postoperative survival is achieved in some instances with conservative treatment. In children with intrahepatic atresia, as well as in patients with liver failure caused by other kinds of non-malignant disease, the decision for transplantation must be based therefore on a highly individualized evaluation of the patient's prognosis, which must remain to be properly evaluated and decided against.

When the first attempts were made to transplant livers in non-malignant, fulminant, or, in this context, it was necessary to wait until such case was clearly non-resectable. Consequently, any transplantation, hepatic coma or renal insufficiency, was usually treated. Hemodiafiltration obviously reduced the chances for success. An attempt has now been made, therefore, to operate before the advance of terminal complications. The success of this move is the fact that prolongation of burnout time for live to at least 30 days has been achieved. The relative importance of liver transplantation in the various non-malignant diseases that can cause liver failure, such as, Lennard's cirrhosis or primary biliary cirrhosis, chronic aggressive hepatitis and Wilson's hepatitis-hepatocellular decompensation, have been achieved.

Donors

Selection of a donor-reipient combination on the basis of similarity in both antigenicity as measured with histoincompatibility (HLA) testing was attempted for many of the early liver transplantations. However, it was found that the results of such matching did not correlate well, if at all, with the clinical results in recipients of nonresected renal and other kinds of homografts. This led to de-emphasis of donor-recipient effort. The present requirements for a suitable donor were a compatible blood type, and a degree of homologous histocompatibility HLA antigens.
only a compatible ABO blood group, the absence of malignancy or generalized sepsis and a reasonable similarity in size of the liver to that of the recipient.

**SURGICAL CONSIDERATIONS**

**Donor.** Whole organ hepatic homografts can obviously be obtained from cadaveric donors only. Since 1968, when brain death criteria were accepted, it has been possible to harvest the grafts without a significant ischemic insult. The liver is cooled at removal and cleared of blood by brief perfusion with a chilled electrolyte solution. The re-duction in temperature protects the organ from anoxic damage by markedly reducing the rate of metabolism. If removal of the graft cannot be delayed until the preparation of the recipient is complete, further storage can be accomplished by connecting the ca-daver to a heart-lung machine or, alternatively, after removal of the liver, by artificial perfusion of the graft in a hyperbaric chamber under hypothermia.

**Orthotopic Transplantation.** In orthotopic liver transplantation, the native liver is removed and replaced by a graft with anatomic reconstruction of the vasculature (Fig. 118-1). This entails end-to-end anastomosis of the portal vein and of the inferior vena cava above and below the liver. When standard hepatic arterial anatomy exists, reconstruction is by end-to-end anastomosis. When there are anomalous arterial branches reaching the liver from the superior mesenteric artery or elsewhere, 2 anastomoses or an anastomosis with a donor's aortic patch to the recipient's aorta may be required. Reconstruction of the biliary tract is most commonly accomplished by anastomosis of the graft gallbladder to the recipient's duodenum after ligation of the common bile duct (Fig. 118-1). Alternative procedures include implantation of the graft common bile duct into the recipient's duodenum or jejunum, and end-to-end anastomosis of the graft and recipient's common bile ducts. The last procedure has the advantage of preserving a distal sphincter, but carries a higher risk of complications associated with bile leakage. It obviously cannot be applied in cases with biliary atresia.

**Heterotopic Transplantation.** An alternative procedure in patients suffering from non-neoplastic liver disease is insertion of a hepatic graft leaving the native liver in place (Fig. 118-2). The possible advantages of retaining the residual function of the diseased native liver are offset, however, by several factors: (1) portal hypertension remains unrelieved unless a shunt procedure is performed; (2) the diseased liver may continue to be a threat to life as a potential site of recurrent disease; (3) the abdominal overdistension caused by the addition of an extra organ often leads to postoperative pulmonary complications; and (4) residual function in a host liver may enable it to function loosely termed “interlever competition,” to deprive the transplant of a good function and survival of the transplant.

**Postoperative Care.** Early in the history of liver transplantation, grafts damaged by ischemia were received by several patients. The postoperative course in these patients was complicated by hypoglycemas, severe clotting abnormalities and the development of a third fluid space with hypoproteinemia as well as severe electrolyte and acid-base disturbances. The early course after the provision of a minimally injured organ, by contrast, is usually not much different from what is seen after other kinds of major abdominal surgery. Careful monitoring of arterial blood gases, serum potassium and glucose with swift and appropriate adjustments in therapy is important. Most patients benefit from the intravenous administration of albumin and diuretics over the first several postoperative days. Vitamin K is given to support the synthesis of prothrombin. Antibiotics covering a broad spectrum of gram-negative and gram-positive bacteria are usually administered during the first postoperative week.

**Technical Complications.** Although portal or caval vascular complications are uncommon, a 5 to 10% frequency of hepatic arterial thrombosis has been reported. If the occlusion is complete, death usually ensues in a few hours. The complication is probably related to the small size of the vessels, especially in children, and the frequency of occurrence of arterial vascular anomalies. Another possible contributory factor is arterial blood coagulation influenced by the liver changes with the evolution of a hypocoagulable state.

**Cholecystoduodenostomy** seems presently to be the best first choice for biliary tract reconstruction, since it does not sacrifice any potentially useful biliary tract tissue. Nevertheless, this kind of anastomosis of the graft gallbladder to the recipient's duodenum has been accompanied by a 5 to 10% frequency of obstruction at the site of the cystic duct. The obstruction results if...
other from surgical error or from infection of the duct wall with agents such as cytomegalo-
virus (CMV). With obstruction, a stasis in serum bilirubin and alkaline phosphatase, fever and gran-negative septicemia are characteristic findings. Secondary proce-
duress employing one of the other methods men tional earlier have been performed but for all patients have died after reope-
ration. Principally responsible for failure in such instances is inability to control compli-
cating intrahepatic abscesses or cholangitis.

Other unusual technical surgical compli-
cations include venous infection of the right adrenal gland secondary to caval in-
section, inadvertent crushing of the right oblong liver with vascular clamps placed on the suprarenal inferior vena cava, and intraoperative air embolism.

IMMUNOLOGIC CONSIDERATIONS

Graft Rejection. Some animal recipients of hepatic homografts, particularly the pig and baboon, have survived for prolonged periods without any immunosuppression. This had led to the conclusion that the liver enjoys an immunologic privilege in these species. A similar situation may also exist in man. If so, however, it appears to offer no minor an advantage that it has yet to be conclusively demonstrated. Occurrence of episodes of rejection is the rule rather than the exception in humans. Moreover, there has been no apparent correlation between the severity of the immunologic attack and the degree of histocompatibility between donor and recipient.

To date, there are no specific tests for the diagnosis of rejection of the hepatic homograft. The most characteristic changes in the standard liver function tests include an increase in serum bilirubin and alkaline phosphatase paralleling the concomitant morpho-

gic, findings of intrahepatic cholestasis. If the rejection progresses, rise in the serum transaminases, prolongation of prothrombin time and other indications of cellular injury occur. The biochemical tests (Chapter 95) thus differentiate poorly between graft rejec-
tion and other forms of hepatic abnormality, such as biliary obstruction, infectious chole-

titis and injury caused by drugs. Intravenious cholangiography (Chapter 121, Part I), hepatic scans (Chapter 96, Part II), needle biopsy (Chapter 96, Part II) and de-
termination of HBsAg in the serum aid in differential diagnosis.

Immunosuppression. The extensive ex-

perience with renal transplantation has pro-

vided the foundation for the immunosup-

pressive regimens used in human hepatic transplantation. The first patients were given 2 immunosuppressive agents: the cy-
cytotoxic drug, azathioprine, and the synthetic
corticosteroid, prednisone. During the first few years, horse antihuman lympho-
cyte globulin (ALG) has been added to this combination by some transplant teams.

More recently, another cytotoxic agent, cyclophosphamide, has been found to be as effective as immunosuppressant as azathi-

oprine in man. Since it also may be less cy-
cytotoxic, it has been used in the early post-

operative period to replace azathioprine in a triple drug program that has included ALG and steroids. During the first post-

operative weeks, prednisone is given in very high doses; subsequently, the dose is gradu-

ally reduced. If evidence of graft rejection occurs, the steroid dose is again increased. With time, the amount of prednisone required tends to diminish. While the mecha-

nism underlying this "graft acceptance" is poorly understood, it is seen as a major advantage that it has yet to be conclusively demonstrated. Occurrence of episodes of rejection is the rule rather than the exception in humans. Moreover, there has been no apparent correlation between the severity of the immunologic attack and the degree of histocompatibility between donor and recipient.

Inadequate control of homograft rejection has been a major cause of failure in approxi-

mately one third of the patients treated to this time. A second transplantation has been carried out in a few patients when graft in-

sufficiency resulting from rejection became severe. In one case, the recipient of a sec-

ond graft survived for more than a year.

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gram-negative bacteria of the types constituting the endogenous bowel flora. Evidence indicates that the hepatic graft is prone to bacterial infection, probably either as a consequence of the surgical trauma or as a consequence of uncontrolled rejection. Infections have been seen in many patients, and some have been fatal. No other organ has been transplanted so frequently in small children.

RESULTS

Of the still limited number of recipients of orthotopic grafts (some 123 as of January, 1972), only a little more than 10% survived past the first postoperative year. Though three patients survived for more than 2 years, the high incidence of first-year mortality has been a severe deterrent to the use of orthotopic transplant. Some of the causes of death early have been hemorrhage, vascular thrombosis, and septic infection. Death late in the postoperative course, has mostly been due to chronic rejection, infection, and biliary obstruction or the recurrence of preoperative hepatic malignancy. Another possibility is that the rapidity and extent of occurrence of posttransplant metastases in patients treated for hepatic malignancy is related to the immunosuppressive treatment. Loss of the "immunologic surveillance" by which mutant cells may be eliminated or restricted in the host, or growth of the malignant cells out of control, may lead to the development of metastases. Therefore, the success of orthotopic liver transplantation as of January, 1972, is not encouraging. Of the three patients who were treated throughout the first postoperative year, all died of tumor recurrence. Two of the 16 patients, the primary diagnosis of whom was malignant hepatic tumor, developed second malignancy in the graft, biliary fistula or obstruction and rejection. Of the other 14 patients, 11 are alive and free of any malignancy after more than 2 years. Of the 5 patients with an orthotopic liver transplantation at the University of Colorado, 2 of the 4 or more months earlier, 1 is alive and well and has biliary atresia, and 3 are alive and well for at least 1 year. The patient with the longest survival (1½ years) had biliary atresia.

Encouraging results have also been achieved at the University of Colorado in the treatment of hepatolenticular degeneration (Chapter 112). Two teenage boys suffering from this disease are alive and well as of this writing for more than 1 and 3 years, respectively, after orthotopic transplantation. Biopsy specimens have shown no accumulation of copper in the liver. In the second patient, markedly suppressed serum copper and ceruloplasmin have been observed. This experience is consistent with the hypothesis that the metabolic defect in Wilson's disease is liver based, although it does not prove it (Chapter 112). The worst results after transplantation for benign liver disease in the Colorado series have been in patients suffering from Laennec's cirrhosis or primary biliary cirrhosis. None of these patients survived postoperatively beyond 1 year. These poor results are probably due to the unfavorable selection of cases mentioned earlier and should not discourage further efforts to operate on these patients.

Of 16 patients with malignant hepatic tumor who have thus far been reported to have undergone liver transplantation and who lived more than 3 months postoperatively, 11 eventually died of tumor recurrence. Two patients died of other causes and 3 are alive and well with no malignancy after more than 2 years. The malignancy was an incidental finding in 2 of the 16 patients, the primary diagnosis being biliary atresia in one and Laennec's cirrhosis in the other. There has not been an instance of extended survival among the 16 patients treated throughout the world with hepatotopic hepatic transplantation as of January, 1972. Most of the recipients died in the first postoperative months from complications directly related to the grafting procedure; progressive hepatic insufficiency not relieved by the transplantation. Other patients died from septic conditions or circulatory failure. In a few cases, the nonfunctioning transplant was removed from the body before or after the operation. The inherent disadvantages of the method discussed previously probably account for the poor results.

Because of the high proportion of patients with biliary atresia, about 45% of all liver transplant recipients have been younger than 5 years of age. No other organ has been transplanted so frequently in small children.

FUTURE PROSPECTS
Although the difficulties encountered in the field of hepatic transplantation have been numerous, there is every reason to feel that the prospects for success should soon become as good as for cadaveric renal transplantation. Several avenues for improvement are obvious. First, the operation should be performed at an earlier stage, i.e., before the patient's general condition is as agonal as has so often been the case in the past. The responsibility for this important change lies mainly with the referring physician. Second, extensive collaboration within the medical community regarding utilization of organs from patients with brain death would increase the chances of treating more patients at the right time. Third, careful preoperative evaluation of vascular and biliary anatomy, primarily with radiographic techniques, might prevent some of the technical complications. Fourth, patients with hepatic malignancy should probably be excluded from consideration, at least for the time being. Finally, further improvements in the means for controlling the immune response are crucial.

With improved results, the indications for hepatic transplantation can be expanded. In addition to the numerous patients suffering from severe destructive hepatic disease, the procedure would benefit a large number of patients with liver-based errors of metabolism.

REFERENCES