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Figure 118–1. Orthotopic liver transplantation. *A*, Anatomic reconstruction of the inferior vena cava above and below the liver, the portal vein and the hepatic artery. Biliary drainage is effected by cholecystoduodenostomy after ligation of the common bile ducts of the graft and the recipient. *B* and C, Arterial reconstruction used in 2 patients where the homograft had a double arterial blood supply; *B*, 2 anastomoses; *C*, anastomosis of donor to recipient aorta. Several other variations have been necessary in other patients. (Reproduced by permission of Annals of Surgery *168*:392, 1968.)

Figure 118–2. Heterotopic liver transplantation. *A*, The incision. *B*, Portacaval shunt performed prior to transplantation. *C*, The hepatic graft revascularized in the lower abdomen. The portal inflow is from the patient's inferior vena cava; the inferior end of the graft vena cava has been closed. The hepatic artery of the graft is anastomosed to the recipient aorta. Biliary draninge is accomplished by cholecystoenterostomy to a Roux-Y loop. An alternative used in other patients involves anastomosis of the portal vein to the splenic or mesenteric vein, thereby providing inflow of splanchnic blood into the graft. (Reproduced by permission of Archives of Surgery *93*:107, 1966.)

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Chapter 118

Liver Transplantation

Carl G. Groth and Thomas E. Starzl

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 through at least temporary return to a normal life. With better selection of patients, increased experience with surgical techniques and improved methods of immunosuppression, the results can be expected to improve further in the near future.

PATIENT SELECTION

Recipients. In principle, all patients with life-threatening liver disease for which no other form of treatment is available should be considered as possible candidates for hepatic transplantation. Practically, however, several limiting criteria must be taken into account. The existence of any severe 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 it is always necessary to compromise the patient's immunologic response after transplantation. Finally, patients over 55 years of age should ordinarily not be considered for this kind of treatment because the ability to thrive under immunosuppressive treatment has been found to be markedly reduced with advancing years.

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The presence of a nonresectable, malignant liver tumor was initially believed to be an important indication for total liver replacement. Great care was exercised before proceeding with transplantation in patients with primary hepatic malignancy to exclude the existence of extrahepatic metastases. Nontheless, disseminated tumor spread occurred after transplantation in the majority of these cases, whether the original tumor consisted of hepatoma, cholangiocarbinoma or sarcoma. As a consequence, interest in the transplantation of patients with hepatic malignancies abated.

NONETHELESS

Because of its inexorable course, noncorrectable, congenital extrahepatic biliary atresia is presently the most definite indication for liver transplantation. However, liver transplantation for intrahepatic biliary atresia is tempered by the fact the prolonged 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-neoplastic disease, the decision for transplantation must be based, therefore, on a highly individualized evaluation of the patient's prognosis, should transplantation be decided against.

When the first attempts were made to treat patients with non-neoplastic liver disease, it was necessary to wait until there was clearly no hope. Consequently, gastrointestinal bleeding, hepatic coma or renal insufficiency was usually present. Such conditions obviously reduced the chances for success. An attempt has recently been made, therefore, to operate before the advent of terminal complications. Justification for this move is the fact that prolongation of human life for at least 3½ years has been achieved. The relative importance of liver transplantation in the various non-neoplastic diseases that can cause liver failure, such as Laennec's cirrhosis or primary biliary cirrhosis, chronic aggressive hepatitis and Wilson's hepatolenticular degeneration, has yet to be determined.

Donors. Selection of a donor-recipient combination on the basis of similarity in tissue antigenicity as measured with histocompatibility (HL-A) 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 nonrelated renal and other kinds of homografts. This led to de-emphasis of this kind of effort. The present requirements for a physiologically satisfactory donor include

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 reduction 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 cadaver to a heart-lung machine or, even 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 lever 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 hepatoma formation; (3) the abdominal overcrowding 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, by a process loosely termed "interliver competition," to depreciate the chances of 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 hypoglycemia, 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 frequent occurrence of arterial vascular anomalies. Another possible contributory factor is alteration in blood coagulation influenced by the liver changes with the evolution of a hypercoagulable 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 ei-

ther from surgical error or from infection of the duct wall with agents such as cytomegalovirus (CMV). With obstruction, a rise in serum bilirubin and alkaline phosphatase, fever and gram-negative septicemia are characteristic findings. Secondary procedures employing one of the other methods mentioned earlier have been performed, but so far all patients have died after reoperation. Principally responsible for failure in such instances is inability to control complicating intrahepatic abscesses or cholangitis.

Other unusual technical surgical complications include venous infarction of the right adrenal gland secondary to caval dissection, inadvertent crushing of the right phrenic nerve with vascular clamps placed on the suprahepatic 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 so 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 an hepatic homograft. The most characteristic changes in the standard liver function tests include an increase in serum bilirubin and alkaline phosphatase paralleling the concomitant morphologic findings of intrahepatic cholestasis. If the rejection progresses, rises 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 rejection and other forms of hepatic abnormality, such as biliary obstruction, infectious hepatitis and injury caused by drugs. Intravenous cholangiography (Chpater 121, Part I), hepatic scans (Chapter 96, Part II), needle biopsy (Chapter 96, Part II) and determination of HBAg in the serum all aid in differential diagnosis.

Immunosuppression. The extensive experience with renal transplantation has provided the foundation for the immunosuppressive regimens used in human hepatic transplantation. The first patients were given 2 immunosuppressive agents: the cytotoxic drug, azathioprine, and the synthetic adrenal corticosteroid, prednisone. During the last few years, horse antihuman lymphocyte globulin (ALG) has been added to this combination by some transplant teams.

More recently, another cytotoxic agent, cyclosphosphamide, has been found to be as effective as immunosuppressant as azathioprine in man. Since it also may be less hepatotoxic, it has been used in the early postoperative period to replace azathioprine in a triple drug program that has included ALG and steroids. During the first postoperative weeks, prednisone is given in very high doses; subsequently, the dose is gradually 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 mechanism underlying this "graft acceptance" is poorly understood, it is prerequisite for long-term success because the side-effects of prolonged administration of high doses of prednisone are prohibitive.

Inadequate control of homograft rejection has been a major cause of failure in approximately one third of the patients treated to this time. A second transplantation has been carried out in a few patients when graft insufficiency resulting from rejection became severe. In one case, the recipient of a second graft survived for more than a year.

The Compromised Host. The dilemma of chronic immunosuppression is to provide enough therapy to prevent rejection, yet not so much that the patient dies of immunologic invalidism. This fine balance may not be achievable in a given case. The postoperative course in a large number of patients is complicated by severe pulmonary or systemic infections. Often, the infectious agent is an opportunistic organism that becomes pathogenic only in an immunologically compromised host. Examples of such agents are candida, aspergillus, nocardia and cryptococcus among the fungi; cytomegalovirus, herpes simplex and varicella-zoster among the viruses; and a nonclassified microorganism, *Pneumocystis carinii.* Infections with all these organisms have been encountered in recipients of hepatic transplants. In many patients these infections have contributed to early or late postoperative death.

Recipients of liver transplants also have a high incidence of septicemia caused by

gram-negative bacteria of the types constituting the endogenous bowel flora. Evidence indicates that the hepatic graft, during biliary obstruction or when afflicted by rejection, readily becomes infected with intestinal bacteria. The latter then enter the systemic circulation. Large septic infarcts develop in some patients, probably as a consequence of uncontrolled rejection. Frequent blood cultures are mandatory in caring for these recipients. Demonstration of gram-negative bacteria in the blood stream is strong evidence of graft obstruction, rejection or serious injury from other causes, including hepatic vascular thrombosis.

Another possibility is that the rapidity and extent of occurrence of post-transplantation metastases in patients treated for hepatic malignancy is related to the immunosuppressive treatment. Loss of the "immunologic surveillance" by which mutant cells can be eliminated or restricted in their potential growth has been postulated as instrumental in the immunologically compromised patients.

RESULTS

Of the still limited number of recipients of orthotopic grafts (some 123 as of Jaunuary, 1972), only a little more than 10% survived past the first postoperative year. Three patients survived for more than 3 years and 2 of them are reported to have remained in excellent health. Death early after hepatic transplantation has been found to result from many causes: hemorrhage, vascular thrombosis, focal septic necrosis in the graft, biliary fistula or obstruction and rejection. When death ensued several months after the operation, it was usually due to chronic rejection, carcinomatosis or serum hepatitis. Fatal sepsis occurred both early and late in the postoperative course. A small group of patients died from nonseptic disease afflicting organs other than the liver.

The results obtained at the University of Colorado, the institution in the United States with the greatest experience to date with liver transplantation, are considerably better than those reflected in the total series. Of 56 patients who had an orthotopic liver transplantation at the University of Colorado 4 or more months earlier, 19 lived for at least the first 4 months and 11 survived for at least 1 year. The patient with the longest survival (3½ 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 grafts; in the second patient, markedly suppressed serum copper and ceruloplasmin have normalized. 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 no discourage further efforts to operate upon such 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 afterward, 11 eventually died of tumor recurrence. Two patients died of other causes and 3 are alive 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 35 patients treated throughout the world with heterotopic hepatic transplantation as of Jaunary, 1972. Most of the recipients died in the first postoperative months from complications directly related to the grafting, or from progressive hepatic insufficiency not relieved by the transplantation. Other patients died from septic conditions or circulatory or respiratory failure. In a few cases, the nonfunctioning transplant was removed at a second 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

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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 numberous patients suffering from severe destructive hepatic disease, the procedure would benefit a large number of patients with liver-based errors of metabolism.

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