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ORTHOTOPIC LIVER TRANSPLANTATION[1]

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ABSTRACT Numerous recipients of liver transplants have had chronic survival, but further improvement will necessitate new and better techniques of immunosuppression.

INTRODUCTION

There are two kinds of liver transplantation. One involves the placement of an extra (auxiliary) liver at some heterotopic site such as the right paravertebral gutter, leaving the diseased native liver in place. Optimum revascularization of auxiliary livers includes portal inflow from the splanchnic venous system. There has been only one example of long survival after clinical auxiliary transplantation, that being of a patient treated for biliary atresia more than six years ago by Fortner of New York. Forty-two other attempts throughout the world including four from our center failed within a short time (1).

The second and far more widely accepted kind of liver transplantation is liver replacement (orthotopic liver transplantation) after removal of the diseased native organ. The following remarks will pertain solely to orthotopic liver transplantation.

METHODS

Indications For Transplantation

Amongst the first 141 recipients treated by us (2, 3) there were 74 infants and children (Table 1). The most common

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diagnosis in this pediatric group was biliary atresia. Chronic aggressive hepatitis was a distant second. Eight patients had the inborn errors of metabolism summarized in Table 1. It has been established that liver based inborn errors are permanently rectified by providing livers of normal phenotypes.

TABLE 1
INDICATIONS FOR TRANSPLANTATION (1963-1977)
IN PATIENTS ←18 YEARS

BILIARY ATRESIA	48
CHRONIC AGGRESSIVE HEPATITIS	12
INBORN METABOLIC ERRORS	8*
HEPATOMA	3
NEONATAL HEPATITIS	2
CONGENITAL BILIARY CIRRHOSIS	1
TOTAL	74
*INBORN ERRORS	
ALPHA$_1$-ANTITRYPSIN DEFICIENCY	4
WILSON'S DISEASE	2
TYROSINEMIA	1
TYPE IV GLYCOGEN STORAGE DISEASE	1

There were 67 adults among the first 141 liver recipients. The reasons for proceeding are listed in Table 2. These indications are all still considered valid with the exception of primary hepatic malignancies. Excluding hepatic malignancies, the most common indications for operation were chronic aggressive hepatitis and alcoholic cirrhosis.

TABLE 2
INDICATIONS FOR TRANSPLANTATION (1963-1977)
IN PATIENTS 19 TO 70 YEARS OLD

CHRONIC AGGRESSIVE HEPATITIS	23
PRIMARY LIVER MALIGNANCY	16
ALCOHOLIC CIRRHOSIS	15
PRIMARY BILIARY CIRRHOSIS	5
SCLEROSING CHOLANGITIS	4
SECONDARY BILIARY CIRRHOSIS	2
MASSIVE HEPATIC NECROSIS (B VIRUS)	1
BUDD-CHIARI SYNDROME	1
TOTAL	67

Three of our liver transplantations in children and 16 in adults were carried out to treat nonresectable hepatomas, duct cell carcinomas, angiosarcomas, and cholangiocarcinoma. Ten of these patients lived beyond three months and nine of them later developed metastases which usually contributed to or were primarily responsible for their deaths after a few months to several years. Similarly, the recurrence rate in the Cambridge-King's College series in England has been 70% (4). As more and more such cases have been documented, we have had less and less enthusiasm for and indeed we usually avoid transplantation for malignancy.

In the future, the leading indications for transplantation in adults undoubtedly will be chronic aggressive hepatitis and Laennec's cirrhosis. The presence of HB_S Ag viremia is not a contraindication since effective postoperative treatment can be given with hyperimmune serum (4). Cases of cirrhosis pose a supreme technical challenge. If results are to be improved, candidates will need to be selected at an earlier time. Too often in the past, the recipients have been moribund by the time of operations.

Relative contraindications include advanced age (beyond 50 years) and infection. Judgment must be exercised not to proceed too soon in the natural history of the patient's disease, and not to make the equally or more serious error of waiting too long.

Operative Procedure

Liver replacement is simple in principle. However, its performance may be one of the most difficult undertakings in surgery. Blood loss may total thousands of milliliters. In cirrhotics, the combination of venous hypertension and deficient clotting factors may make hemostasis completely impossible until the arrival of a new liver. Then, the synthesis of clotting factors by the homograft, combined with portal venous decompression through the transplant, can lead to a nearly miraculous cessation of hemorrhage.

Since 1968, practically all liver homografts used in Denver have been removed from heartbeating cadaveric donors. Even with this advantage, organs that have been irreparably damaged are still occasionally used. Unfortunately, there are no present methods to rule out this kind of pre-existing ischemic injury.

Homograft preservation is started by infusing cold electrolyte solution just as the donor blood supply is interrupted. Our usual practice is to infuse only the portal vein. With the so-called Collins solution which was first used to store kidneys, preservation of cold livers has been possible in dogs for as long as one day. Similar results have been reported by

Calne et al using a modified plasma solution (4). These developments in preservation have permitted the successful shipment of livers from city to city in the United States, and also in the English program of Calne and Williams (4).

The first anastomosis performed is of the suprahepatic vena cava. As the vena caval anastomoses are constructed, slow infusion of electrolyte solution is continued via the portal vein. Air bubbles can be seen floating out of the graft. If infusion is not provided during this time, the air bubbles in the homograft may be flushed into the circulation after revascularization. Then, they may pass through abnormal right to left venous communications (secondary to liver disease) and on to the brain. A high incidence of cerebral air embolus was encountered in our early experience. This was eliminated with the infusion technique.

The hilar structures have smaller calibers. Increasingly in infants and young recipients, we have used microvascular techniques, particularly for reconstruction of the hepatic artery and portal vein. Otherwise, pediatric recipients will have a high incidence of thrombosis in these vessels.

Biliary tract reconstruction has caused more complications than any other part of the operation (3). In our early experience, one of every three recipients subsequently had biliary duct obstruction or biliary fistula. Even without obstruction or fistula, there was a high incidence of bacteremia, probably because of constant contamination of the biliary ducts through the cholecystoduodenostomies that were being used in those early days.

Now we think that duct to duct reconstruction (choledochocholedochostomy) is the best method. If this is not feasible (as for example in patients with biliary atresia), we use cholecystojejunostomy or choledochojejunostomy (to a Roux-Y limb).

RESULTS

Non-Immunologic Complications

The procedure has been followed by a long list of complications. Such complications have been responsible for more than half of all deaths within the first year (2,3,5). Included have been vascular thromboses, hemorrhage, the unknowing use of ischemically damaged grafts, and biliary tract obstruction and/or fistulization to provide a very incomplete accounting. These complications have influenced postoperative immunosuppressive management.

It is now realized that biliary tract complications (especially obstruction) frequently have been the cause of postoperative jaundice that developed after an initial period of

bilirubin clearing. Better diagnosis and management of biliary complications were made feasible by increasing the use of cholangiography (percutaneous, retrograde endoscopic, or T-tube).

Another recent change in policy has been the more frequent use of needle biopsy. Evidence of virus hepatitis has thereby been obtained in a suprising number of cases. Severe or lethal homograft hepatitis has been caused by HB_S Ag virus, herpes, chicken pox, and adenovirus.

Immunosuppression

All of our liver recipients have had double drug therapy using a cytotoxic agent, azathioprine (which can be used interchangeably with cyclophosphamide), and prednisone. To the double drug regimen we have often added heterologous antilymphocyte globulin (ALG). Irreversible hepatic rejection has usually been prevented with these techniques but too often at the cost of fatal infection. The possibilities for more effective immunosuppression are discussed below, and it is upon such advances that the next major jump in survival will undoubtedly depend.

Survival

In reporting our experience (2,3,5), we have divided our cases of orthotopic liver transplantation into three series. Series 1 consisted of 111 consecutive patients treated between March, 1963 and July, 1976. Of these, only 31 (28%) survived for as long as one year (Table 3). The rate of chronic survival improved only slightly during this time.

TABLE 3
CASES OF LIVER REPLACEMENT AT THE UNIVERSITY OF COLORADO
(FOLLOW-UP TO JANUARY 1, 1980)

	TOTAL	LIVED 1 YEAR*	ALIVE NOW (YEARS)
SERIES I (3/63-7/76)	111	31 (28%)	13 (4-10)
SERIES II (7/76-1/78)	30	15 (50%)	13 (2-3 1/2)
SERIES III (3/78-1/79)	23	6 (26%)	5 (1-1 3/4)

*Late deaths after 1 to 6 years.

Subsequent to one year (12 to 72 months postoperative), 18 more deaths occurred in Series 1 leaving today only 13 alive after 4 to 10 years. The most common cause of death after one year was chronic rejection, although recurrent neoplasm, unrecognized biliary tract obstructions, and hepatitis all contributed.

In July, 1976, a Series 2 was begun. It was completed in December, 1977. The operative, diagnostic, and management improvements alluded to earlier were used. Of the next 30 consecutive recipients, 13 are alive after 2 to 3 1/2 years (Table 3). A fourteenth recipient, a child, died at 23 months of systemic chicken pox and bacterial infection. A fifteenth patient died after 16.5 months with chronic rejection and portal vein thrombosis. Thus, the one-year survival in this experience was 50% (Table 3).

It is disquieting to report that these improved results have not been sustained at our center in a subsequent, smaller experience of 23 more consecutive cases for which a minimum potential follow-up of one year is now available (Table 3). Of the 23 recipients, only 6 (26%) lived for a full year. As in earlier times, faulty case selection, technical complications, use of damaged organs, and complications of immunosuppression were the main causes of death. By personal communication it was learned that a recent decline in survival was also noted by the English team in 1978 and early 1979.

DISCUSSION

We have shown in renal transplant recipients that preoperative lymphoid depletion by thoracic duct drainage can practically eliminate rejection. Such an improvement in immunosuppression should be applicable for other organs, but there may be special problems in liver recipients. Prospective liver recipients are so fragile that a month of TDD pretreatment may impose significant risks. For one thing, the lymph drainage in patients with hepatic disease tends to be voluminous, particularly if ascites is present. In our experience, the output may exceed one liter per hour. Nevertheless, as our liver program reopens, we are attempting to provide pretreatment with TDD or alternatively by removing peripheral lymphocytes (lymphapheresis).

Another possibility for improvement could be better drug treatment. A promising new agent, the fungus extract, Cyclosporin A has permitted spectacular success after skin and/or whole organ transplantation in rats, rabbits, dogs and pigs and has been used by Calne in a limited clinical trial of renal homotransplantation at Cambridge, England.

Calne says that several human recipients of cadaver kidneys have been treated with this drug and discharged from the hospital in good condition even though no corticosteroids were given. It has been stated that Cyclosporin has significant hepatotoxicity. To the extent that this is true, its value will be diminished.

At the University of Colorado the first American trials of Cyclosporin A in kidney transplants are underway. So far, 15 cases have been compiled. No irreversible rejections have been encountered although one kidney was lost because of ureteral necrosis. No examples of severe hepatotoxicity have been seen. Thus, the stage has been set for a trial of Cyclosporin A in liver transplantation.

SELECTED REFERENCES

Perusal of the references below will provide a nearly complete picture of the history and present state of liver transplantation. Scholars interested in original publications will be able to track these easily, especially in Reference 2.

1. Fortner, J.G., Yeh, S.D.J., Kim, D.K., Shiu, M.H. and Kinne, D.W. (1979). The case for technique of heterotopic liver grafting. Transplantation Proc. 11, 269.
   This collection of 43 clinical auxiliary liver transplantations from many different centers was presented to the International Transplantation Society in Rome, September, 1978. The case for auxiliary transplantation is presented optimistically, perhaps excessively so in view of the poor results.
2. Starzl, T.E. (with the assistance of Putnam, C.W.) (1969). "Experience in Hepatic Transplantation." W.B. Saunders, Philadelphia.
   This text contains the total world literature (299 references) on experimental and clinical liver transplantation to the spring of 1969. An account is given of all 42 human liver homotransplantations attempted to that time including 29 (25 orthotopic, 4 auxiliary) at the University of Colorado. Surgical and anesthetic techniques, and metabolic and immunoglobulin changes following liver transplantation are described. The laboratory development and clinical practice of immunosuppression for all transplanted organs is reviewed. Two chapters by Professor K.A. Porter of St. Mary's Hospital and Medical School, London, constitute a complete monograph of the pathology of animal and human auxiliary and orthotopic liver homografts as well as two chimpanzee to human heterografts.

3. Starzl, T.E., Koep, L.J., Halgrimson, C.G., Hood, J., Schroter, G.P.J., Porter, K.A. and Weil, R., III (1979). Fifteen years of clinical liver transplantation. Gastroenterology 77, 375.

The first 141 orthotopic liver homotransplantations at the University of Colorado are described. These include the 74 pediatric cases of this chapter plus 67 adult cases. There is a detailed documentation of causes of early and especially late deaths. The recent literature of clinical liver transplantation is brought up-to-date. This is the most recently written review of liver transplantation.

4. Calne, R.Y. and Williams, R. (1979). Liver transplantation. "Current Problems in Surgery 16, 3-44. (Ravitch, M.M., Ed.)." Yearbook Medical Publishers, Inc., Chicago.

The important clinical series of 74 cases from the Cambridge-King's College London group are described, as well as laboratory research in these institutions. Although almost all of the recipients were adults, the opinions expressed have applicability to pediatric cases. Opinions about patient selection, biliary tract reconstruction and immunosuppression are somewhat different that those held by us.

5. Starzl, T.E., Koep, L., Porter, K.A., Schroter, G.P.J., Weil, R., III, Hartley, R.B. and Halgrimson, C.G. (IN PRESS). Decline in survival after liver transplantation. Arch. Surg.

This is a detailed account of the 23 patients in Series III and an effort to explain the excessive mortality in this late Denver experience. A number of these recipients had thoracic duct drainage (TDD) established on the same day as their transplant.