

THE LIVER

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Liver Transplantation—1978

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IN THE 2 years since the last meeting of this Society, the prospects in liver transplantation have improved. Thus, the following remarks will focus mainly on recent history. In so doing, they will also emphasize some troubling questions that remain in this field. Most of these unresolved issues in liver transplantation have been developed from two large series: one, our own, and the other, that originated from the combined Cambridge-King's College effort in England. Other workers throughout the world have had less extensive and, for the most part, unreported experience that we have not been able to accurately compile for this meeting.

WHY HAS LIVER REPLACEMENT BEEN SO DANGEROUS?

For a long time, the high acute mortality after liver transplantation made the procedure profoundly experimental. Between March 1963 and July 1976, we treated 111 consecutive recipients of orthotopic liver

grafts. Of these, only 31 (28%) survived for as long as a year (Table 1). The rate of chronic survival improved only slightly during this time. Among the first 50 recipients in this original series of 111, there were 11 (22%) who lived for as long as a year. Among the next 61 patients, there were 20 (33%) who survived for 1 year.

Of the 31 1-year survivors, 16 died subsequently for reasons that are considered in another article in this issue.¹ The late deaths were after 12 months–6 years.

Fifteen of the original 111 patients remain alive today with follow-ups of 2 $\frac{2}{3}$ –8 $\frac{2}{3}$ years. Twelve of the 15 are now more than 4 years postoperative, and 7 are more than 5 years. Since 1 of the 16 late deaths was a patient who lived for 6 years, our center has so far had 13 liver recipients who survived in excess of 4 years and 8 who lived more than 5 years.

The details of all our cases, the indications for operation, and most importantly the reasons for the high acute mortality have been described elsewhere.^{2,3} The major causes of early death were technical misadventures, including biliary tract complications, vascular accidents of the homograft blood supply, hemorrhage, and the use of livers damaged by ischemia. In addition, many postoperative problems were caused by high-dose immunosuppression in patients who were incorrectly diagnosed as having rejection but who actually had other problems, such as biliary obstruction, cholangitis, and hepatitis.

Because of these findings and conclusions, surgical and management changes were instituted in the summer of 1976. Microvascular

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Table 1. Total Number of Patients March 1963 Through July 1976 (Follow-Up to September 1, 1978)

Total	111
Lived > 1 year	31 (28%)†
Alive Now*	15 (after 2½–8½ years)

*The 16 late deaths were after 1–6 years.

†With patients < 18 years old, 1-year survival was 21/61 (34%). Among adults, 1-year survival was 10/50 (20%).

techniques were increasingly employed for vascular and often for biliary tract anastomoses, particularly in pediatric recipients. Postoperative hepatic dysfunction was not so easily ascribed to rejection. Instead, frequent liver biopsies were obtained and cholangiography (transhepatic, T-tube, or retrograde endoscopic) became routine if the explanation of postoperative jaundice was not obvious.

A new series was begun in July 1976, and completed in December 1977. Thirteen of the next 30 patients are alive, 11 beyond a year (Table 2). A fourteenth recipient, a child, died at 23 months of a sudden overwhelming infection. A fifteenth patient died after 16½ months with chronic rejection and portal vein thrombosis. Although 2 of the survivors are not quite 1-year postoperative, they are well. Thus, the 1-year survival in this most recent experience is almost certain to be 50% (Table 2).

There has been a similar improvement in the Cambridge–King's College units managed by Calne and Williams, respectively.⁴ Among the first 35 recipients treated by the English groups, there were only 3 1-year survivors, but among the next 39 patients, 9 have already lived more than a year and 6 more are alive with shorter follow-ups.⁴

Table 2. Liver Transplantation August 1976 Through December 1977 (Follow-Up to September 1, 1978)

Total cases	30*
Alive	13†
Dead	17‡

*With patients < 18 years old, 1-year survival is projected at 7/12 (58%). With adults, 1-year survival is 8/18 (44%).

†Two of these patients are postoperative 9 and 10 months, respectively.

‡One death was at 23 months, another at 6½ months.

Throughout the English series, as in ours, the role of purely technical surgical complications has been emphasized. The quality of homografts used in England and in the United States has reached parity since the acceptance in Britain of brain death.

HOW SHOULD THE BILIARY TRACTS BE RECONSTRUCTED?

Realization that the biliary tract was the Achilles' heel of liver transplantation has prompted major reforms both at our center and in England. We believe that the ideal form of reconstruction is choledochocholedochostomy using a T-tube stent (Fig. 1A). A postoperative retrograde endoscopic cholangiogram obtained 4 months postoperatively after this kind of reconstruction is shown in Fig. 2. This patient will require repeat cholangiography every 4 or 6 months until the significance of the nonobstructing stricture can be determined with certainty. The necessity of careful late follow-up has been illustrated by our own experience, whereby biliary obstruction has led to the death of several patients or required reoperation as long as 6 years after the original transplantation.¹⁻³

Choledochocholedochostomy is often not feasible and as alternatives we perform cholecystojejunostomy or choledochojejunostomy to a Roux limb (Fig. 1 B and C). The advantage of cholecystojejunostomy is that the anastomosis is of a large caliber even in pediatric recipients and requires no stenting or drainage. The disadvantage is that obstruction to the cystic duct has necessitated reoperation and conversion to choledochojejunostomy (Fig. 1B to Fig. 1C) in 20%–35% of the cases. Furthermore, the Roux limb or the jejunostomy below it have developed perforations in several patients.⁵ This complication has carried a high mortality.

Calne and his associates have advocated that the common duct and gallbladder be made into a common chamber with anastomosis of the gallbladder fundus to the recipient common duct (or sometimes to a Roux limb).⁶ The anastomosis is stented with a

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BILIARY TRACTS BE RECONSTRUCTED?

The biliary tract was the first transplantation has been done both at our center and elsewhere. We believe that the ideal reconstruction is choledochocholedochostomy (Fig. 1A). A T-tube is placed in the recipient common duct. The patient usually requires 6 months postoperatively until the obstruction is shown to be permanent. The need for repeat cholangiography has been illustrated, whereby biliary obstruction has resulted in the death of several patients as long as 6 months posttransplantation.¹⁻³ In some cases, choledochostomy is often not performed. We perform choledochocholecystojejunostomy (Fig. 1B and C). The advantage of choledochostomy is that the large caliber even in the recipient requires no stenting. The advantage is that obstruction is necessitated reoperation to choledochojejunostomy (Fig. 1C) in 20%-35% of the patients. The Roux limb or the recipient have developed perforations.⁵ This complication has been reported. Associates have advocated the recipient and gallbladder be placed in a chamber with anastomosis of the fundus to the recipient. Sometimes to a Roux limb is stented with a

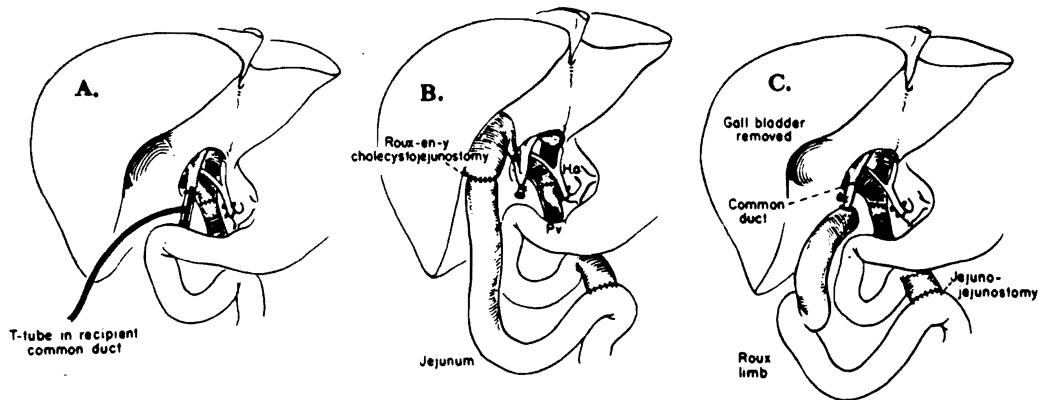


Fig. 1. Techniques of biliary duct reconstruction acceptable to us for most transplantation recipients. (A) Choledochocholedochostomy. Note that the T-tube is placed, if possible, in recipient common duct. (B) Cholecystojejunostomy. (C) Choledochojejunostomy after removal of gallbladder.

T-tube, enabling the biliary system to be frequently studied or irrigated. They have been satisfied with this procedure^{4,7} and with it, biliary tract complications have been substantially reduced. Experience alone will tell if this somewhat more complicated approach is necessary or desirable.

WHAT ARE APPROPRIATE INDICATIONS FOR LIVER TRANSPLANTATION?

Anyone with chronic end-stage liver disease who is less than 45 or 50 years old, who is not infected, who has a hopeless prognosis, and who does not have widespread



Fig. 2. Cholangiogram obtained 4 months postoperatively by the retrograde endoscopic technique. Reconstruction was with choledochocholedochostomy (Fig. 1A). The T-tube was removed by the patient after 1 month. Note the low-grade anastomotic stricture (arrow).

malignancy is a potential candidate for liver transplantation. However, there are important differences in the attitudes of the Cambridge-King's College and American physicians and surgeons. For example, the English team does not perform the procedure on pediatric recipients. Besides their difficulty in obtaining pediatric livers, they are concerned with the growth retardation that is predictable if long-term high-dose steroid therapy is necessary. Our own experience with infants and children has actually been better than with adults (Tables 1 and 2). Thus, we consider the pediatric recipient to be favored.

Another major difference between the English and Colorado series is the high proportion of cirrhotics in our experience. Among the 68 adults treated by us from 1963 through 1977, 45 have had Laennec's cirrhosis or chronic aggressive hepatitis. The difficulty of the operations in some of these patients in our hands is hard to describe. The procedures may last for 12-18 hours and may necessitate the use of dozens of liters of blood. Nevertheless, we have continued to treat these patients, believing that this is where the most important future application of liver transplantation lies. From a technical point of view, the adult patient with primary biliary cirrhosis is ideal. They do not have severe portal hypertension, and their diseased livers are so soft and compliant that the technique is almost comparable in simplicity to that in normal animals.

We have been increasingly disenchanted with the use of liver transplantation for primary hepatic malignancy. Eight of our 9 patients who have survived 3 months or more after liver replacement for hepatomas, duct-cell carcinomas, cholangiocarcinoma, and angiosarcoma have eventually developed recurrence. One of our patients with duct-cell carcinoma died of metastases more than 2 years later, and another one is alive 4 years postoperatively but with known recurrence. A third patient is still alive almost 2 years postoperatively with known metastases from a

sclerosing cholangiocarcinoma. The only patient cured of a hepatic malignancy by us was a child who had a small incidental hepatoma in her liver that was removed for the indication of biliary atresia rather than because of the unsuspected hepatoma. She is now 8 $\frac{2}{3}$ years postoperative.

A high incidence of recurrence has also been reported from Cambridge-King's College (about 70% in those with extended survival). However, their view of liver replacement for hepatic malignancy is more optimistic than ours, particularly with respect to hepatomas.^{4,7} Like us, they have uniformly had recurrence for duct-cell carcinomas. However the picture is stated, the yield from liver replacement for primary hepatic malignancy is apt to be limited since the eventual outcome is so heavily weighted by the biologic behavior of the original lesion.

Parenthetically, another difference between the Colorado and Cambridge series has been our use of antilymphocyte (or antithymocyte) globulin for immunosuppression (Fig. 3). Both groups use azathioprine, cyclophosphamide (on occasion), and prednisone.

HOW EFFECTIVE IS PRESERVATION?

Short-interval preservation techniques have had extensive trials in England and in Colorado with the shipment of livers from city to city. The Cambridge-King's College team has used a plasma solution for cold infusion of the homografts,⁸ and we have employed Collins solution.⁹ In dogs, the two approaches yield comparable results and permit safe preservation for up to 12 hr. The same has been achieved in humans.

McMaster, Calne, et al.¹⁰ have drawn attention to the possible selective injury of biliary ducts with such techniques. They suspect that ischemia or perhaps the bile left within the major ducts or even the minor intrahepatic ones may cause autolysis and set the stage for later serious mechanical difficulties. They have advocated much more thorough washing of the biliary tree than has been generally practiced.

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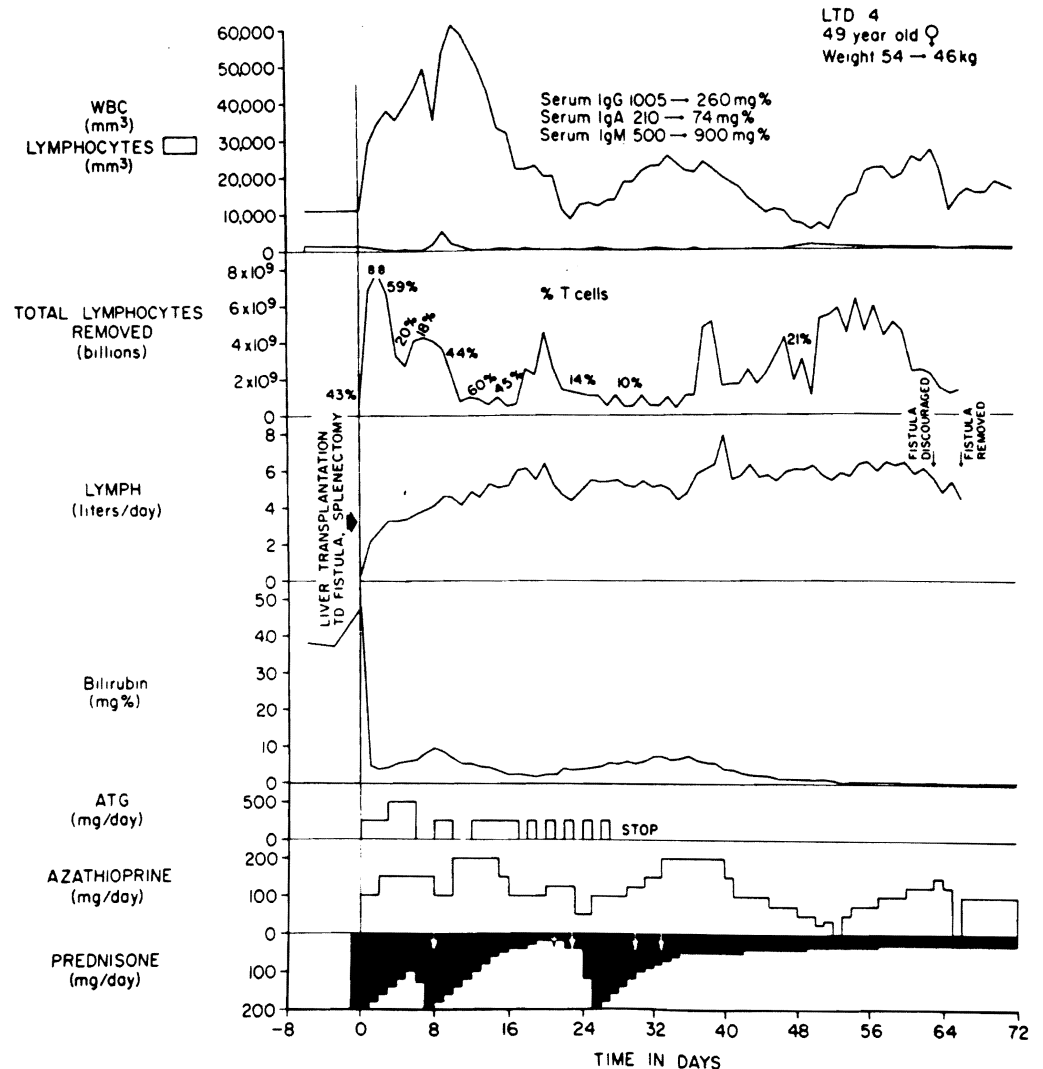


Fig. 3. The course of a patient treated with thoracic duct drainage after orthotopic liver transplantation for primary biliary cirrhosis. Note that azathioprine, prednisone, and antithymocyte globulin (ATG) provided basic immunosuppression. The two rejections were mild and easily controlled with steroids.

WHAT IS THE ROLE OF TISSUE TYPING?

It has never been possible to give typing techniques a fair trial in liver transplantation. Almost all of the matches in our series have been bad ones. For example, in the last 100 Colorado cases only 2 patients have received livers with 3 or 4 antigen matches. It is unlikely that shopping for well-matched livers will be possible in the near future, since the

need for transplantation is so pressing in appropriate candidates that it is obligatory to proceed with the first available organ.

Because of this, a number of liver transplantations have been performed despite the presence in the recipients of cytotoxic antibodies that are anti-donor-specific. We have carried out 10 liver transplantations under these circumstances. There have been no examples of hyperacute rejection and, in fact,

Table 3. Positive Cytotoxic Crossmatches

Number of cases	10*
Hyperacute rejection	0
Survival > 2 months	7
Survival \geq 6 months	5†

*OT 58, 63, 71A, 101, 114, 119, 122, 103B, 138, 151.

† Longest survival—2 years.

no demonstrable harmful effects have been seen at a later time (Table 3). Seven of the patients lived for more than 2 months and 5 for more than 6 months. We and Calne and Williams have concluded that the liver is highly privileged, at least in confrontations with preformed cytotoxic antibody states.

On the other hand, recent experience has made us uneasy about breaching blood group barriers. We have been forced to do this on 11 occasions (Table 4). The livers did not function well in two of the recipients leading to death or retransplantation. The blood violations were B to O and B to A. The excised livers had superficial infarcts and focal necrosis. In desperation we still perform transplantation despite blood group incompatibility, but we avoid doing this if possible. Except in the two exceptional cases, the other patients have not seemed to have been harmed (Table 4) by hyperacute rejection.

IS THERE A NEED FOR BETTER IMMUNOSUPPRESSION?

With such strong emphasis on nonimmunologic factors as causes of failure after liver transplantation (see earlier), it might be erroneously concluded that immunosuppression is satisfactory. In fact, much remains to be learned about the clinical-pathologic correlations of rejection. In a number of patients who become jaundiced postoperatively, the homografts are free of mononuclear cell invasion, do not have evidence of hepatitis, and do not seem obstructed, although there is centrilobular cholestasis.^{2,11} Myburg et al.¹² have referred to this as cholestatic rejection. In such patients, a painfully slow response to high-dose steroid ther-

Table 4. Blood Group Incompatibility

Number of cases	11*
Hyperacute rejection	2†
Survival > 2 months	8
Survival \geq 6 months	6‡

*OT 59, 60, 61, 98B, 100, 102A, 104, 113, 132, 137, 148A.

† Retransplantation attempted after 17 and 12 days. The blood group compatible second grafts were also rejected in much the same way as the first.

‡ Longest survival—23 months.

apy can sometimes be obtained. In other cases, the penalty for control of such questionable or even unquestionable rejection with high-dose steroid therapy can be fatal infection, to which liver recipients are especially prone because of frequent contamination of the homograft with enteric organisms.^{2,11,13}

In an effort to reduce steroid requirements and to facilitate "graft acceptance," we recently treated 9 patients with thoracic duct fistula, which was established on the same day as liver transplantation in 7 recipients and 14 and 26 days postoperatively in 2 more.¹⁴ Seven of the nine patients are alive, including five of the seven who had thoracic duct fistulas established on the day of liver transplantation. These five patients have either had no demonstrable rejection or have had mild and rather easily controlled rejections (Figure 3). So encouraging has been our experience with thoracic duct fistula that we plan to continue its use on all cases in the immediate future.

SUMMARY

The development of liver transplantation has been made difficult because of the enormous technical difficulties of the procedure and because the postoperative management in early cases was defective in many instances. With surgical and medical improvements, the prospects for success have markedly increased recently. The wider use of thoracic duct fistula as an adjuvant measure during the first 1 or 2 postoperative months is being explored.

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