Liver Transplantation*

THOMAS E. STARZL

Department of Surgery, University of Colorado Medical Center, Denver, Colorado

Abstract  From March 1963 through June 1976, 111 patients received orthotopic liver homografts. Forty-two of the recipients had congenital biliary atresia. Other common diagnoses were chronic aggressive hepatitis, Laennec’s cirrhosis, and primary hepatic malignancy. There were also other assorted, less common diagnoses. Thirty-one of the 111 patients (28%) lived at least one year and 15 are still alive with follow-ups of 2½ to 8½ years. Seven of the patients lived for more than five years, and 6 of these 7 are still alive. In 1975 and 1976, clinical-pathologic correlations on all these patients were carried out with Professor K. A. Porter of London. The most common causes for failure were technical misadventures, including biliary tract problems, vascular thromboses, and the use of ischemically damaged livers. Rejection was less of a problem than had been realized. In view of these findings, improvements in intraoperative and postoperative management were made with particular reference to biliary tract drainage and to the use of microvascular techniques. Treatment of a new series of 30 patients was begun in July 1976, and completed in December 1977. After 6 to 22 months, 15 of the 30 most recently treated patients are alive, all living outside the hospital. Thus, the outlook after transplantation appears to have greatly improved, and a one-year survival rate of 50% is projected.

In this paper, I would like to discuss what is still classified as an experimental operation, namely total removal of the liver and its replacement with a cadaveric hepatic homograft.

EXPERIMENTAL BACKGROUND

Before discussing transplantation in humans, I would like to sketch in some of the background work which preceded our clinical efforts by a number of years. Following liver replacement in dogs, the new liver functions for the few first postoperative days (1–3), but after four or five days (as also with renal and cardiac grafts) rejection supervenes. The animals become progressively jaundiced, and serum transaminase levels become elevated, denoting necrosis of the graft. Almost all animals die within 10 days. Survival of an outbred dog for more than a month without immunosuppressive treatment has never been recorded.

Histopathologically, the rejected canine grafts are overrun with mononuclear cells, mostly lymphocytes, which are the hallmarks of cell-mediated graft rejection. There is evidence as well of massive tissue necrosis caused by the rejection process.

About 14 years ago, we showed that it was possible in some dogs to prevent rejection by the administration of azathioprine (Imuran®, Burroughs Wellcome) as the sole immunosuppressive treatment (4). The dog whose course is shown in Fig 1 received a liver graft in March 1964. This animal never became jaundiced. Furthermore, we realized from the early experiments that many such animals could have immunosuppression discontinued, sometimes at surprisingly early times (in the case shown in Fig 1 after only 4 months), and with subsequent long survival. This dog lived for 12 years postoperatively, finally dying of a combination of old age and partial biliary tract obstruction.

The only other agent in the experimental laboratory that has substantially prolonged liver graft survival has been antilymphocyte serum (ALS) or antilymphocyte globulin (ALG) (5, 6). In some experiments, big doses of ALS or ALG were given before the arrival of the graft but no treatment at all was provided postoperatively. One such canine recipient of a nonrelated mongrel liver graft lived for several years after the transplantation.

My personal background for liver transplantation thus was acquired in laboratories, first in Chicago and later at the University of Colorado. I would be remiss not to specifically note the great pioneering work in experimental liver transplantation performed by Dr. Francis D. Moore of the Peter Bent Brigham Hospital (1, 7). Moore’s contributions and publications have been completely annotated elsewhere (6).

INDICATIONS FOR CLINICAL TRANSPLANTATION

Leaving the laboratory behind, I turn now to clinical liver transplantation, starting with possible indica-
ORTHOTOPIC LIVER TRANSPLANT

3-23-64

DIED
12-8-75

ALKALINE PHOSPHATASE (Bodansky Units)

SGOT (S.F. Units)

BILIRUBIN (mg/100 ml)

AZATHIOPRINE

Fig 1. Serum biochemistries during the 11 years and 8½ months of survival following canine orthotopic liver transplantation on March 23, 1964. The values recorded during the last eight months of life represent individual determinations. All other points on the graph are mean values for each time period; the brackets indicate 1 SD above and below the mean. Beginning with the 7th year of follow-up, bilirubin concentrations, if normal, were reported as < 1.2 mg/100 ml. The upper limit of normal in our laboratory for each test is marked by the horizontal broken line.


Alcoholic cirrhosis is one of the most important potential indications for liver transplantation, but the timing of operation may be difficult to decide, particularly if abstinence from alcohol is not achieved in advance. Furthermore, the damage done to the central nervous system by hepatic failure, and the consequential damage to other organ systems inflicted by self abuse or metabolically constitute a severe handicap. One of our most noted patients with Laennec’s cirrhosis was the former King Peter of Yugoslavia, who was deposed during the second World War. He was unconscious when he was taken to the operating room. His new liver functioned perfectly, but he died without regaining consciousness. Only recently have our results with Laennec’s cirrhosis provided any encouragement.

Chronic aggressive hepatitis has been another common indication for liver transplantation. The ideal patient would be virus free, but some transplant recipients have had preexisting Australia antigenemia. The first long term survivor who had the HBsAg marker became Australia antigen-negative as judged by agarose gel and complement fixation methods and remained that way for about two months (Fig 2). Her course indicated that the major focus of the virus had been in her native liver but later testing with the more sensitive radioimmunoassay showed that trace quantities of HBsAg were always present. About two months postoperatively, at about the time when she would have expected to develop serum hepatitis had she been infected de novo at the time of transplantation, she had increases in bilirubin, rises in transaminases, joint pains, and a return positive HBsAg as determined by all the screening tests. Immunosuppression was not increased. She recovered spontaneously, but remained HBsAg-positive and slowly recapitulated a variation of her original disease. She died after almost two
years. In spite of this experience, we doubt if the presence of a virus in these patients contraindicates liver transplantation. It has become possible to treat such patients with specific hyperimmune globulin starting on the day of operation when the titer of the virus is made low by removal of the native liver. We have obtained clearing of the virus for many postoperative months, as have Calne et al. (8).

Another indication which is especially interesting to pediatricians is a group of inborn errors of metabolism which are liver-based. It seems clear that all hepatic based inborn errors of metabolism are curable by successful hepatic transplantation, even some disorders in which the exact enzyme defect is not known. As example of the latter is Wilson's disease, victims of which accumulate copper in the liver, brain and elsewhere. This accumulation of copper causes the lesions of Wilson's disease, which include the typical Kayser-Fleischer rings in the eyes. Wilson's disease is an inherited disorder in which most patients have reduced or absent serum ceruloplasmin. After hepatic transplantation for Wilson's disease, the ceruloplasmin increased in one of our patients from essentially zero to normal levels, and it remained normal for more than seven years post-transplantation (Fig 3). After operation, decoppering was evident in a cupruresis of many months' duration (Fig 3). In this patient, whose most important indication for operation was progressive neurologic disability, the nervous system changes reversed over several years and between two and three years postoperatively the Kayser-Fleischer rings disappeared.

Other examples of inborn errors that we have treated include alpha-1-antitrypsin deficiency, congenital tyrosinemia, and Type IV glycogen storage disease. The possibilities for further research with other inborn errors are obvious.

Finally, I would like to say something about hepatic transplantation for the treatment of hepatic malignancy. When we initially carried out liver replacement, we thought that primary liver tumors would be an ideal reason for proceeding. The idea was that otherwise non-resectable hepatomas which were still localized to the liver could be treated by removal of the entire liver. This proved to be a vain hope for the most part, since recurrence of tumor has been seen in more than 90% of such trials with hepatomas, small duct cell carcinomas (Klatskin tumors), and other less common malignancies including hemangioendothelial sarcoma (6, 9). With hepatomas, serial alphafetoprotein determinations have helped follow the evolution of metastases. With all kinds of tumors, a striking tendency has been seen for the recurrences to "home" back to the graft itself.

As with every rule, there is an exception to the tumor recurrence story. The exception in our series is a little girl who had a hepatoma as an incidental finding in a liver that was afflicted with biliary atresia. Preoperatively, she had a positive alphafetoprotein examination. The abnormal protein disappeared after the surprisingly
long interval of four months. She has remained alphafetoprotein negative and tumor-free since that time. She is now 8½ years post-transplantation and the longest surviving liver recipient in the world.

In addition, significant palliation has been possible in some other cases in spite of tumor recurrence. We have treated two men with small duct cell carcinomas (Klatskin tumors) at the confluence of the right and left hepatic ducts. One lived for two years before dying of metastases. The other is surviving but with recurrent tumor; it has been four years since his operation. We have a female patient for whom we performed liver replacement almost two years ago for a sclerosing cholangiocarcinoma. She has small quiescent pulmonary metastases which have been present since the time of transplantation. Perhaps the door is not entirely closed on hepatic malignancy as an indication for liver transplantation, although for the reasons I have stated, the yield in terms of cure will be small.

To summarize indications in more general terms, we think: 1) ideal recipients should be less than 40 years old. Those who are older cannot stand the rigorous immunosuppression which must be imposed. 2) The patient should have a hopeless prognosis, a point to which I will return in a moment. 3) The patient should not have cancer. 4) The patient should not have an infection. As I have already implied, we have violated each of these guidelines from time to time. If two adverse conditions are present, the outlook is virtually hopeless.

I would like to focus momentarily on the question of what constitutes a hopeless prognosis. We have treated patients with acute liver disease caused by halothane, isoniazid, and viruses—patients who seemed to have no hope for survival. Yet they have recovered fully with supportive care including ventilation, exchange transfusion and renal dialysis. Because of such admittedly uncommon experiences, we are reluctant to proceed with liver replacement for acute disease. Perhaps in such cases auxiliary transplantation could play a role, whereby a second ectopically placed liver could be used temporarily to tide the patient over the crisis and to allow recovery of the native liver.

In patients with chronic liver disease, it is important to have a longitudinal view of their course of illness before accepting them for transplantation. Such a view has been made possible by collaboration with a number of students of liver disease. We have developed a network of communication with many prominent hepatology centers in the United States. When referrals come from such sources, we have confidence that the time is ripe for treatment, even if our own opportunity for observation is limited. When a patient becomes invalided so he or she cannot function in society and cannot work, we believe further delay is inadvisable. The past practice of taking...
moribund patients to the operating room for such an extensive procedure will not permit an improvement in results.

TECHNIQUE OF LIVER REPLACEMENT

The essential first step in liver transplantation is to obtain a good cadaveric organ from a brain dead donor in whom circulation is still effective. The organ can be excised in an orderly way and chilled by infusing cold fluid such as lactated Ringer's solution (with or without low molecular weight dextran) through the portal vein. The cooled liver will tolerate several hours of ischemia.

An important practical breakthrough in the last two or three years has been the infusion of cadaveric livers with special solutions which mimic plasma (10) or alternatively which have an electrolyte composition similar to that in cells (11). The latter fluid, which is known as Collins' solution, has permitted the cold preservation of canine livers safely in our laboratories for 12 to 18 hours. As a clinical extension, it has been possible for us to harvest human livers in California, Minnesota and other distant places, carry the livers to Denver on commercial airplanes, and successfully transplant the organs in Colorado. Thus, the possibility of a national liver procurement network has emerged.

In the meanwhile, the recipient operation is usually done through a basic subcostal incision, very often with an extension into the right chest through the seventh intercostal space or with a superior midline extension including excision of the xiphoid process (Fig 4). There usually are formidable technical problems because
of the extensive venous collaterals which can render hemostasis almost impossible. The problem is compounded by the fact that clotting factors are never normal. In our early experience, most adult patients with cirrhosis lost 30 to 50 units of blood. Some technical modifications have improved the situation. Of these, the most important is removal of the liver by transecting all of the structures entering it, removing it from below while pulling on the hilar structures, and ligating all of the tissues that are cut behind. When the upper end of the liver is reached, a clamp can be placed across the suprahepatic vena cava, and a cuff of the vena cava can be developed for suture by dissecting off the cirrhotic liver (Fig 5).

In concept, liver transplantation is a simple operation which consists of connecting the blood vessels coming into and going out of the liver in as normal a way as possible and then reconstituting biliary drainage (Fig 6). There are two vena caval anastomoses, one below and one above the liver. For the last two years, we have continuously infused the homografts through the portal vein during the time of the vena caval anastomoses, allowing air bubbles trapped in the homograft to come out as the suture lines were completed (Fig 7). Omission of this precaution in early cases resulted in air embolus, particularly in adult recipients (12). The air floated to the right heart and because of the extensive venous anastomoses from right to left in patients with liver disease, these emboli passed straight to the left heart and up to the brain, causing grave neurologic damage.
For biliary reconstruction in most of our early cases, cholecystoduodenostomy (Fig 6A) was used because it was the simplest and fastest way to complete a long and tiring operation. The patients had an extraordinary incidence of symptomatic or asymptomatic bacteremia (6). It seemed as if the liver itself was the focus of and the entry for bacteria that passed into the general circulation and then caused infections elsewhere. Ultimately, it became obvious that contamination with gastrointestinal contents was causing cholangitis.

Consequently, we now believe that the ideal way of reconstructing the biliary tract is simple end-to-end common duct anastomosis (Fig 6D). Of course in many patients (children with biliary atresia, for example) this option is not available. Then, we perform cholecystojejunostomy (Fig 6B) or choledochojjunostomy (Fig 6C), anastomosing gall bladder or the common duct to a Roux limb of jejunum. The Roux principle de-functionalizes a loop of the intestine, theoretically allowing the gastrointestinal stream to pass distally to the liver without seriously contaminating it.

**IMMUNOSUPPRESSION**

Immunosuppressive therapy in liver recipients (6, 9) is much the same as was developed at our center for kidney transplantation. It consists of triple drug therapy (Figs 2 and 3) with azathioprine (which may be replaced with cyclophosphamide), with prednisone and with heterologous antilymphocyte globulin (ALG). ALG is purified immunoglobulin obtained from the serum of horses or rabbits immunized against human lymphocytes. Thus ALG administration is an attempt at lymphoid depletion. The only really dose-maneuverable component of the triple drug regimen is prednisone, which is raised or lowered according to the presence or absence of rejection.
POSTOPERATIVE COMPLICATIONS AND CAUSES OF FAILURE

The high mortality after liver transplantation has prevented wide application of this procedure. In the summer of 1975, I had the opportunity during a sabbatical leave in London to review the first 93 consecutive Colorado cases with Professor K. A. Porter, who is a world authority on transplantation pathology. We tried in each case to determine the reasons for success or failure. The details of this work have been published (9). I would like to briefly recount the central findings, because they changed our attitudes about management for all subsequent cases.

One expected cause of failure was uncontrolled acute rejection. However, it was surprising how relatively infrequently (about 20% of the patients) this was the primary reason for death. Similarly, chronic rejection, with its typical occlusive vascular lesions and parenchymal fibrosis, accounted for only a few failures.

What then were the main reasons for the exorbitant mortality up to that time? The majority of deaths were found to result from technical or mechanical problems. These included thrombosis of the hepatic artery or
forking-EN-Y cholecystojejunostomy, as depicted in Figure 6B. A. Minimal obstruction. B. Moderate obstruction. C. Severe obstruction with leak and abscess formation (A) near site of common duct ligation. D. Very severe obstruction. At reoperation the common duct was necrotic. C = common duct; CD = cystic duct; GB = gallbladder; J = jejunum; large arrows = sites of common duct ligation.


Fig 8. Transhepatic cholangiograms in four patients whose original biliary reconstructions were with Roux-en-Y cholecystojejunostomy, as depicted in Figure 6B. A. Minimal obstruction. B. Moderate obstruction. C. Severe obstruction with leak and abscess formation (A) near site of common duct ligation. D. Very severe obstruction. At reoperation the common duct was necrotic. C = common duct; CD = cystic duct; GB = gallbladder; J = jejunum; large arrows = sites of common duct ligation.


portal vein, the use of grafts damaged by ischemia, the development of cerebral air embolus as discussed earlier, and hemorrhage, to mention just four examples.

However, by far the greatest single technical cause of mortality was failure of the biliary tract reconstruction. In the 93 consecutive cases analyzed in London, almost 35% of the patients had either obstruction of or fistula formation from their biliary tracts (13). Half of these patients were not treated with reoperation. One excuse was that the reconstructions usually had been with cholecysto- or choledochoenterostomy. It was not possible to make the diagnosis by means which are now standard, such as percutaneous transhepatic cholangiography using the so-called skinny (Chiba) needle. We awakened to the fact that patients who became jaundiced in the postoperative period were not necessarily undergoing rejection, but that there was a good possibility of obstruction.

Using cholangiography frequently, the kinds of obstructive lesions seen in Fig 8 were discovered with increasing frequency and ducts were reconstructed secondarily. Reoperation and secondary repair of these dilated duct systems was shown to be safe (13).

**CLINICAL RESULTS**

I have presented an overview of some general principles in liver transplantation, and will conclude with some statistics and follow-ups which were recently brought up to date. The material can be split into two phases.
TABLE I
Total Number of Patients*

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<table>
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<tbody>
<tr>
<td>Total</td>
<td>111</td>
</tr>
<tr>
<td>Lived &gt; 1 year</td>
<td>31 (28%)</td>
</tr>
<tr>
<td>Alive now</td>
<td>15 (After 2½–8½ years)</td>
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To June 1976

The first phase was prior to the clinical-pathologic correlations which began in the summer of 1975 and were completed in early 1976. There were 111 consecutive patients who were treated between 1963 and June 1976. Only 31 (28%) lived for as long as 1 year (Table I). Of the 31 patients that lived for a year, 15 are still surviving after 2½ to 8½ years.

Amongst the 111 original patients, there were 50 adults (Table II), including 13 with malignancies. Several of these 13 died of recurrent malignancy as stated earlier, before or after 1 year. Chronic aggressive hepatic and alcoholic cirrhosis were the other common diseases treated. In all of the major diagnostic categories, extended survival was uncommon. Only 10 (20%) of the 50 patients lived for as long as a year, and 5 are still surviving with follow-ups as short as 28 months and as long as about 4 years. The woman with the Budd–Chiari syndrome has had a baby. The patients who died late had survivals of 13½ to 25 months (Table II).

In the first 111 patients there were 61 who were 18 years or younger. In this pediatric subdivision there were 42 examples of biliary atresia with a one-year survival of only 12 (29%). In the assortment of other diagnoses were included the inborn errors of metabolism, hepatomas, and chronic aggressive hepatitis (Table III). Twenty-one (34%) of the total pediatric series of 61 lived for a year. Ten are still alive with follow-ups of 3½ to 8½ years (Table IV). The 12 late deaths were after one to six years. The most remote death was a particularly tragic one caused by a biliary duct complication six years following liver replacement for Wilson's disease. Thus, the overall survival in the pediatric series was better than among adults but still poor.

After June 1976

Improvements in technical and diagnostic care were instituted after the case reviews which took place in 1975 and early 1976. These included the use of microvascular techniques for vascular anastomoses and the more liberal use of postoperative cholangiography and needle biopsy. Since then and with a cut-off of December 1977, we accumulated 30 more cases (Table V). The survival in the latest group is now 50%. Fourteen of the 15 survivors are more than 6 months postoperative and 9 are more than a year postoperative. All of these patients are out of the hospital, and from past experience it seems clear to us that the one-year overall mortality of liver transplantation is now approximately 50%.

A breakdown of the recipients in the adult and pediatric subgroups is given in Table VI. The survival in both categories is about double that of the original series. Perhaps a new era in liver transplantation is at hand.

SUMMARY

The development of liver transplantation has been a tortured and often sad story, just as was the story of renal transplantation. It appears that substantial advances have been made mostly because of better surgical techniques and because of better management. It has been necessary for surgeons to act more like internists,

1 As of July 17, 1978, no further deaths had occurred.

TABLE II
Fate of First 50 Adult Patients*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Examples</th>
<th>Survival 1 Year</th>
<th>Alive Now‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant tumor</td>
<td>13</td>
<td>2 (15%)</td>
<td>1 (44 months)</td>
</tr>
<tr>
<td>Chronic aggressive hepatitis</td>
<td>17</td>
<td>5 (30%)</td>
<td>1 (32 months)</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>11</td>
<td>1 (9%)</td>
<td>1 (49 months)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>4</td>
<td>0 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Secondary biliary cirrhosis</td>
<td>1</td>
<td>0 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Sclerosing cholangitis with ulcerative colitis</td>
<td>1</td>
<td>0 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Massive hepatic necrosis due to hepatitis B virus</td>
<td>1</td>
<td>0 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Budd–Chiari syndrome</td>
<td>1</td>
<td>1 (100%)</td>
<td>1 (43 months)</td>
</tr>
<tr>
<td>Congenital biliary hypoplasia</td>
<td>1</td>
<td>1 (100%)</td>
<td>1 (28 months)</td>
</tr>
</tbody>
</table>

† 7 hepatomas, 4 duct cell carcinomas, 1 cholangiocarcinoma, and 1 hemangioendothelial sarcoma. The patient who is still alive had a small obstructing duct cell carcinoma.
‡ The 5 deaths after 1 year occurred after 13½, 15½, 19, 20½, and 25 months.
and to be more suspicious and inquisitive about the reasons for post-transplantation liver dysfunction rather than to ascribe hepatic perturbations to rejection. With these nonspecific improvements, there has been movement of liver transplantation into the area of actual service.

Before the next great step will be made, it is my feeling that there must be an improvement in immunosuppression of the kind which will also permit a more satisfactory level of service to be achieved in renal and other kinds of transplantation. Just exactly what the improvement will consist of I do not know. The state of the art of immunosuppression has been frozen in its present form for almost ten years. Nothing in medicine is likely to move until it is made to move.

REFERENCES


