

291

Experience in Orthotopic Liver Transplantation

Indications, results and future Prospects

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Since the first liver transplantation in man was performed in Denver in March 1963, 162 such operations have been performed throughout the world. Approximately one third of the patients have been treated at the University of Colorado Medical Center and the Denver Veterans Administration Hospital. This report will discuss our experience with the indications for hepatic replacement, the results obtained and the prospects for future improvement.

We have not transplanted the liver for metastatic malignancy, as has been attempted in other centers, because of the strong possibility of other extrahepatic metastases. With the exception of one case where the tumor was adherent to the pylorus which also required resection, we have not performed transplants for primary hepatic malignancies which have extended beyond the confines of the liver.

Indications

Replacement of the liver is indicated in patients with serious liver disease whose life expectancy can be measured in days or weeks or perhaps a few months. The reasons for operation in our center are listed in Table 1.

Table 1 Indications for Orthotopic Liver Transplantation

<i>Disease</i>	<i>Number of Transplantations</i>
Biliary Atresia	26*
Primary Hepatic Tumors	13
Cirrhosis	9
Chronic Aggressive Hepatitis	5
Wilson's Disease	2
Lupoid Hepatitis	1
Retransplantation for severe rejection	4
Total	60

*One patient had an incidental hepatoma.

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As our experience has grown we have become progressively more disappointed with the results of transplantation for primary malignant disease of the liver as we shall indicate later. We now rarely recommend transplantation for this indication.

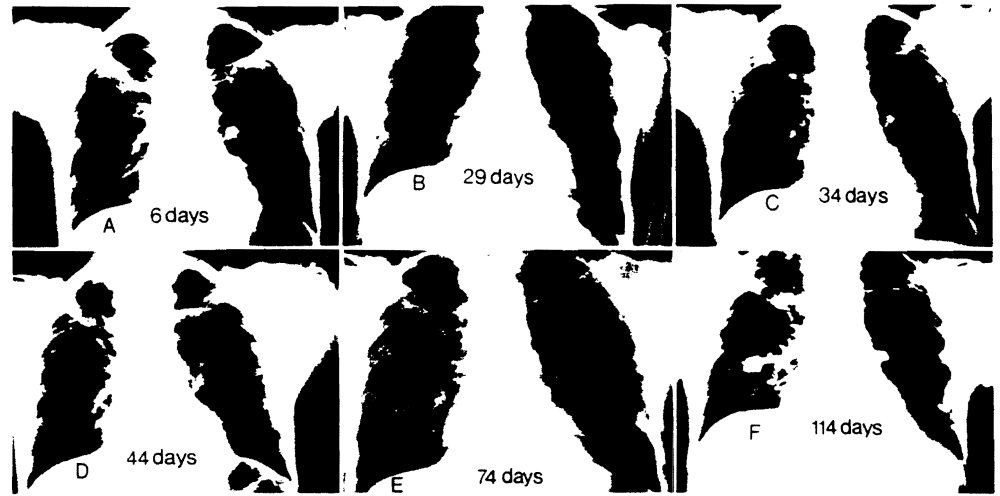


Fig. 1a The extremely rapid development of pulmonary metastases in a patient who underwent liver replacement for hepatoma. A. The chest is clear six days after transplantation. B. Twenty-nine days post-operative. Two metastases are visible in the lower left lung field (arrows). C. Five days later the tumor deposits previously seen have grown in size (horizontal arrows) and a third focus is now present in the right lobe (vertical arrow). D. Forty-four days. Metastatic growths are scattered throughout the lungs (arrows). E. Seventy-four days post-operative. F. Four months after transplantation. Transient dyspnea was first noticed a few days later. The patient died of pulmonary and hepatic insufficiency 143 days after operation.

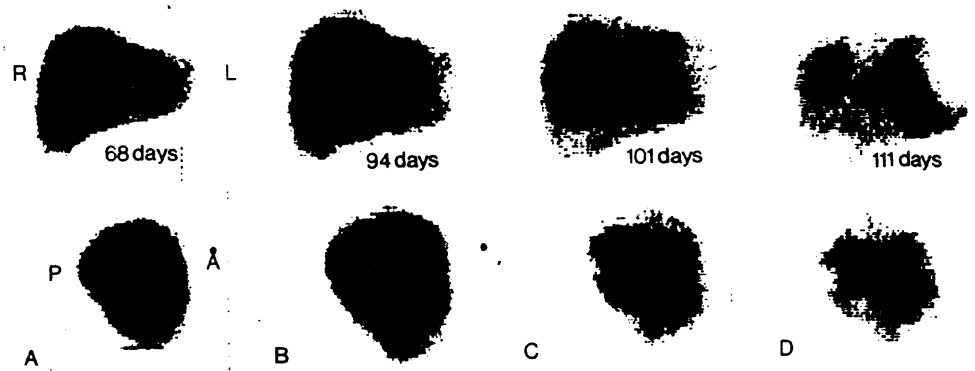


Fig. 1b Destruction of the hepatic homograft by tumor recurrence, as demonstrated by serial technetium liver scans. A. 68 days — The scan appears normal. B. 94 days — The patient had become jaundiced. Hepatomegaly is evident. C. 101 days — Multiple areas of poor isotope concentration are now visible. D. 111 days — The process has continued its rapid progression. By the time of death the homograft was almost completely replaced by tumor.

Results

Long term survival can be achieved after liver transplantation. In experiments in dogs and pigs we have had many survive more than a year. One dog is still alive more than 8 years after transplantation. In our first 42 patients, in whom a minimum followup of 12 months was available, 11 survived at least one year (Table 2). Three of these recipients lived more than 2 years. One patient, who was the longest survivor in the world, died 3½ years after transplantation.

Table 2 11 One-year Survivors after Orthotopic Liver Transplantation

Alive	3, 11 — 1½ to 2½ years
Died	8, 11 — 1 to 3½ years
12 Months — Cancer*	
12 Months — Serum hepatitis, liver failure	
14 Months — Cancer	
15 Months — Cancer	
15 Months — Rejection, liver failure	
20 Months — Disseminated nocardia infection**	
30 Months — Rejection, liver failure	
42 Months — ? Rejection, liver failure	
*This patient actually died a few days short of one year.	
**The homograft showed severe chronic aggressive hepatitis, just as in her previously removed native liver.	

At the present time 8 patients are alive at 1½, 1, 1½, 3½, 10, 14, 28, and 34 months post-transplantation respectively.

Primary malignant tumors of the liver. In our early experience it was hoped that hepatic replacement might be useful therapy for primary malignant tumors of the liver. However, as long term survival was achieved it became obvious that metastases were a major problem. In 6 of 7 patients treated for hepatoma and followed from 2 to 14 months after transplantation metastases appeared in the lungs, brain and even in the homografts.

An example is the patient in Fig. 1a. He was a 15 year old boy from whom a large hepatoma was removed. No secondary deposits were apparent at the time of transplantation. Twenty-nine days later pulmonary metastases appeared and subsequently became larger and more numerous. Serial scans of the homograft also showed progressive replacement with tumor, Fig. 1b. The patient died of pulmonary and hepatic insufficiency 143 days after transplantation. At autopsy the lungs and the homograft showed extensive invasion by tumor (Figs. 1c and 1d).



Fig. 1c Lungs showing multiple large metastases.



Fig. 1d Invasion and nearly complete destruction of the liver homograft by recurrent hepatoma. At autopsy almost all the transplanted hepatic tissue was replaced by tumor. (By permission of W. B. Saunders Co., 1969.)

This disheartening experience has been repeatedly seen in other cases. The sole exception was in a child aged almost 4 years who was operated upon for severe congenital biliary atresia. An incidental finding in the liver specimen was a hepatoma about 2 cm in diameter. The patient has now been followed for close to 2½ years with no clinical, radiologic or serologic (α -fetoprotein estimations) evidence of recurrent tumor.

It is possible that slower growing tumors, such as cholangiocarcinomas may have a better prognosis, but thus far we have not treated any such cases. However, we have had the opportunity to treat one patient with an unusual tumor which does not commonly metastasize outside the liver, primarily because it usually kills through extensive replacement of the hepatic parenchyma leading to liver failure, or by causing fatal hemorrhage. The tumor was a hemangioendo-

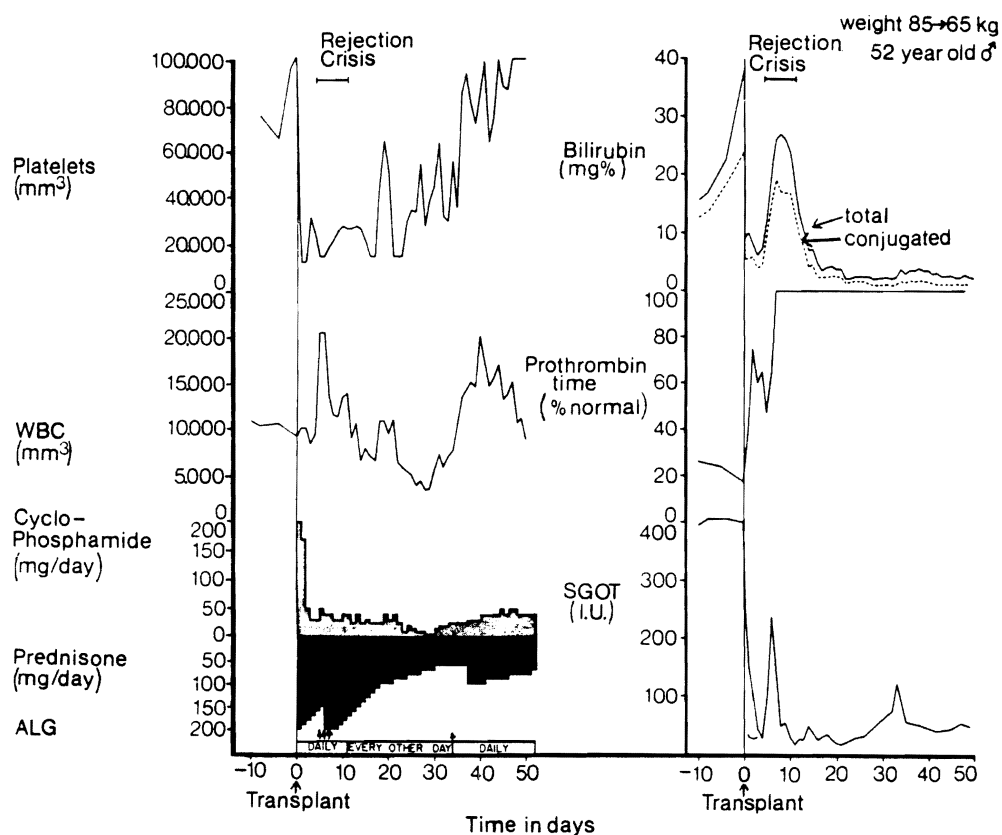


Fig. 2 The early course of a 52 year old male who had liver replacement as treatment for a hemangioendotheliosarcoma. After transplantation, there was a severe rejection crisis. The protracted thrombocytopenia postoperatively is often noted after liver transplantation and is probably due to thrombocyte sequestration in the homograft. ALG — horse antilymphocyte globulin; SGOT — serum glutamic oxalacetic transaminase in international units; and ARROW — 625 milligrams of methyl prednisolone intravenously. (By permission of Surg. Gynec. Obstet. 133:981, 1971).

theliosarcoma. The patient's course is illustrated in Fig. 2. At the time of transplantation he was gravely ill with severe hepatic dysfunction and a serum bilirubin of 40 mgm¹⁰⁰. Following operation there was initial good function of the hepatic homograft. The patient then successfully weathered a bout of severe rejection after which liver function remained satisfactory for approximately 3 months when his condition deteriorated and he died.

At autopsy examination, there were numerous metastases in the lungs and the homograft itself was the seat of large tumor deposits. These various experiences with hepatic malignancies have made us adopt a policy of restricting liver transplantation almost exclusively to patients with benign hepatic disease.

Congenital biliary atresia. Encouraging results have been obtained in this group of patients. Two patients lived at least one year after transplantation, two more survived more than two years and a further patient for 3½ years. His course is illustrated in Fig. 3. Despite a very poor tissue match the patient had only two minor rejection episodes in the early postoperative period. Thereafter, he enjoyed good health and excellent liver function till shortly before his death. A biopsy of the homograft at 914 days showed almost normal liver architecture. Terminally the patient developed a febrile illness which led to massive hepatic necrosis and death. It is not known for certain whether this was caused by a virus infection or was a manifestation of late rejection.

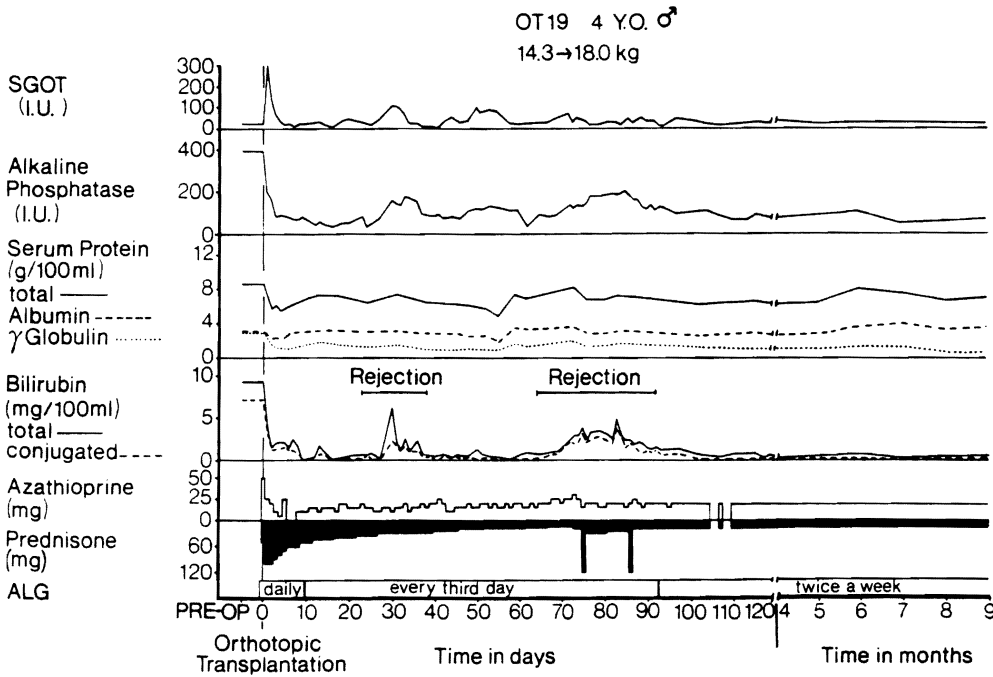


Fig. 3 The early course of a 4 year old child who survived for 3½ years after liver transplantation performed as treatment of congenital biliary atresia. Note the rejection episodes at 1 month and 2½ months, which were easily controlled. (By permission of W. B. Saunders Co., 1969.)

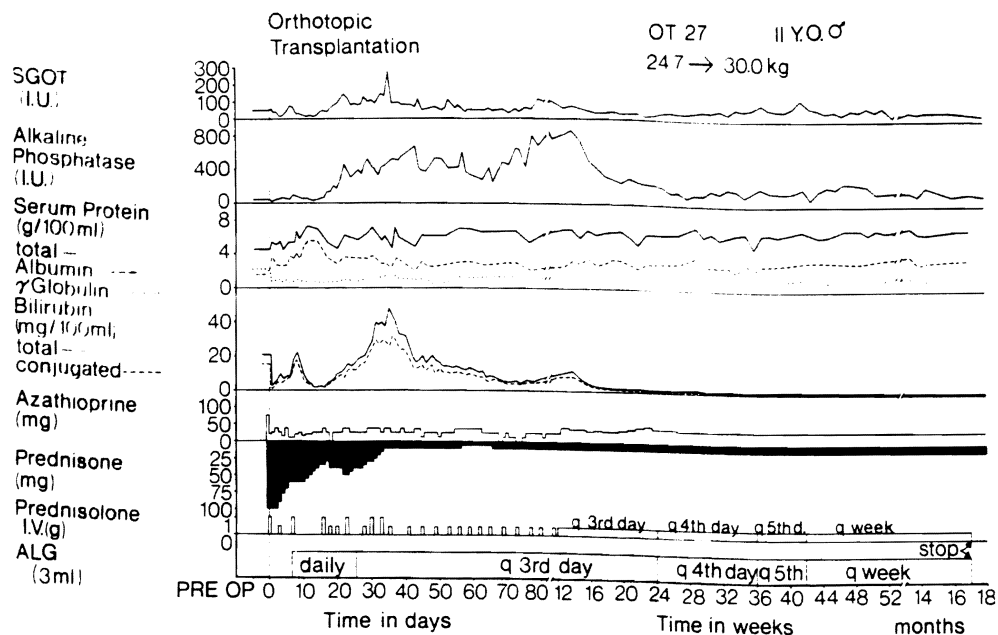


Fig. 4a Postoperative course of an 11 year old recipient of a liver homograft for cirrhosis secondary to *Wilson's disease*. A severe rejection crisis beginning about 3 weeks post-transplantation eventually reversed and hepatic function has been essentially normal since the sixth postoperative month. The patient remains in good health almost 3 years after operation.

Wilson's disease. Our experience with liver transplantation has given us a better understanding of this metabolic disorder. The condition is believed to be caused by an enzyme deficiency which causes disturbed copper metabolism leading to its extensive deposition in the liver, basal ganglia, the corneas (*Kayser-Fleischer rings*) and other tissues. The main clinical manifestations are severe cirrhosis, or neurologic disturbances or both. Experience with liver transplantation suggests that the enzyme deficiency may be compensated for by replacement of the diseased liver with a healthy one and that copper metabolism may be restored to normal. The results in one such patient are illustrated in Fig. 4a. The patient was seriously ill with advanced

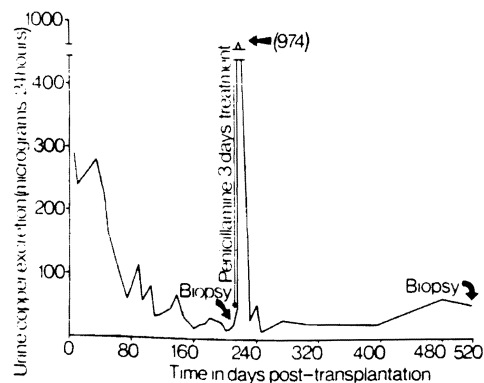


Fig. 4b There was massive urinary excretion of copper following transplantation. This lasted 6 months. A secondary peak of copper excretion occurred in response to a 3-day test course of penicillamine. (By permission of *Lancet* 1:505, 1971).

cirrhosis. After transplantation the homograft underwent the worst rejection crisis that we have ever observed in any of our liver transplant recipients. The bilirubin rose to almost 50 mgm % with associated rises in the alkaline phosphatase. Fortunately, it was possible to reverse the immunologic reaction and the patient has enjoyed virtually normal liver function ever since. He is nearly 3 years post-transplantation and is attending school. Large amounts of copper were passed in the urine for 6 months

after operation (Fig. 4b) and biopsies of the homograft at 6, 18 and 30 months showed a normal copper concentration within the organ.

Similar results were obtained in the case of another boy aged 15 years, who in addition to advanced cirrhosis had severe neurologic symptoms. He is now more than a year post-transplantation. One and a half months after the operation he developed jaundice, and elevations of the SGOT (Fig. 5) and the alkaline phosphatase. Simultan-

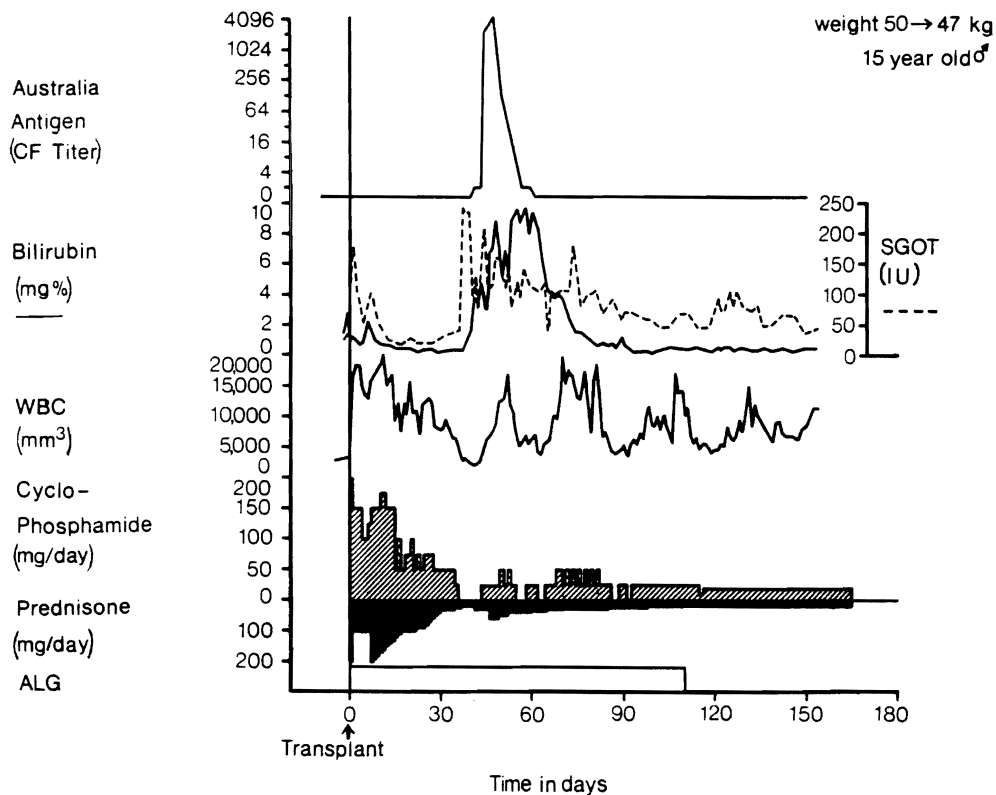


Fig. 5 Triple drug therapy with cyclophosphamide, prednisone and horse antilymphocyte globulin (ALG) in a patient who underwent liver transplantation for *Wilson's disease*. Rejection has never been diagnosed postoperatively. The temporary deterioration in hepatic function in the second postoperative month was accompanied by Australia antigenemia detected by the complement fixation (CF) technique and consequently was thought to be a manifestation of serum hepatitis. (By permission of Surg. Gynec. Obstet. 133:981, 1971).

ously his serum became positive for the Australia antigen. He was diagnosed as having serum hepatitis and immunosuppressive therapy was not increased as would have been the case had rejection been suspected. The abnormal liver chemistries gradually returned to normal and the patient has remained in good health. This case illustrates a vitally important point — that post-operative elevation of the bilirubin and alkaline phosphatase is not synonymous with rejection. In fact, they may also be caused by serum hepatitis as in this case, but ob-

struction of the extrahepatic bile ducts or hepatotoxicity of the immunosuppressive drugs may be responsible as will be discussed later. It is imperative to establish the correct diagnosis as each condition requires a different form of treatment.

Hepatitis. Hepatitis occurs post-transplantation in more than 20% of our renal homograft recipients. As illustrated by the last case it may also occur in hepatic homograft patients who are exposed to many risks including those imposed by the much larger blood transfusions required in liver

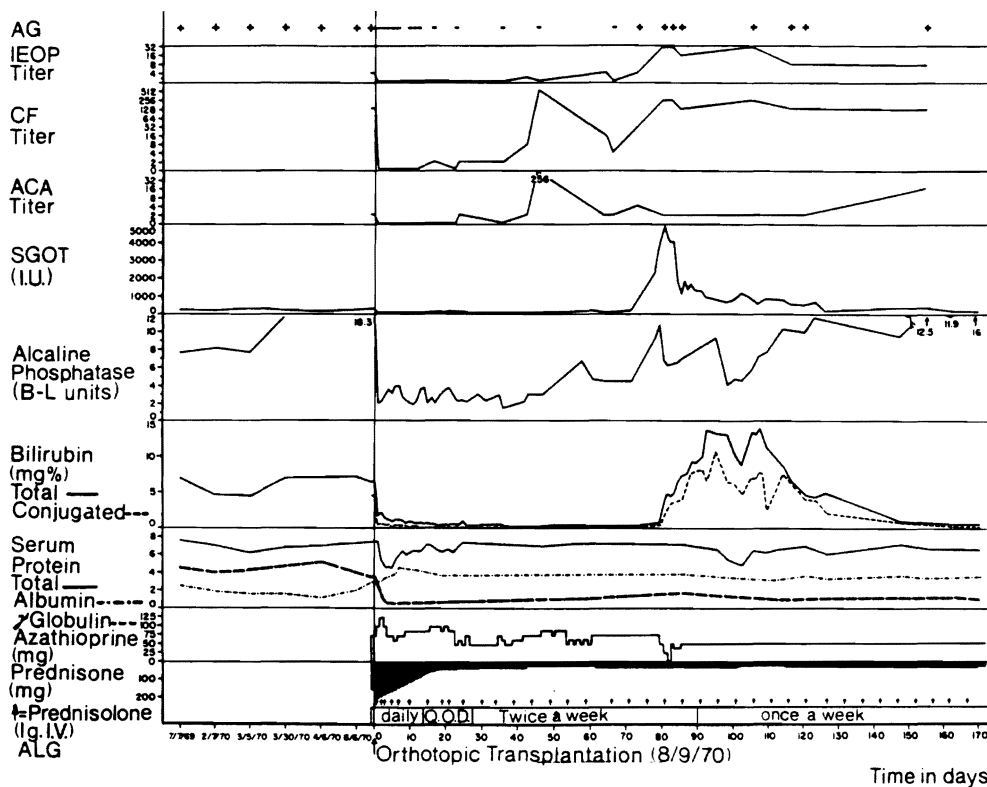


Fig. 6 Orthotopic hepatic transplantation for liver failure caused by chronic aggressive hepatitis. The Australia antigen which had been detectable in multiple serum samples for one year before operation, disappeared within hours after removal of the patient's own liver. However, the Australia antigen reappeared in her blood stream about 2 months post-transplantation at a time when she developed a clinical episode of hepatitis.

replacement. In view of these findings is there any hope of treating lethal serum hepatitis with liver transplantation? In the present state of our knowledge it is not possible to give a definite answer to this question. We have no experience with hepatic replacement in the treatment of acute fulminating hepatitis, although it has been unsuccessfully attempted elsewhere. However, we have performed liver replacement in cases of hepatic failure caused by chronic aggressive hepatitis, Australia antigen positive. Fig. 6 shows the course of a 28 year old woman with this disorder. Her serum had been persistently positive for the Australia antigen for 2 years. At the time of admission to the hospital she was gravely ill with severe ascites, large pleural effusions, a serum albumin of less than 2 gm/100 ml and a prothrombin time of less than 20%. Following transplantation her serum promptly became negative for the Australia antigen and remained so for approximately 2 months when it again became positive. Soon afterwards her liver chemistries became abnormal and it was apparent that she again had hepatitis. Despite slowly deteriorating liver function she was restored to a useful life among her family and friends for 20 months, when she died of a disseminated nocardia infection. At autopsy, there was recurrence of chronic aggressive hepatitis.

Technical problems affecting results. Orthotopic liver transplantation is a difficult procedure as most of the patients have severe portal hypertension. Removal of the recipient's own liver is complicated by the presence of extensive venous collaterals and by coagulation defects. In previous publications we have mentioned problems with anatomic abnormalities, clotting of vascular anastomoses, phrenic nerve palsy and other hazards.

In this report we wish to concentrate on a complication of biliary drainage which we

have encountered in 4 recently treated patients. Our usual technique of biliary reconstruction is by means of a cholecystoduodenostomy after having ligated the common bile duct distal to its junction with the cystic duct (Fig. 7). This area is potentially

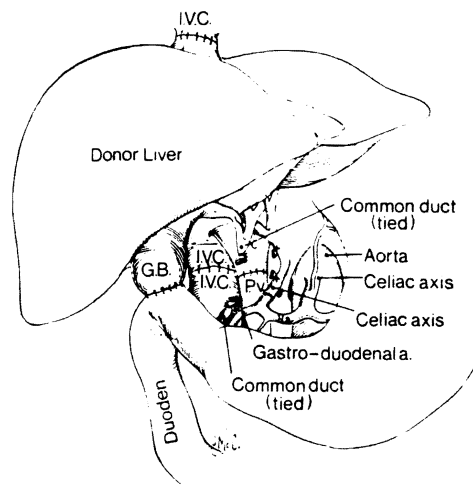


Fig. 7 Orthotopic liver transplantation-cholecystoduodenostomy has been performed for biliary drainage. G. B. = gall bladder; H. A. = hepatic artery; I. V. C. = inferior vena cava; P. V. = portal vein. (By permission of *Ann. Surg.* 168:392, 1968).

vulnerable and may become obstructed with inspissated bile or possibly with cellular debris cast off into the lumen in the course of rejection. In the 4 recent cases mentioned above biliary obstruction developed after an initial period of normal bile drainage. Two of the patients were operated upon in an attempt to relieve the obstruction which was confirmed by operative cholangiography (Fig. 8). However, surgery was undertaken too late and the patients died of hepatic damage caused by the obstruction, complicated by ascending cholangitis. In the other 2 patients the lesion was found at autopsy examination. In each case the epithelial cells

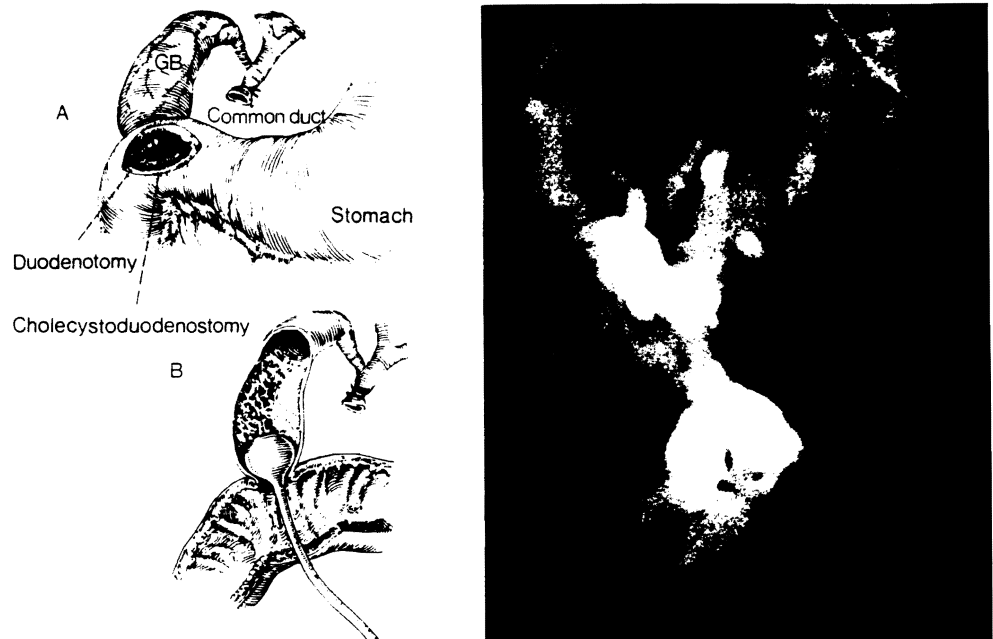


Fig. 8 Cholangiography of a hepatic homograft in which biliary reconstruction was with cholecystoduodenostomy. LEFT — Technique of dye injection through a duodenotomy and the anastomosis. RIGHT — Obstructed duct system. Despite re-exploration and conversion to choledochoduodenostomy, the recipient died of uncontrolled sepsis 46 days after transplantation.

of the bile ducts were swollen and contained large numbers of cytomegalovirus inclusions, which were also present in the large accumulations of intraluminal debris. It appears possible that these obstructions were caused or at least contributed to by cytomegalovirus infection.

In an attempt to avoid this complication choledochoduodenostomy was attempted in 4 subsequent cases using a new method illustrated in Figs. 9a and 9b. However in one case the implanted bile duct retracted out of the duodenum causing a fatal biliary peritonitis. We have since reverted to using cholecystoduodenostomy.

Future Prospects

As experience has accumulated we have learned to avoid many technical pitfalls which we encountered in our early cases. The biliary drainage problems mentioned above have made us adopt a policy of early exploration in any cases of prolonged postoperative jaundice, with cholangiography and, if necessary, biliary reconstruction. If warranted, antiviral therapy with cytosine arabinoside will also be instituted. It is hoped that these measures will improve our long term results.

Another reason for hope that we may improve on our 26% one year survival fig-

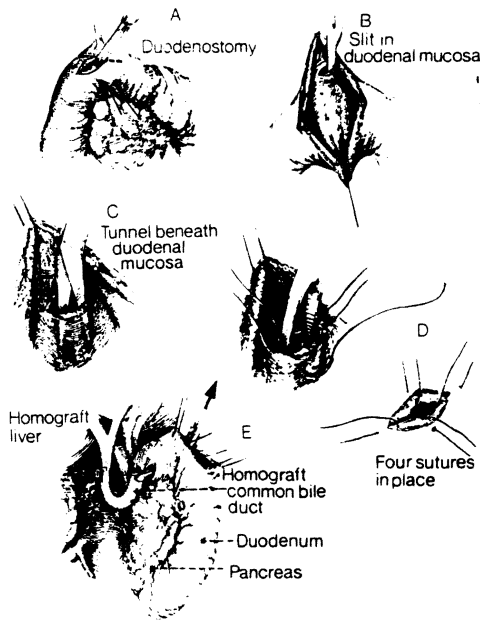


Fig. 9a Technique of choledochoduodenostomy. After opening the duodenum (A), a sub-mucosal tunnel is created (B, C) through which the homograft common bile duct is passed (E).

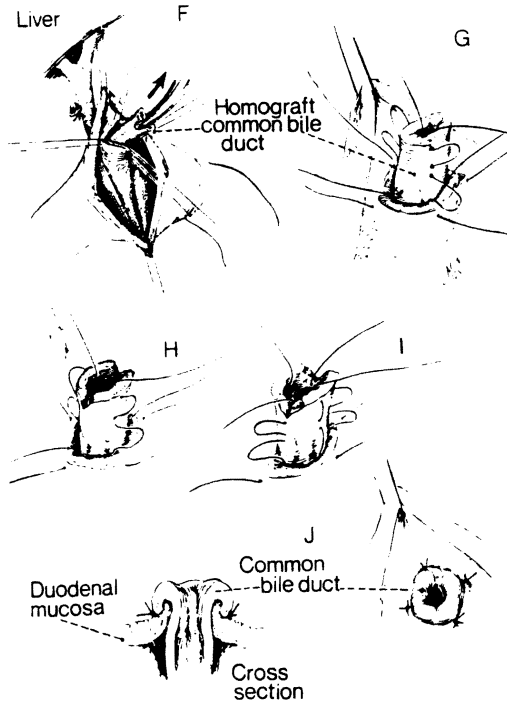


Fig. 9b Choledochoduodenostomy (continued). The homograft bile duct is secured in place with four fine sutures (G, H, I) in such a way as to create an everting nipple (J).

ure hinges on new developments in immunosuppression. Studies in renal homograft recipients during the past 15 months have shown that Imuran can be effectively replaced as an immunosuppressive agent by small doses of cyclophosphamide, which do not appear to be as hepatotoxic. Furthermore, a poorly functioning liver may fail to metabolize Imuran properly. Cyclophosphamide, on the other hand, is given in its metabolically active form and should be effective no matter what the state of hepatic function. In our most recent experience using cyclophosphamide in combination with prednisone and ALG, 4 of 5 liver re-

ipients have done well from 1 to 4 months after operation. If these preliminary encouraging findings are confirmed by further experience we may be on the threshold of a major new advance in liver transplantation.

Summary

The prime indication for liver replacement is advanced benign hepatic disease. A 26% one-year survival rate is currently being achieved. Avoidance of technical pitfalls and improvements in immunosuppressive therapy may result in better long term survival figures.

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