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Surgical Progress

Transplantation of the Liver

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Liver transplantation has had a long gestation period in being accepted as standard therapy. The main reason for this is the formidable operation to which the patient is subjected and because of this, referral of cases tends to be too late. Increasing confidence in the operation should result in earlier surgery. The low incidence of uncontrollable rejection is an encouraging finding which should, in the future, make the results of grafting for nonmalignant parenchymatous liver disease better than those currently obtained with kidney grafts from cadaver donors. The surgery requires a large team of strongly motivated doctors, nurses and technicians, who must have continuing experience with technically successful orthotopic liver grafts in experimental animals.

THE EXPERIMENTAL BACKGROUND for liver grafting in man was established initially by the work of Welch and his colleagues in the 1950's using the extra or accessory heterotopic liver graft as an experimental model.[8,22] Subsequently Moore in Boston[11,12] and Starzl in Denver[16,17] independently developed techniques for orthotopic liver grafting in the dog. The pattern of rejection was documented and it was found that immunosuppressive agents effective in preventing rejection of renal allografts could also prolong survival of experimental liver allografts.[10]

A variety of techniques have been described for transplanting an additional liver but each has disadvantages. The sheer bulk of the liver may be difficult to accommodate in the abdomen and can splint the diaphragm leading to postoperative pneumonitis. Wherever the liver is placed, venous drainage is vulnerable, especially when the hilus faces medially necessitating venous drainage *via* the infrahepatic vena cava. Microvascular techniques may be developed for transplantating small portions of the liver, the main surgical difficulty is the establishment of satisfactory bile drainage. Even if small portions of the liver could be successfully transplanted they would have a nutritional handicap compared with the patient's own liver and would only be expected to be effective if the patient's own liver was very severely damaged. This is a disappointing prognostication since transplanting a small portion of the liver is an attractive approach to provide missing enzymes in patients with otherwise good liver function. For orthotopic liver grafting in the dog and the pig it is necessary to decompress the portal and caval systems by draining blood from the inferior vena cava and portal vein into the superior vena cava during the anhepatic phase. If this is not done, congestion occurs in the bowel and the lower part of the body which can lead to death. In primates, including man, external shunts are not usually necessary, nevertheless this pooling effect still occurs and requires careful management.

In dogs, liver allograft rejection follows a similar pattern to that observed with kidneys but immunosuppressive drugs are relatively more effective. Perivascular round cell infiltration with parenchymal destruction and vasculitis are the salient features of rejection. In pigs such changes are often minimal and may regress spontaneously.[4,6,13] The first successful orthotopic liver

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allograft in man was performed by Starzl in 1963.[18] In the last report of the Transplant Registry published in July 1977, 259 orthotopic liver grafts had been recorded. The Denver series now exceeds 140 cases with a one-year survival rate of approximately 50%, the results being better in children (60%) than in adults (45%) (Starzl, personal communication). The Cambridge/King's College Hospital series is now 76 cases mainly adult patients. Although a number of other centers have performed a few liver transplants, there is no other large series reported and of the 43 heterotopic liver grafts reported to the Transplant Registry, the longest survivor is a patient of Dr. Fortner now four years after operation (Fortner, personal communication). In Denver and in the United Kingdom only orthotopic liver allografts are performed, the liver being placed in the normal position after recipient hepatectomy. I feel this is the best surgical operation and until a more reliable technique of heterotopic grafting is described the orthotopic position will remain the operation of choice. I will confine my remarks in this article to orthotopic grafts.

Clinical liver transplantation, although practised for 15 years is not yet widely accepted as a therapeutic procedure. Errors have been made in all aspects, especially in case selection, diagnosis of rejection and details of surgical technique. In order, the liver follows the heart as far as results are concerned but in one respect liver transplantation is more fortunate. There is a low incidence of uncontrollable rejection in which respect the human seems to resemble the pig more closely than the dog. Many patients have probably been treated excessively with immunosuppressive drugs.

Indications

One of the most difficult aspects of liver grafting is to decide when to offer this treatment to a patient. There are two main categories of disease which require consideration, namely primary malignancy of the liver and parenchymatous disease. In Denver the majority of patients have been children suffering from biliary atresia, the results in this group have been the best. We have been reluctant to offer liver grafting to children because of the uncertain prognosis and the undoubted discomfort associated with investigation and caring for patients, pre- and postoperatively and the unpleasant side effects of immunosuppressive drugs, particularly steroids. A stunted child with Cushing's syndrome and good liver function is a sad result. Fortunately, many of Starzl's patients have not suffered too severely from steroid treatment. No doubt, eventually, better immunosuppressive agents will become available and then our reservations concerning transplanting children will disappear. The oldest of our 76 patients was 65-years-old, the median age was 43. Only five were aged 17 or less. We do not have an upper age limit but assess each patient according to what we feel to be the biological age. Starzl considered 45 to be the upper age limit but we have had good results with patients in their fifties. Metastatic cancer in the liver is not in our opinion an indication for transplantation since the four cases we have treated all developed rapid recurrence of growth. Excluding metastases is difficult in primary malignant disease of the liver. No matter how extensive the screening for secondaries, micrometastases in lymph nodes, bone and lung may be missed. If liver cancer is confined to one lobe then a partial resection is the best treatment. If both lobes are involved or the remaining liver is cirrhotic then liver grafting may be indicated. We have transplanted 12 cases of cholangiocarcinoma and the four who survived more than three months developed recurrent cancer within a year. Starzl (personal communication) has one patient alive more than a year with no evidence of recurrence. Most patients with cholangiocarcinoma involving the major hepatic ducts have had a previous laparotomy with biopsy and manipulation of the duct. It is likely that such procedures cause metastases but one of our patients with a Klatskin tumor had never been interfered with until the liver transplant operation, when a needle biopsy was performed. Nevertheless, he developed metastases a year after grafting. I feel therefore that in these cases palliative intubation as advocated by Terblanche[19,20] is preferable to liver transplantation.

Primary hepatoma in Europe and North America can pursue a relatively slow course even when it is associated with cirrhosis, the behavior being in marked contrast to the rapidly fatal disease which is so common in parts of Asia and Africa.[1,5] It is important to determine that the tumor really is malignant and not a benign hepatoma. Histological features of malignancy are the presence of growth in venules and infiltration of the parenchyma without evidence of capsule formation. Fifty per cent of our cases of primary hepatoma have had raised alphafetoprotein levels in the blood. The disappearance of this protein after grafting is evidence of removal of the disease. Although hepatoma has often recurred, some patients have been free of the disease more than a year after grafting. Our longest survivor died of cholangitis more than five years after operation and there was no evidence of recurrent growth at postmortem examination. In nonmalignant liver disease the timing of transplantation is of the utmost importance. Recurrent coma or bleeding when there is insufficient hepatic function for a shunt procedure and portosystemic encephalopathy after shunting are indications for

liver transplantation. It is hopeless to offer the operation to moribund patients who will not survive surgery. We have found that patients with systemic blood pressure below 100 mmHg prior to surgery usually perish in the perioperative period. Patients with alcoholic cirrhosis are often unsuitable for transplantation due to their unreliable personalities. Australia antigenemia is a serious complication presenting hazards to nursing, surgical staff and other patients. It is not an absolute contraindication to surgery. Three of our patients who were Australia antigen positive were treated by immune gamma globulin during the anhepatic phase and postoperatively. One of these patients is still free from Australia antigen more than two years after operation. The other patients also became Australia antigen negative.

Chronic active hepatitis, primary biliary cirrhosis, idiopathic cirrhosis, cirrhosis secondary to bile duct surgery and alpha$_1$ antitrypsin deficiency may be suitable for transplantation. Chronic sepsis may cause fatal septicemia after liver grafting. Patients with Budd Chiari syndrome who do not respond to conservative treatment have a grave prognosis and liver transplantation can produce excellent results.[15] Acute liver necrosis is not an indication for transplantation, since patients in deep coma have an uncertain prognosis and some will recover completely.

Assessment

It is important to establish that a liver tumor is in fact a primary growth. If the serum alphafetoprotein level is high this is strong evidence of primary hepatoma. Histological interpretation can be difficult. One of the most important features of hepatoma is the formation of bile by the tumor. Scanning with sulpha colloid and selenomethionine may show specific uptake of the hepatoma by selenomethionine. Routine investigation includes chest x-ray, intravenous urography, barium meal, barium enema, sigmoidoscopy, bone scans and angiography of the inferior vena cava, hepatic and superior mesenteric arteries.

In patients with nonmalignant liver disease, the serum albumin and prothrombin levels are important prognostically as are a history of repeated variceal bleeding, recurrent coma or encephalopathic attacks. Descending venacavography is performed in cases of Budd Chiari syndrome and splenoportography or films of the venous phase of mesenteric angiography may be necessary to demonstrate a patent portal vein.

The chief obstacle to good results in liver transplantation is the surgical procedure itself and the early postoperative care. Small errors at any stage are likely to prove fatal.

The Donor

The donor should be a case of "brain death" with an intact circulation maintained on a ventilator, the criteria being the same as those required for kidney transplantation. There must be no infection or systemic malignancy. It is important that the donor liver is not too large for the recipient. We have transplanted a liver from a 3½ year old child into an adult and prefer not to use donors older than 50 years. We have always used donors of a compatible red cell blood group, but although HL-A tissue typing is performed on donor and recipient and cytotoxic antibodies looked for, we do not pay attention to these findings from the point of view of case selection. Experience in Denver has shown it is possible even to transgress red blood cell group rules in liver transplantation and we have transplanted across a positive lymphocytotoxic crossmatch, where the recipient serum killed 100% of donor lymphocytes, without there being evidence of serious rejection in the six months postoperative course. In view of the scarcity of suitable liver donors most donor and recipient matching has been extremely poor and there has been no evidence of a relationship between HL-A matching and results. The liver can survive an immunological handicap that would be expected to result in rapid destruction of a kidney from the same donor. Kidneys are always removed at the same time as the liver. Both kidneys and the liver are skeletonised until only the vascular attachments remain (Fig. 1). The main technical difficulty is to ensure that if there are anomalous arteries, these are preserved (Fig. 2). The gall bladder is mobilized with its main blood supply intact before the liver is removed. Ten thousand units of heparin are given intravenously, Bardec cannulas are inserted into the aorta and inferior vena cava *via* the right common iliac vessels. These cannulas are declamped and a third Bardec cannula is inserted into the portal vein via the superior mesenteric and perfusion of the liver is commenced with 1 l of Hartmann's solution containing heparin 1,000 units/liter at 4° with 1 m of gravity drainage from a drip stand. The kidneys are removed while the *in situ* liver perfusion is in progress and they should therefore suffer no warm ischemic damage. The Hartmann's solution is followed by 400 ml of plasma protein fraction (PPF) solution with additives.* The liver is then removed and transferred to a circular plastic bowl containing ice cold saline and the hepatic artery is perfused with 100 ml of the PPF with additives, *via* a Bardec cannula. The

* To each liter of PPF is added: 2,000 IU of Heparin, 250 mg of Hydrocortisone, 500 mg of Ampicillin, 6 ml of 0.1 N HCl, 5 ml of 10% Magnesium sulphate, 250 mg of dextrose, 15 mEq of Potassium phosphate.

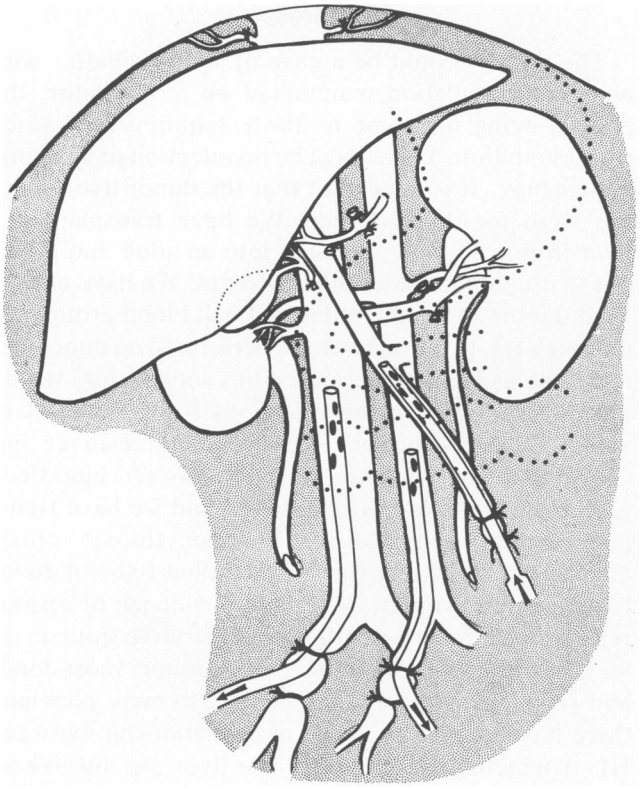

FIG. 1. Diagram of the donor operation showing skeletonisation of the liver and both kidneys. Cannulas have been inserted via the right common iliac vessels and superior mesenteric vein. (Courtesy of Current Problems in Surgery).

liver is then transferred to another bowl containing ice-cold saline and this is inserted into a sterile plastic bag which is inserted into another similar bag. This is then placed in a polystyrene box surrounded by ice cubes. The box is small enough to be transported by plane, helicopter or car.[21]

Thirty livers have been transported from institutions other than our own, to our hospital where the transplant operation has been performed. The period of ischemia has varied between 2–10½ hours. Twenty-eight livers functioned as life-sustaining grafts, two did not have a chance to function because the patients had developed severe hemorrhage before the livers were revascularised. The Denver group have reported similar good results with liver preservation in man using Collins' solution.[2] Six of seven livers functioned after between 6¾–10 hours of preservation. One liver could not be revascularised because of thrombosis in the portal vein.

The experience is now sufficient to demonstrate the advantages of simple preservation, effective for at least ten hours. There can be no mechanical or electrical failure, bacterial contamination is unlikely and the process is straightforward and cheap. These factors argue in favor of ice storage rather than the use of perfusion apparatus.

Recipient Operation

The technique used by Starzl and colleagues has been the basis of all clinical orthotopic liver transplants. Very close collaboration with the anesthetists experienced in the procedure is of great importance. The patient will be ill prior to surgery and the operation causes drastic interference with the cardiovascular system.

In the absence of a severe coagulopathy, a high epidural anaesthetic with light general inhalation anesthesia is preferred. The epidural is continued for 4–5 days postoperatively and allows the patient to breathe deeply and cough normally immediately after operation. Patients with severe coagulation defects cannot be given an epidural anesthetic and the postoperative phase is more difficult to control. When the donor liver has been removed and cooled the timing of the recipient anesthesia and laparotomy is planned so that the liver will be in the operating room shortly after the skin incision has been made. Full intraoperative monitoring of the patient is required and there must be large intravenous lines in tributaries of the superior vena cava. The arterial and central venous pressures, EKG and pulse rate are recorded continuously. The serum potassium, calcium and arterial blood gases and pH are estimated frequently. The incision is shown in Figure 3; the chest is not opened. There may be severe bleeding from thin-walled dilated veins due to the high venous pressure and impaired coagulation. Meticulous suture ligation with small bites of all tissue to be divided

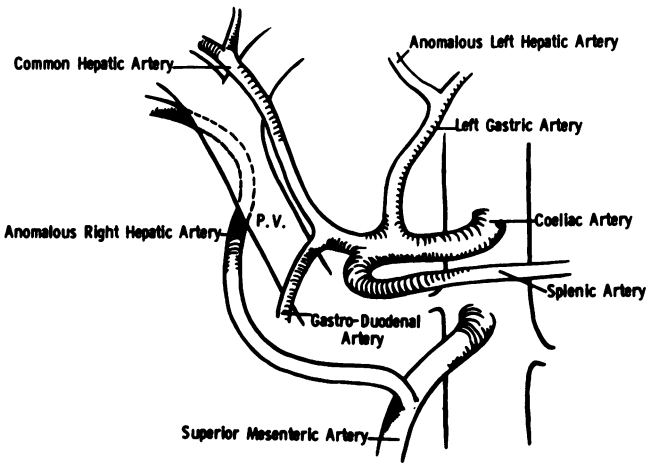

FIG. 2. Diagram to show the main anomalous hepatic arteries, the right hepatic artery coming from the superior mesenteric and passing posterior to the portal vein (17%) and the left hepatic artery coming from the left gastric (23%). (Courtesy of Academic Press (London) Ltd.)

is essential, with minimal reliance on diathermy. The structures in the free edge of the lesser omentum are separated from each other and the common bile duct is ligated and divided as close to the liver as possible. The peritoneal attachments of the liver are divided. Dissection behind the liver is the last part of the operation, since bleeding here is difficult to control before the organ is removed. Trial clamping of the inferior vena cava below the liver is made. This may cut the return of the blood to the heart by 50% and cardiac arrest may occur. If the cardiovascular state remains stable, then the hepatic artery is ligated and divided, the portal vein clamped and divided and the vena cava clamped and divided below and above the liver. It is important that the interval during which the liver is devascularised, but still connected to the venous system *via* the hepatic veins, is as short as possible since manipulation of the ischemia liver can lead to sudden outpouring of potassium ions into the right side of the heart.[3] If trial clamping of the inferior vena cava below the liver results in profound hypotension, further operative procedures are deferred until more blood has been transfused and monitoring reveals a stable state.

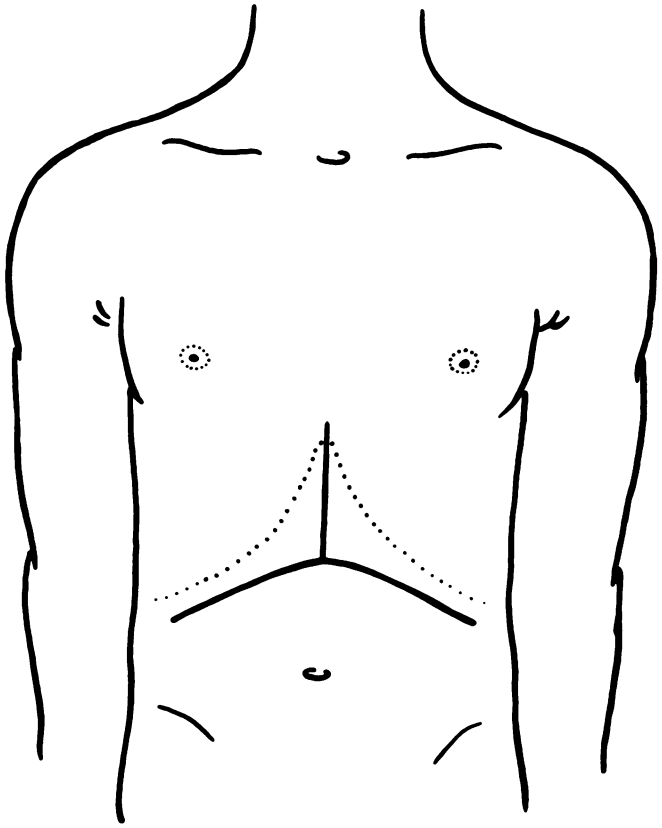

FIG. 3. Diagram of standard incision for most hepatic resections, including transplantation. An extensive subcostal incision with extension up to the xiphoid. (Courtesy of W.B. Saunders Company Ltd.).

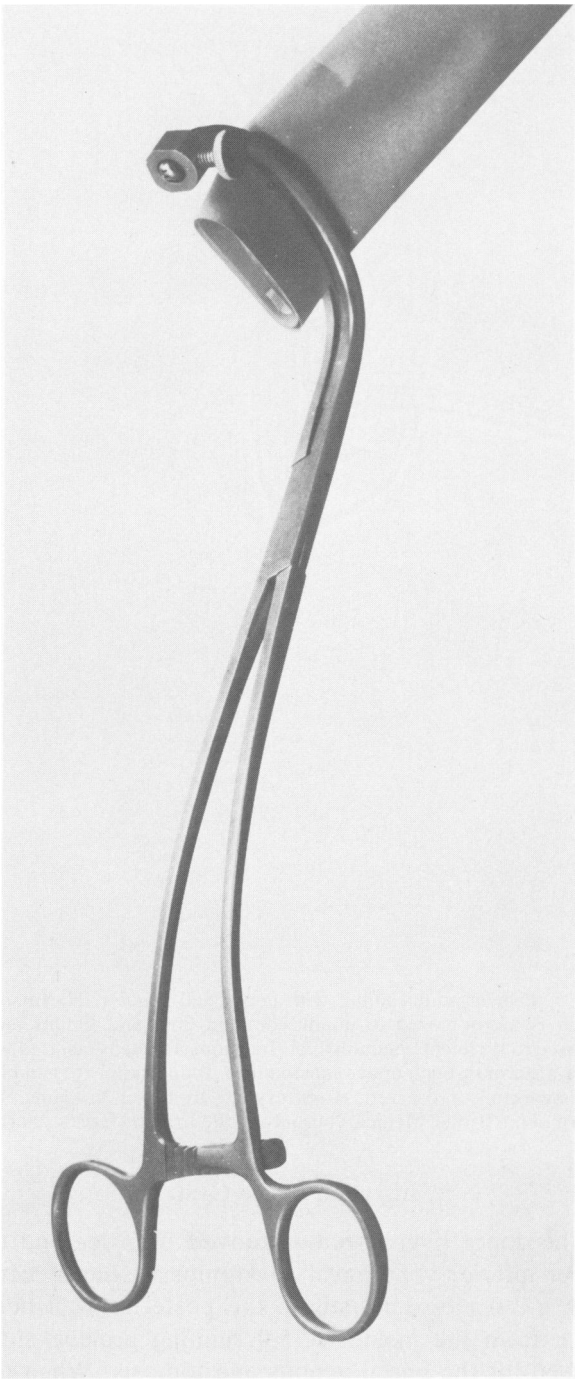

FIG. 4. Clamp for control of suprahepatic vena cava with protective screw clip. (Courtesy of Current Problems in Surgery).

Very rapid infusion of stored blood may aggravate cardiac failure by causing a sudden increase in serum potassium. The circulation should not be overloaded but the central venous pressure must be kept positive to avoid the danger of an air embolus. A special clamp is used for the inferior vena cava above the liver which has a screw clip to prevent loosening (Fig. 4).

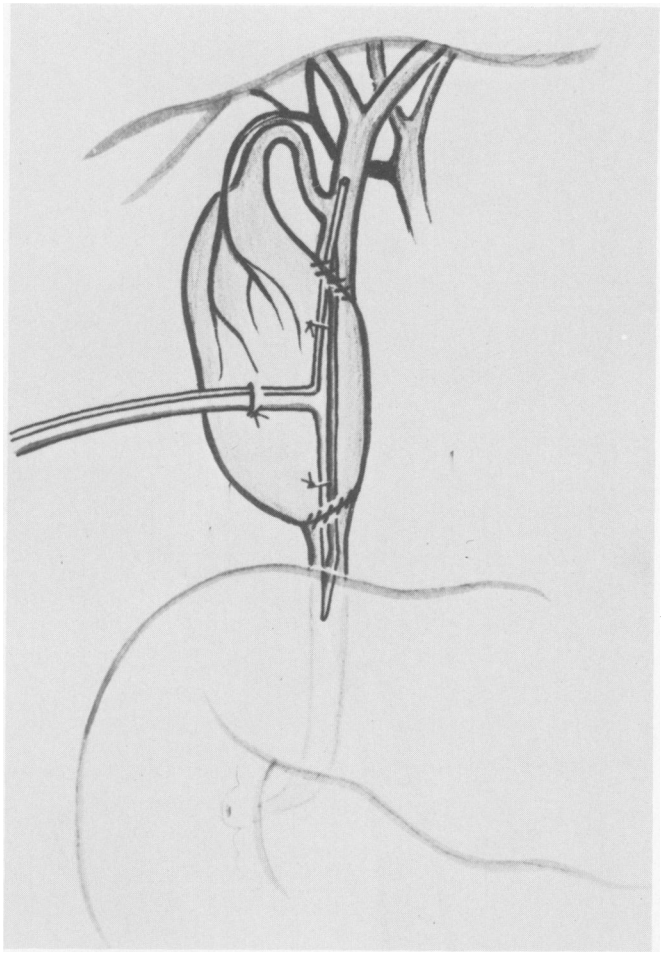

FIG. 5. Pedical graft conduit with donor gall bladder. Hartmann's pouch is anastomosed to donor common duct and fundus anastomosed to recipient common duct. Irrigating T-tube is inserted with irrigating arm through upper anastomosis. Blood supply to gall bladder is carefully preserved. (Courtesy of Dr. Roger Williams, The Editor of the British Medical Journal and the British Medical Journal.

Insertion of the Graft

The donor liver is now removed from ice and the upper inferior vena caval anastomosis is constructed with a 3-0 mersilene stitch, the posterior wall being sewn from the inside. A 5-0 running prolene stitch is used for the portal venous anastomosis. When this is almost completed a Bardec catheter is introduced and the portal vein is infused with 400 ml of PPF at room temperature containing no additives, to wash out potassium and acid metabolites, accumulating as a result of anoxia and from the additives in original cooling solution. The effluent runs out of the vena cava below the liver. The portal venous anastomosis is then completed, the inferior vena cava below the liver is clamped and the portal venous clamp is removed as is the suprahepatic IVC clamp. Intravenous calcium and bicarbonate may be required at this stage. The IVC below the liver is now anastomosed donor to recipient, using a 4-0 running prolene stitch. The recipient hepatic artery is dissected so as to provide access for clamping of the main hepatic artery and gastroduodenal artery. The vessel is cut obliquely and anastomosed with a 6-0 prolene stitch to the trimmed Carrel patch of aorta containing the orifice to the celiac artery. If an anomalous right hepatic artery is present arising from the superior mesenteric, this can be anastomosed to the orifice of the splenic artery of the donor. On release of the clamps from the artery there should be a good blood supply to the gall bladder. The donor common bile duct is trimmed back until it bleeds and is cut obliquely to provide a maximum sized orifice and anastomosis. If it does not bleed the cystic duct is ligated and the common hepatic duct is cut backwards until it bleeds. Incisions are made in the fundus, the body and the Hartmann's pouch area of the gall bladder and using a 4-0 chromic catgut stitch, the Hartmann's pouch incision is anastomosed to the donor common bile duct or common hepatic duct and a special irrigating T-tube is inserted with the irrigating arm threaded into the common hepatic duct. The other guttered arm is threaded through the anastomosis between the fundus of the gall bladder and the obliquely cut recipient common bile duct (Fig. 5). The long limb of the T-tube is brought out through a stab incision below the main wound. A small biopsy is taken from the anterior surface of the left lobe of the liver. The falciform ligaments of donor and recipient are stitched together with interrupted linen stitches. Two large silicone tube drains are brought out from the subdiaphragmatic and subhepatic spaces on each side *via* the extremities of the wound.

Postoperative Care

All the monitoring conducted during the operation is continued postoperatively and the patient's body temperature and urine output are watched. Patients with good lung function can usually be extubated immediately, especially if they have an epidural anaesthetic. Severely ill cirrhotics may require 24 hours of ventilation before the endotracheal tube is removed. The T-tube is irrigated continuously, one litre of Hartmann's solution containing 1,000 units of heparin each 24 hours from a drip stand 1 m high. The effluent is allowed to drain into a sterile collecting bag *via* the second channel of the T-tube. One drain is removed each day from the second day on. In view of the danger of infection during the agonal hours of the donor and the long operative procedure in the recipient we usually give the patients five days of Gentamycin. Repeated cultures are taken from the blood, wound drains, T-tube, urine, mouth, nose and perineum.

Bile Drainage

Most deaths after liver grafting have been due to complications of biliary drainage. Techniques using the gall bladder and cystic duct with anastomosis of the gall bladder to the gastrointestinal tract have the disadvantages of a blind sump of common bile duct below the cystic duct, which may fill up with biliary sludge and the narrow cystic duct which may become blocked. Cholangitis is a hazard because there is no protection from the sphincter of Oddi. Starzl uses 18 inch long Roux loops to lessen the chances of cholangitis.

The most anatomical drainage is a direct duct-to-duct anastomosis. When the ducts are of sufficient length and caliber and there is a good blood supply to the donor duct, this can produce excellent drainage. The anastomosis is splinted by a T-tube, the long arm being brought out through the recipient duct (Fig. 6).

We have used a new technique for the past two and a half years in which the gall bladder acts as a conduit between the donor and recipient ducts without relying on cystic duct drainage. Tension is avoided and as wide an anastomosis as possible can be made. The extrahepatic biliary system is irrigated with heparinized Hartmann's solution, 1 l/day for the first seven to ten postoperative days, and if the cholangiogram is then satisfactory, the T-tube is spigotted but left in place to be removed after three months, if a cholangiogram

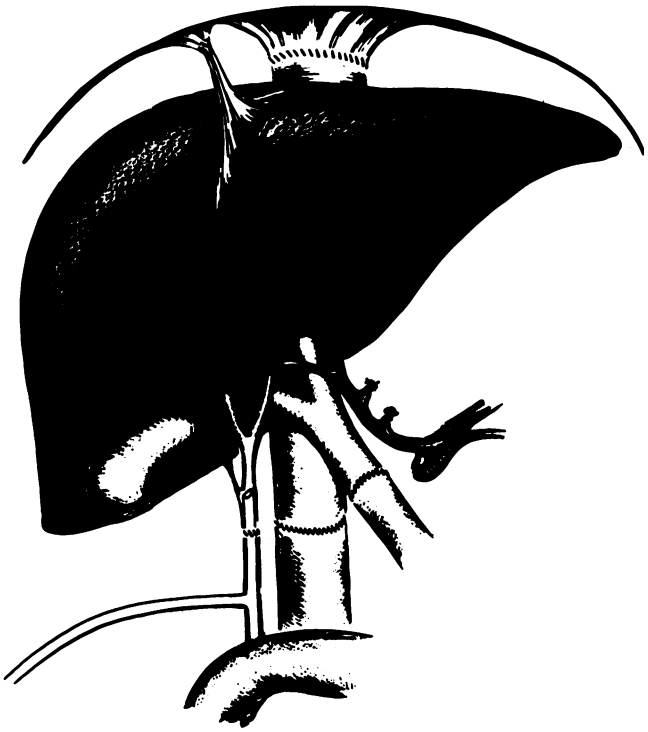

FIG. 6. Diagram of orthotopic liver transplantation with drainage of bile via a choledochodochostomy over a T-tube. (Courtesy of the British Journal of Surgery).

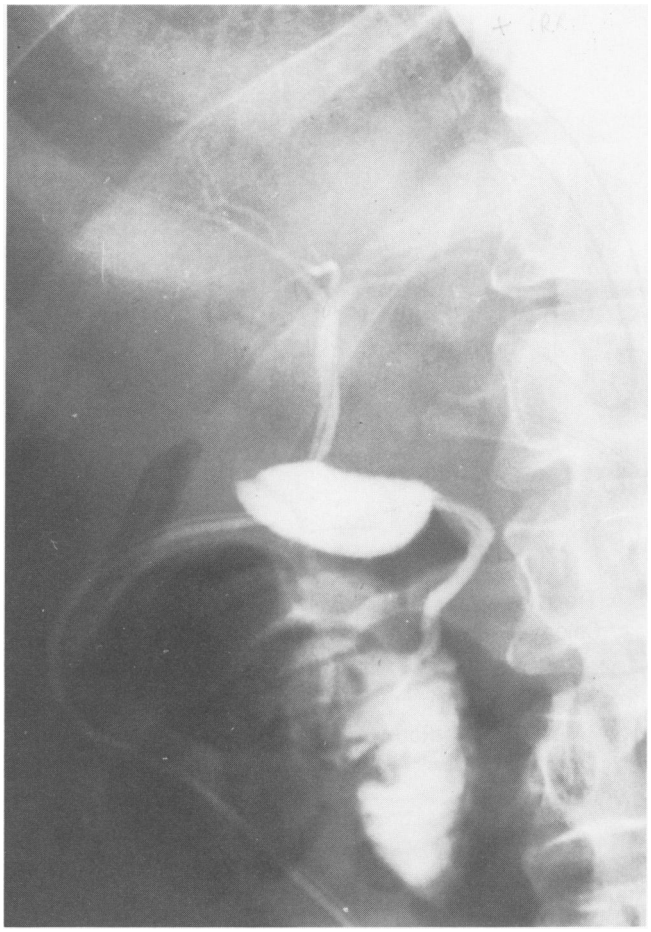

FIG. 7. T-tube cholangiogram of patient with orthotopic allograft with gall bladder used as a pedicle graft conduit. (Courtesy of the British Medical Journal).

is still satisfactory (Fig. 7). If the recipient common duct cannot be used for anastomosis, for example after previous duct surgery, the gall bladder conduit has been used for the upper part of the anastomosis, and the fundus of the gall bladder joined to a long Roux loop (Fig. 8). The new technique has been used in 27 cases, with complications in nine. In seven of these cases further operative procedures were carried out. The presence of the gall bladder allowed access to areas of stenosis or obdurating sludge and good early results were obtained in all cases. One patient lost to follow-up developed recurrent jaundice dying a year after operation. With this one possible exception, the new technique of bile drainage has eliminated the expected fatal complications that caused the death of 15 out of 31 cases where other techniques of biliary drainage were used (Table 1). The common form of biliary sludge secondary to stasis has been encountered where there has been significant stenosis. Another form of sludge described by McMaster et al.[9] seems to be peculiar for liver transplant patients. It consists of an

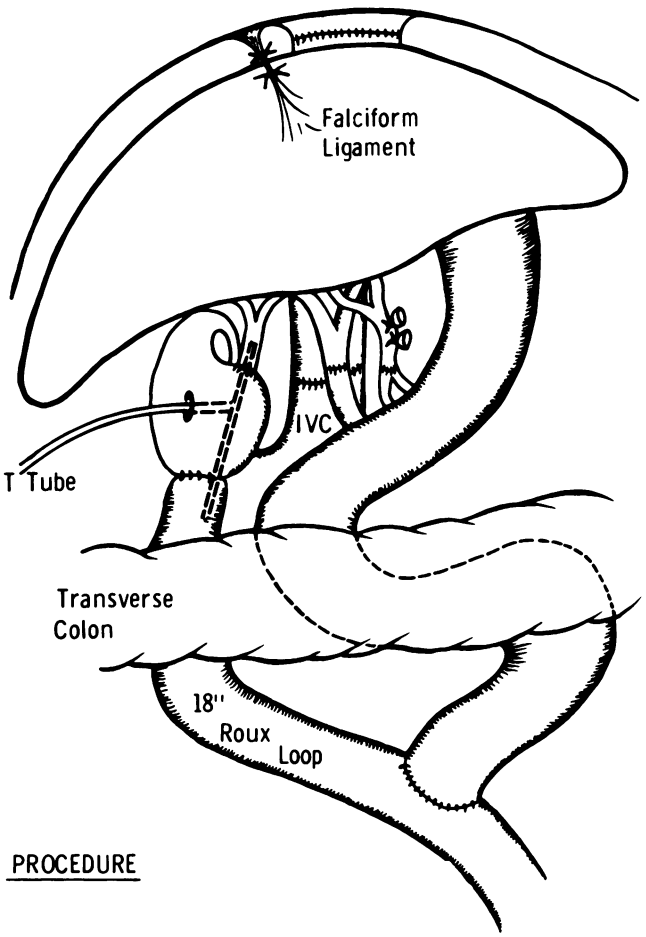

FIG. 8. Diagram of the use of the vascularised gall bladder as a conduit between the donor common duct and a long Roux loop of jejunum in a patient whose own common duct could not be used. Hartmann's pouch is anastomosed to the common bile duct of the donor and the fundus of the gall bladder to the Roux loop. (Courtesy of the World Journal of Surgery).

insoluble sticky conglomerate, composed mainly of collagen, believed to result from ischaemia damage to the walls of the bile ducts. This primary sludge has been less common in the last two years during which time the "brain dead heart-beating donors" have been used.

Immunosuppression

Starting on the day of transplantation, the patient is given three days of Cyclophosphmiade at 2 mg/kg and hydrocortisone 500 units intravenously. On the fourth day the Cyclophosphamide is changed to Azathioprine 2 mg/kg and the hydrocortisone to prednisolone 50 mg/day. The dose of the Prednisolone is gradually reduced and may be omitted after some weeks. This is in marked contrast to the recipients of cadaver kidney transplants in whom the steroid dosage has to be continued indefinitely. The Denver patients also receive antilymphocyte globulin. There has been a tendency for patients with liver grafts to receive unnecessarily large doses of immunosuppressive agents and this has undoubtedly lead to serious infective complications. Rejection is very difficult to diagnose and needle biopsies are not easy to interpret. If liver function deteriorates, with a normal T-tube cholangiogram and a positive leucocyte migration test,[7] then rejection is the presumed diagnosis and high doses of steroids are given with a regime similar to that used in kidney transplant patients, that is 200 mg/day Prednisolone for three days, falling by 25 mg every two days.

Rejection was the cause of death in under 10% of the Denver cases[14] and in only four of our patients. This is a much lower incidence than that observed in kidney grafts. A feature in three of our cases was predominant destruction of small bile ducts, the appearances resembling primary biliary cirrhosis. It is possible that biliary epithelium within the liver is especially vulnerable to rejection in man. Clinically these patients developed progressive cholestatic jaundice with good parenchymal function until just before death, when liver failure occurred.

TABLE 1. *Primary Causes of Death and Other Serious Complications in 74 Cases*

Deaths in first postoperative week		14
Hemorrhage	8	
Cardiac arrest	2	
Septicemia	2	
Pneumonia	1	
Acute rejection	1	
Deaths from complications of biliary drainage		15
Deaths from recurrent tumor		14
Deaths from sepsis in the presence of satisfactory biliary drainage		10
Deaths from chronic rejection		3
Other causes of death		6
Thrombosis of IVC and portal vein	2	
Hepatic artery thrombosis	1	
Spontaneous colonic perforation	1	
Myocardial infarction	1	
Lost to follow-up ? cause of death, after 1 year	1	
	Total	62
Other Serious Complications		
Reticulum cell sarcoma	In patient dying after 6 months from sepsis	
Operative cardiac arrest successfully resuscitated	In patient surviving more than 3 years	
Development of adenocarcinoma of rectum	In patient dying after one year from recurrent cholangiocarcinoma	

TABLE 2. *Seventy-four Orthotopic Liver Allografts*

Year	Deaths					Alive
	No. of Cases	First Week	First Week to 6 Months	6 Months to 1 Year	More Than 1 Year	
1968–1974	35	11	19	2	2 (5.3 yr) (2.1 yr)	1 (3.10 yr)
1975–1977	39	3	15	6	4 (1 yr+)	11 (1: 2 yr) (4: 1 yr+) (5: 5–10 mths) (1: 1 week)
Total	74	14	34	8	6	12

Results

The overall survival of our 74 cases at the end of 1977 is shown in Table 2. Between 1968 and 1978 there were 11 deaths during the first postoperative week, out of 35 cases. Of the 39 cases grafted between 1975 and 1977 there were three deaths in the first week.

We have recently transplanted more patients with nonmalignant cirrhotic disease, as shown in Table 3, the perioperative deaths have been confined to these cases who are more serious operative risks. The preoperative blood pressure seems to be of importance prognostically. A systolic pressure below 100 mmHg is thought to be due to impaired myocardial function resulting from the chronic liver disease. In such cases a relentless fall in pressure tends to occur following anesthesia, leading to poor perfusion and cardiac arrest. We have no satisfactory form of management for such ill patients and the only reasonable policy is to select the patients earlier and operate on them before they pass into a moribund state. The decrease in perioperative mortality since 1975 is thought to be due to increasing experience of both anesthetists and surgeons and the transferring of preserved livers which has increased the pool of potential donors and permitted transplantation of patients at an earlier stage in their diseases.

Many patients with cancer have received palliation from liver grafting and some patients appear to have been cured. Our longest survivor lived 5¼ years, dying of biliary tract infection, secondary to biliary calculi. There was no evidence of recurrent growth at autopsy. Our longest current survivor is four years after operation with no evidence of hepatoma recurrence. When the operative procedure has been satisfactory, recovery from operation has often been rapid, patients being discharged from hospital three to four weeks after surgery and returning to normal life shortly thereafter.

In a review of 103 patients transplanted in Denver[14] more than a year previously, 29% survived a year or more and the mortality rate fell markedly in patients surviving beyond the first year, half the one-year surviving patients being currently alive more than two after operation, eight more than three years and four more than five years. The longest survivor is more than 7½ years with normal liver function, living at home and attending school. One patient has had a normal pregnancy after liver graft, giving birth to a healthy child (Starzl personal communication). In our series, 12 patients lived more than a year and currently 14 are alive with good liver function.

In patients with primary malignancy of the liver, liver transplantation is analagous to major resectional surgery in patients with cancer of the lung, stomach or colon. Palliation is hoped for and sometimes patients are cured. In the future parenchymatous liver disease rather than malignancy will probably be the main indication for liver transplantation.

Acknowledgments

Much of the material in this chapter results from the experience of the combined Cambridge/King's College Hospital, London series

TABLE 3. *Indications for Orthotopic Liver Transplantation in 74 Patients Treated Between May 2, 1968 and December 31, 1977*

Diagnosis	No. of Cases	
Primary malignancy of liver		36
Hepatocellular carcinoma	22	
Cholangiocarcinoma	12	
Kupffer cell sarcoma	1	
Hemangioendothelioma	1	
Hepatic metastases		4
Cirrhosis		30
Cryptogenic	9	
Primary biliary	7	
Alcoholic	4	
Posthepatitic	3	
Secondary biliary	3	
Subacute hepatic necrosis	1	
Alpha$_1$ antitrypsin deficiency	1	
Hemochromatosis	1	
Galactosaemia	1	
Budd-Chiari Syndrome		2
Extrahepatic biliary atresia		2

of orthotopic liver transplants. I am indebted to my many colleagues in both hospital concerned in this programme, particularly Dr. Roger Williams. I thank the Department of Medical Illustration, Addenbrooke's Hospital for their help with the illustrations.

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