Liver Transplantation In The Adult

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SELECTION OF PATIENTS AND PRE TRANSPLANT EVALUATION

Transplantation should be considered whenever a patient with a progressive or otherwise fatal liver disorder is no longer able to live a reasonable existence but is still well enough to withstand the considerable trauma **of** the surgery involved. In practice, the decisions as to which patients should be treated in this way and when, can be very difficult. Included in the Cambridge/King's College Hospital series as in most transplant programmes is almost every type **of** end-stage liver disease (Table). When transplantation is carried out above the age of **40,** cardio-pulmonary complications become increasingly frequent, although we have successfully transplanted a **63**-year old woman with a primary cholangiocarcinoma. The risks are considerably greater if the patient has had upper abdominal surgery previously, which greatly increases the hazard of dissection and the likely blood loss.

The pure nutrition and wasting of patients with chronic parenchymatous liver disease is a major adverse factor. Body defences against infection are known to be reduced in such patients and every effort must be made to eradicate infections preoperatively before exposure to the added risks of immunosuppression. Abnormalities in cardiac and respiratory function are also common in long-standing cirrhosis, and those with major limitations will need to be excluded. Of major importance is the coagulation disturbance. In an analysis from Starzl's group **(1)** of **70** adults with end stage liver,disease intra-operative blood usage was shown to be closely correlated to the severity of coagulation abnormality present pre-operatively. Blood usage and survival, perhaps not surprisingly, were inversely related, this correlation being largely dependent on the number of deaths directly related to massive operative bleeding.

SPECIFIC DISEASES AND RISK OF DISEASE RECURRENCE

1. Malignant Tumours of the Liver. All the published experienced points to a significant risk of tumour recurrence in these patients. Of the **55** patients grafted in the Cambridge/King's College Hospital series to August **1, 1985,** tumour recurrence was detected during life or at autopsy in **19** patients. Of the remaining **36, 14** are currently alive and well, five at more than **2** years after the transplant.

Certain tumours are no longer considered suitable for liver grafting, namely carcinoma arising from the hepatic ducts (Klatskin tumour) and hepatic metastases even when the primary growth has been removed years previously. Nevertheless, the younger patient with a relatively slow growing primary hepatocellular carcinoma, a-fetoprotein negative and without underlying liver disease, can be a very suitable candidate. The general condition of such patients is usually good and recovery from the operation is rapid. The fibrolamellär variant, which tends to metastasize late, is thought to ba a particularly favourable type. The long-standing cirrhotic in whom hepatoma development has been recognised

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at an early pre-symptomatic stage by ultrasound or a-fetoprotein screening is also beginning to figure more prominently in transplant series.

Despite the variety of methods now available for the detection of extrahepatic spread prior to transplantation including thoracic and abdominal CAT scan, abdominal lymphangiography and radio-isotope bone scan, small tumour deposits may still not be detected. Indeed, in the study of Mittal et al (2) where the accuracy of pre-operative CAT scan was compared with gross pathological examination of the resected specimen, between 20 and 47% of the various patient groups had tumour nodules evident macroscopially that were not apparent on the scan. For this reason in our programme a final search by mini-laparatomy is now carried out routinely before the decision is taken to go ahead with a liver graft.

2. Cirrhosis and Other Chronic Disorders. Most of the patients within this general category have had end stage cirrhosis from chronic active hepatitis, cirrhosis of the crytogenic variety or biliary cirrhosis, either primary or secondary to sclerosing cholangitis (Table). In the latter patients, the relief of pruritus and of the deep jaundice and pigmentation following transplantation is remarkable. Patients with chronic encephalopathy in association with a large spontaneous or surgically-induced (shunt) collateral circulation and inactive liver disease, who are poorly controlled by dietary restriction and lactulose therapy, represent a small group of patients who can also show a dramatic response to successful transplantation. The procedure should also be considered for the cirrhotic patient with recurrent variceal haemorrhage in whom all other measures have been tried.

Selecting the optimum time for grafting in patients with cirrhosis will be dependent on both clinical and biochemical criteria. Assessment of likely prognosis without a transplant is less difficult for the patient with primary biliary cirrhosis. Here it has been shown that once the serum bilirubin has exceeded 100 umol/L the prognosis is less than 2 years and a prognostic index based on 6 independent variables, and which can be calculated at the bedside, has also been developed (3).

A mild recurrence of PBC has been observed in several patients who have survived for three or more years after liver grafting (4). Althougn Fennel et al (5) on the basis of material available from Starzl's series, have suggested that such changes in liver histology are the consequence of a continuing rejection process, they are in our experience quite distinct. In auto-immune chronic active hepatitis, where, as in PBC, immune mechanisms play a major

Table - I

Orthotopic Liver Transplantation: Cambridge/ King's College Hospital Series (May, 1968-August 1,1985)

	No. of Patients
Malignant disease	
Primary liver tumor	59
Hepatocellular carcinoma	44
Intrahepatic cholangiocarcinoma	11
Sarcoma	4
Carcinoma of the hepatic ducts	8
Hepatic metastases	6
Nonmalignant disease	
Cirrhosis	111
Primary biliary cirrhosis	41
Chronic active hepatitis	25
Cryptogenic cirrhosis	17
Alcoholic	6
Sclerosing cholangitis	7
Secondary biliary cirrhosis	3
Galactosemia	1
a, -Antitrypsin deficiency	6
Wilson's disease	4
Primary hyperoxoluria	1
Budd-Chiari syndrome	13
Subacute hepatic necrosis	3
Fulminant hepatic failure	1
Biliary atresia	13
Neonatal hepatitis	2
Total	216

role in pathogenesis, recurrence of the disease might also be anticipated and we have recently reported this in a 21 year olr woman who had a transplant (6).

HBsAg positive patients, if active viral replication (HBe antigen positive) is continuing, sholud not be transplanted owing to the risk of reinfection of the donor liver by hepatitis B virus. Although the use of high titre immunoglobulin at the time of surgery was effective in clearing the circulation of HBsAg in four patients in our series, testing of stored sera from these patients subsequently revealed that all were HBeAb positive.

The proportion of patients with alcoholic cirrhosis who will constitute suitable candidates for transplantation is likely to be small. Not only is there the risk of a return to previous drinking habits but the heavy use of alcohol is associated with cardiac and cerebral impairment which, in addition to malnutrition, will add to the hazards of the operation.

In severe instances of Budd-Chiari syndrome, transplantation probably carries less risk overall than a side to side shunt and furthermore offers

the chance of a complete cure. Experience with such cases has shown the necessity to maintain the patients on long-term anticoagulation following the transplant otherwise thrombosis of the main portal vein (and hepatic veins less frequently) may occur. There may well be a primary coagulation abnormality in these patients. The longest survivor in our series is now over eight years and the actual one-year survival for the whole group of 10 patients is 50%.

3. Inborn Errors of Metabolism: Grafting may be curative in a number of these congenital disorders where the primary defect not only resides in the host liver but leads to irreversible damage to that organ. These include *tti* -antitrypsin deficiency (and following transplantation, the *ai* -antitrypsin phenotype changes to the donor type), some glycogen storage disorders and galactosaemia. Another is Wilson's disease. Not only the chronic disease with disabling neurological and/or hepatic disorder but also the fulminant variety which carries a very high mortality, can be treated in this way with restoration to normal of the disordered copper metabolism. A number of inherited metabolic diseases, in which the liver though involved in the defect is not the major organ affected have also been transplanted, as in a recent patient with familiay hypercholesterolaemia treated by combined heart and liver grafting (7).

Sufficient low-density lipoprotein receptors were present in the normal donor liver to restore lipid metabolism to normal. The grafting of a normal liver together with a kidney in a recent patient of the Cambridge/KCH series with renal failure from primary hyperoxaluria, was shown to correct abnormal oxolate pools (8).

4. Severe Hepatic Failure. There are many difficulties surrounding transplantation for sub-acute or fulminant hepatic failure (9).

These patients usually deteriorate very rapidly and the donor organ has to be available during the short time when it is apparent that all other treatment measures are failing and yet the patient is still "well" enough for surgery. However over the pasi 12 months it has been possible to transplant four such patients and three of them are alive and well. Despite the very considerable prolongation of prothrombin time (up to 60 seconds) at the time of surgery, bleeding was not a major problem and the operations on these patients went surprisingly smoothly. Starzl has had experience of such patients with deep coma not recovering consciousness and succumbing to brain death after transplantation although the liver functioned satisfactorily. If there is any evidence of cerebral oedema then the chances of this must be greater. In a recent report from Wall in Canada mention is made of two patients with Grade 4 coma from fulminant hepatic failure and in both instances consciousness was regained (10). Interestingly, one of them developed a hepatic illness on the 7th day after transplantation, thought to be a recurrence of the non-A, non-B infection which was the original cause of the patient's illness.

THE DONOR HEPATECTOMY

Introduction

There is no means of assessing the viability or functional ability of an organ for transplantation once that organ has been removed from its donor. It is therefore mandatory that life-supporting organs such as the heart and the liver are in the best possible condition when removed from the organ donor. This in turn implies that organ removal must be carried out under optimal conditions. Suitable organ donors are usually individuals who have sustained severe and irreversible brain stem destruction and have been certified brain dead. These donors are the victims of spontaneous intra-cranial haemorrhage or severe head injury. In such cases, it is advantageous to maintain full ventilation and circulatory support of the donor throughout the surgical dissection and preparation of the organs which are to be removed. Mechanical ventilation and circulatory support may then be withdrawn just prior to organ removal.

Donor Selection

The criteria for a liver donor are as follows:

Age - 1-55 years
No prolonged hypotension
No systemic infection
No history of cancer
Hepatitis B antigen negative
A B O compatibility with the potential recipient
No history of chronic liver disease or alcohol abuse
Normal liver function tests
A gall bladder should be present.

Size — Infants require grafts which are well matched for size.

Gross appearance of the potential liver graft should be normal at laparatomy.

The Donor Operation

At least the liver and both kidneys will be mobilised and removed for transplantation. Frequently there is also interest in the pancreas and the heart or heart and lungs. For this lengthy and important procedure, the services of an anaesthetist are a great advantage but, where no such facility is available, supervision of the donor pretreatment and

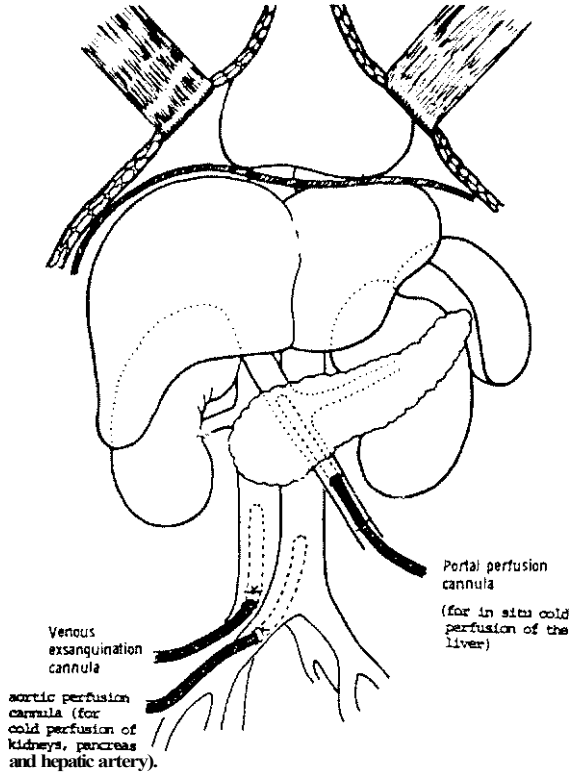

Fig. **1. Completed abdominal disssection of donor.**

important procedure, the services of an anaesthetist are a great advantage but, where no such facility is available, supervision of the donor pretreatment and preoperative management with intravenous fluid support and cardiovascular monitoring, may be accomplished by a House Officer, nurse or theatre technician. Immediately prior to surgery, broad spectrum antibiotics are given intravenously. Our current regimen is Gentamicin 120 mgs, Cefoxitin 2 grams, and benzyl-penicillin 2 mega-units. A neuromuscular blocking agent is necessary to prevent reflex contraction of the abdominal wall muscles when the first incision is made. A slow infusion of Mannitol (50 grams) is started to assist diuresis throughout the operative procedure. Extensive dissection is involved in mobilisation of the liver and both kidneys and intravenous fluid replacement is necessary to cover blood and urine losses. Cross-matched blood is the ideal replacement fluid but where this is not available, colloidal plasma expanders such as plasma protein fraction or haemaccel (Hoechst) supplemented with normal saline, are usually adequate to maintain both blood pressure and a diuresis.

The most suitable incision for multiple organ donation is a long mid-line incision from the jugular notch to the symphasis pubis. In the extremely large donor, lateral extensions of this incision below the costal margins can be made. The median sternotomy facilitates dissection of the retrohepatic vena cava and the bare area of the liver by allowing easier access. It also saves time later if the heart is to be removed.

After a thorough laparatomy to exclude any unsuspected disease, attention is first turned to the liver. The structures in the free edge of the lesser omentum are dissected from each other and the common bile duct is ligated and divided at the upper border of the duodenum. The portal vein and hepatic artery are controlled with rubber slings. The common hepatic artery is then dissected back to the aorta, ligating all non-hepatic branches. Care must be taken to preserve all accessory hepatic arteries where present as any part of the liver graft deprived of its arterial supply, will undergo patchy infarction. The incidence of accessory hepatic arteries is high. 23% of individuals have an accessory left hepatic artery arising from the left gastric artery, and 17% have an accessory right hepatic artery arising from the superior mesenteric artery and passing to the porta hepatis posterior to the portal vein (11). The falciform ligament and the left triangular ligament are next divided. The bare area of the liver is then dissected from the diaphragm and the inferior vena cava is defined above, behind and below the liver where it is controlled with a tape. Three phrenic veins are suture ligated where they enter the suprahepatic vena cava. The right adrenal vein is ligated and divided thus completely freeing the retrohepatic vena cava from the posterior abdominal wall. With the liver now fully mobilised and attached by its vascular connections only, attention is turned to the kidneys which are similarly dissected, taking great care to identify and preserve aberrant arteries. When all the required intra-abdominal viscera are fully mobilised 15,000 units of Heparin are given intravenously and cannulae are placed in the lower abdominal aorta, the inferior vena cava below the level of the renal veins and the portal vein via the superior mesenteric vein (Figure 1). tit this point ventilatory support is withdrawn and the cold "in situ" perfusion of the abdominal viscera is commenced. The liver is perfused via the portal vein with one litre of ice cold Ringer's lactate solution followed by 400 mis of purified protein fraction. Cold perfusion of the kidneys proceeds using ice cold Marshall's hypertonic citrate solution which is infused into the aorta with a total volume of 2-3 litres (12). Exsanguination of the donor is important to ensure good cold perfusion and this takes place via the cannula placed in the inferior vena cava.

When in situ perfusion is complete, the viscera

will be pale and palpably cold. Each organ is then carefully removed and placed in a bowl of ice cold normal saline. Both kidneys are then packed away in sterile plastic begs and placed in boxes loosely surrounded by ice. Some bench work is required on the liver before it too is packed away in ice. The donor gall bladder is mobilised from its bed, starting at the fundus, and being careful to preserve the cystic artery. The gall bladder is then fenestrated in three places and thoroughly washed out with cold PPF as bile has been shown to cause mucosal necrosis of the biliary tract if left in contact with it during the cold storage period (13). Hartmann's pouch of the gall bladder is then anastomosed to the common bile duct. This anastomosis is splinted with one limb of a T tube. On reimplantation into the recipient the fundus of the gall bladder is anastomosed to the recipient common bile duct, thus using the donor gall bladder as an interposition conduit (Fig. 2) (14). Finally the liver is packed away in ice for transport tc the recipient hospital. Using the empirical method of liver preservation, grafts have been successfully stored for up to ten hours.

The key to successful management of the liver donor is flexibility. When removing organs at another transplant centre, the renal transplant surgeon at that centre may wish to remove the kidneys before dissection of the liver beings. This is perfectly reasonable but problems may arise when the kidneys have multiple arteries necessitating removal of large Carrel patches of aorta. Furthermore the "en bloc" technique of kidney removal favoured by some surgeons may put at risk the arterial supply to the liver if a large accessory right hepatic artery should arise from the superior mesenteric artery. Such potential problems are easily overcome by prior riscussion. If the donor's blood pressure cannot be adequately maintained by infusion of fluids alone during the extensive dissection involved when mobilising the liver and kidneys, a Dopamine infusion of 2-20 micrograms/kg/minute may be helpful but doses above 25 micrograms/kg/minute are likely to reduce organ perfusion and thus cause ischaemic damage. Similarly the use of adrenaline, noradrenaline and isoprenaline infusions are counter-productive as blood pressure is maintained at the expense of kidney and liver perfusion. In the extremely rare case when fluid replacement and pharmacological support fails to maintain donor circulation and blood pressure, heparin should be given immediately and cannulae placed as previously described so that cold in situ perfusion of the abdominal viscera can be started without delay. Dissection of the organs is then continued during the "in situ" perfusion and cooling. Finally it should be stressed that successful organ procurement is not simply a well co-ordinated surgical exercise, but is only made possible by the good will and cooperation

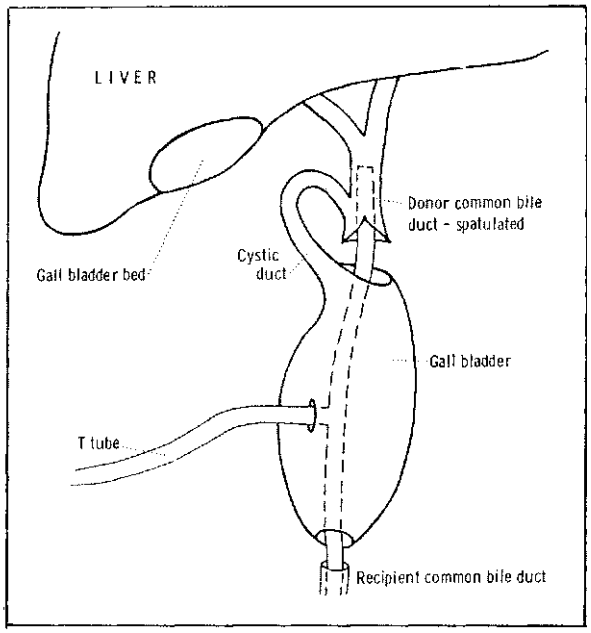

Fig. 2. Construction of the gallbladder conduit. Reproduced by kind permission of Grune and Stratton, Inc., from Liver Transplantation, R.Y. Calne, editor, 1983.

of patients, relatives, nurses and doctors who may be quite remote from the field of organ transplantation.

THE RECIPIENT OPERATION

We have not been able to predict blood loss before surgery. The operation may be completed with a need for only four to six units of blood, but occasionally more than 50 units may be required, especially for those who have had previous upper abdominal surgery and have portal hypertension and impaired clotting factors. An attempt is made to suture ligate every piece of tissue that is cut, even subcutaneous tissue and all adhesions to the liver. In some places it is difficult to suture ligate potential bleeding areas and we have found the infrared coagulator helpful in providing haemostasis. Conventional diathermy is also used. Positive venous pressure is maintained by the anaesthetist so that any breech of the venous system will not result in an air embolus, but rather in bleeding. The peritoneal attachments of the liver are divided *nd the first vessel to be isolated is the inferior vena cava below the liver which is trial clamped. If this causes embarrassment of the circulation, a right groin incision is made and the saphenous vein and superficial femoral arteries are cannulated for bypass. If trial clamping of the vena cava is well tolerated the operation proceeds without bypass.

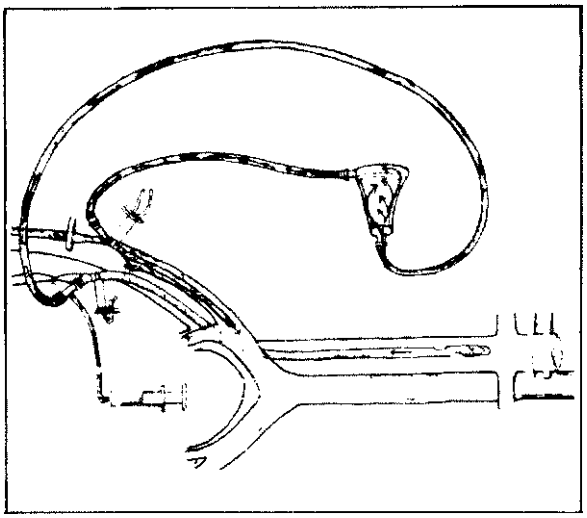

Fig. 3. Diagram of venoarterial bypass circuit. Blood from the vena cava is removed via the long saphenous vein and pumped into the right common iliac artery. Epoprostenol is infused through the side arm on venous limb. Reproduced by kind permission of the editor, from Lancet 1: 1269, 1984.

Bypass

Pump support of the circulation is not used as a routine, but only in patients who are in a very frail condition, particularly those with severe portal hypertension, poor clotting factors and impaired renal function. Patients who have had extensive upper abdominal surgery may also be managed best by bypass because of the anticipated severe blood loss from venous collaterals. Otherwise, we have a pump technician available but do not prime the apparatus until the results of trial clamping of the inferior vena cava below the liver can be assessed. This is done at an early phase of the operation to determine whether the patient's heart can withstand this sudden reduction in venous return. We use a veno-arterial bypass without oxygenation or heat exchanger since the ventilatory oxygenation of the lungs can keep a satisfactory arterial $P0_2$ • With a short incision over the superficial femoral vessels, the saphenofemoral junction is isolated, a Bardec cannula is inserted up into the vena cava, a small anterial catheter is inserted in the superficial femoral artery and blood is removed from the vena cava through heparin bonded tubing, into which a low dose of prostacycline can be infused. The Biomedicus Pump is used to enhance the arterial circulation bypassing blood from the vena cava to the common iliac artery (Figure 3). We do not decompress the portal vein with a separate line since, due to the porto-systemic collaterals, decompressing the cava below the liver will usually also decompress the portal system.

The hepatic artery, portal vein and bile duct are controlled with slings. The common duct is usually divided where the cystic duct enters it, to provide as wide as possible mouth for anastomosis of the fundus of the gall bladder. We clamp and divide the hepatic artery, portal vein, inferior vena cava below the liver and use a special clamp for the inferior vena cava above the liver. Then the liver is removed, taking care to secure the inferior vena cava above the liver so that it does not slip upwards through the clamp. On one occasion we have controlled the suprahepatic inferior vena cava with a snare within the pericardium and made a vertical incision in the tendonous portion. The first anastomosis is the cava above the liver end-to-end to that of the recipient, using a running O mersilene stitch, then the portal vein of donor and recipient are anastomosed end-to-end with a 5/0 prolene stitch. Before the anastomosis is completed the portal vein is flushed with one unit of plasma protein fraction to remove some of the contained preservation fluid which will have a high content of potassium and acid radicals. The clamp is then removed from the portal vein and the first 100 ces of blood coming into the liver is allowed to go to waste through the cava below the liver to avoid flooding the circulation with blood containing high concentrations of potassium and acid radicals. The cava below the liver is then clamped and the clamp is removed from the cava above the liver. The cava below the liver is now anastomosed to that of the recipient using a running 4/0 prolene stitch and then using loop magnification, the hepatic artery of the recipient is anastomosed to the coeliac artery of the donor with 6/0 prolene. If the recipient's hepatic artery is of extremely small calibre, for example, in children, the thoracic aorta of the donor with the hepatic artery supply intact is anastomosed to the right common iliac artery. If the thoracic aorta is not available a reinforced PTFE 5 mm prosthesis is threaded in front of the right kidney and anastomosed to the right common iliac artery and the donor hepatic arteriy.

There is always evidence of hyperkalaemia when the first blood from the liver returns to the heart as shown by peaked T waves on the ECG and not infrequently hypotension and cardiac irregularities. Administration of calcium and bicarbonate may be needed to overcome these metabolic disturbances. The fundus of the gall bladder is anatomosed to the recipient common duct using interrupted prolene and continuous catgut or PDS stitches. The wound is closed with two drains on each side and the long arm of the T-tube is brought out through a stab incision.

POSTOPERATIVE MANAGEMENT

Antibiotics are given prophylactically for 48 hours against both aerobes and anaerobes. The

monitoring used during the operation is continued in the intensive care ward. An infusion of potassium is usually needed since, as the ischaemic liver recovers, potassium ions that have leaked out during the preservation period are replaced from the serum. Continuing haemorrhage after operation can be difficult to control and it may be necessary to return the patient to the operating room and endeavour to sstop the bleeding. Although usually general oozing is seen without a specific bleeding point, haemorrhage may stop after removal of blood clot from the abdomen. Skilled medical care is required in the postoperative period and senior residents from King's College Hospital look after the patient until he is ready to leave the ICU, usually on the third day. We try to extubate the trachea after twenty-four hours. It is difficult to wean the patient from the ventilation. The prognosis is poor since wasting of the respiratory muscle and lung infection are likely to follow.

IMMUNOSUPRESSION

In all species that have been studied liver grafts are rejected less agressively than other tissues. Nevertheless in man, unfortunately, agressive rejection of liver allografts will occur unless immunosuppression is given We believe that cyclosporin A (CyA) is the most satisfactory drug to maintain immunosuppression in patients with liver grafts, but serious complications from CyA have occurred in the early post-operative phase, especially nephrotoxicity. Chronic liver failure often leads to impairment of renal function. This may be aggravated by other drugs, for example Gentamycin. CyA may cause anurie in such cases. CyA given intravenously in a central line is thought to have caused adult respiratory distress syndrome (15). There are also difficulties with regard to absorption and the metabolism of CyA. If given by mouth, being fat soluble, CyA is not absorbed unless bile salts are present in the gastrointestinal tract. Intravenous administration can lead to high blood levels but the radioimmunoassay (RIA) estimation of blood or serum levels of CyA may be misleading since, if the liver is not functioning satisfactorily, excretion of CyA is impaired and there is a build up of inactive metabolites of CyA which are not distinguished from CyA by RIA. It has been shown in such cases by High Pressure Liquid Chromatography after liver grafting that there may be little active CyA in the blood but only metabolites and this is associated with a high incidence of rejection especially when the CyA has been given by continuous infusion.

For these reasons we have changed the immunosuppressive regimen which had previously been with CyA, to Azathioprine and Prednisone until renal and liver functions are stable. Azothioprine 1.5 *mgl* kg/day and Prednisolone 1 mg/kg/day are given for the first few days after transplantation and then CyA is started at a very low dose of 2 mg/kg/day i.v. when the patient has recovered from the operation and adequate renal function has been demonstrated. Some of our patients have been treated in addition with a monoclonal antibody, CAMPATH-1, which is a complement fixing IgM destroying both T and B cells. Daily doses of 25 mg have been given for 10 days.

When the T-tube is clamped, usually between 10 and 14 days post-operatively, CyA is given by mouth and the intravenous therapy is stopped. The CyA dosage is usually 10 mg/kg/day by mouth for the first three months but it is monitored according to the blood levels trying to maintain a range of between 100 and 300 mg/ml. The long term maintenance dose varies between 4 and 6 mg/kg/day. We routinely use radioimmunoassay estimation of blood levels despite the dangers of misinterpretation referred to above. The T-tube is removed after between two and three months, when the patient's condition is satisfactory and cholangiography shows a normal draining biliary system.

REJECTION

It can be extremely difficult to diagnose rejection of the liver because of the multiple factors that can cause impairment of liver function. If, however, there is good liver function, falling bilirubin and transaminase levels, then rejection can be excluded. Deterioration of liver function, however, may be due to rejection, obstructed biliary drainage, hepatoxicity from drugs, cholangitis, or a major vascular catastrophe. If we suggest rejection we try to perofrm a biopsy early, before clotting is severely impaired, so that the diagnosis can be confirmed by histology.

The fatures of rejection are round cell infiltration of the portal tracts and liver cell death. A particularly sinister form of rejection is associated with progressive jaundice and the absence of intrahepatic small biliary ducts, "the disappearing bile duct syndrome", which does not respond to any treatment. Cellular rejection usually responds weL to bolus doses of one gram of Solu-Medrone given intravenously each day for three days.

FOLLOW-UP

Patients whose courses are satisfactory are allowed up and out of hospital as soon as possible, but we try to keep regular surveillance of the patients, at first once a week and then every two weeks. Eventually the patients are referred to their own doctor's local care, but if possible we like to

get the patient back for review every six months or once a year in the transplant centre.

COMPLICATIONS

REJECTION

If the patient develops relentless, uncontrollable rejection, particularly with destruction of small intra-hepatic bile ducts the only suitable treatment is a retransplant, which should be performed early, since after some months the liver becomes excessively adherent to surrounding structures and the operation may be extremely hazardous. In the first few weeks after transplantation it may be quite easy to retransplant the patient.

COMPLICATIONS OF CYCLOSPORIN A

Nephrotoxicity has already been mentioned. In addition the patient may become hypertensive or develop an idiosyncracy manifested by headaches and acrodynia and paraesthesiae. Increase of body and facial hair and gum hypertrophy are common side effects that get better when the maintenance dose of CyA is lowered. If the patient cannot tolerate the drug, immunosuppression is changed to Azathioprine and Prednisolone in the same dose as used for recipients of kidney grafts. Azathioprine may cause marrow depression and corticosteroids are particularly likely to aggravate bone disease already usually present in patients with chronic liver disease.

INFECTION

Immunosuppressive drugs increase the patient's susceptibility to infection which will already be a serious hazard due to the chronic liver disease. Children who have had the Kasai operation are particularly difficult to manage because of the likely presence of antibiotic resistant organisms of the gastrointestinal tract resulting from previous episodes of recurrent cholangitis.

LONG TERM REHABILITATION AND CURRENT RESULTS

Most of the mortality after liver grafting is within the first **3** months and in those that survive beyond one year, rehabilitation is usually excellent. Many of the patients in the Cambridge/KCH series have returned to full-time work, and of immense satisfaction to the women has been the ability to look after their family and house again. In those dying after a year, the cause of death has either been recurrence of malignant disease or has been unrelated to the transplant or original disease. Thus one patient died from a myocardial infarct and another from a colonic cancinoma. Our longest current survivor, who remains tumour free at nearly 10 years had a hepatocellular carcinoma in association with familial hepatitis B virus infection, one brother having died of a hepatoma a few years earlier.

The occurrence of lymphoma as a complication of the immunosuppressive drug therapy merits patient many years ago who developed a lymphoma in the transplanted liver and very recently another case at 4 years to 8 months after transplantation who died of a rapidly progressive respiratory illness over 10 days, and was found to have a lymphoma in the lung at autopsy (16). She had been maintained on prednisolone and azathioprine. Starzl has described liver and other transplant recipient in whom lymphoma has been controlled by reducing the doses of the immunosuppressive agents being used (17).

In Pittsburg, results have a!*" ^nded to be better in the younger age group, particularly in the earlier series. A recently published analysis of 47 pediatric patients transplanted over the period 1981-1983 showed that 32 were alive from 6 to 29 months later including 7 of 15 patients who required retransplantation. Their published actuarial one-year survival for adults is 64%, although they believe this year's figure will be nearer 75% (19).

Current Results: Examination of the curren. results in different centres is more relevant than looking back at the overall results of series obtained over periods of years during which there have been major changes in surgical technique, patient selection and immunosuppressive therapy. During the past 2 yearsmore patients have been treated in the Cambridge/King's College Hospital programme than in any previous period as the result of the greater availability of donor organs—73 patients compared with 141 in period 1968-1983. Results particularly in the younger age group are very satisfactory with an actuarial predicted 1 year survival of 75% (18).

Actuarial one-year survival figures in Minneapolis 1983-85 for adult patients is 60% and for Memphis 62% for the same period. Results for adults in the Cambridge/King's College Hospital series are similar. Now that patients can reasonably be offered a graft before they are actually in the terminal phase of the disease, immediate survival results will almost certainly improve. In considering one-year survival figures it is important also to take into account the frequency with which retransplantation is carried out. Patients whose grafts do badly for any reason are best treated by early retransplantation. In Starzl's series the figure is around 30% and 5-10% for third graft insertion.

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