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Survival after Orthotopic Liver Transplantation: A Follow-up Report of Two Patients

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Summary: Two adult patients with terminal fatal liver disease were treated by orthotopic transplantation. One survived 11 months and died as a result of recurrent biliary intra-abdominal sepsis; the other patient is alive and well in the 18th month after transplantation and has virtually normal liver function. It is concluded that liver grafting can provide valuable therapy.

Introduction

To provide therapy by liver grafting has proved to be difficult for a variety of reasons; chief among these are shortage of suitable donors at the critical time when the operation is indicated in the recipient. When conventional treatment has failed to alter the inexorable course of fatal liver disease there are no satisfactory means available to restore the patient to a state of health that will enable him to withstand a major operation without serious hazard. Nevertheless, the alternative of early certain death is a greater risk, and faced with the choice, most patients are anxious to take the chance of liver transplantation. Starzl (1969) reported a one-year survival rate of 22% in his first 25 cases and if the patients operated on before 1967 are excluded the one-year figure rises to 33%.

Certain features of our series of liver grafts have already been reported (Calne and Williams, 1968; Calne *et al.*, 1968; Williams *et al.*, 1969; Calne, 1969; Williams, 1970). Of 20 patients receiving orthotopic liver grafts, three failed to survive the operation and four died in the first postoperative week from a variety of causes. Four others died in hospital with survival periods of up to eight weeks. Three who were operated on recently are alive. Six were discharged home well and with excellent liver function—two dying from infection three months after operation, one at 4½ months, and one at 11 months. The remaining two patients are alive—one in the eighth month, the other in the 18th after receiving an orthotopic liver graft. In this paper we describe the course of the last patient and that of the man who survived 11 months.

Case OL 9

This 44-year-old woman presented with abdominal enlargement, pain, and loss of weight. A laparotomy in December 1968 at Welwyn Garden City Hospital showed a large hepatoma rising in the right lobe and a selective coeliac arteriogram indicated multiple small lesions scattered through the rest of the liver. Her condition deteriorated rapidly and she became cachectic.

On 7 February 1969 orthotopic liver transplantation was performed at Newmarket General Hospital, the donor being a four-year-old child, the victim of a road accident. The total ischaemia time of the liver was 168 minutes. The removed liver weighed 4 kg., and histological examination showed the characteristic appearances of a primary hepatocellular tumour with extensive areas of haemorrhage and necrosis but without an underlying cirrhosis.

Postoperatively she made an uninterrupted recovery. She was treated with azathioprine and prednisolone. At the end of the first week there was a minor episode of impaired liver function that may have been a rejection episode. On the 10th day the serum bilirubin rose to a maximum of 5·8 mg./100 ml. The dose of prednisolone was temporarily increased to 200 mg. and by the 22nd day the serum bilirubin had fallen to 1·5 mg./100 ml. She was discharged home without symptoms and was fully ambulant on the 30th day; since then she has remained remarkably well.

Clinical photograph Case OL 9.

A liver biopsy in October 1969 showed normal histological appearances, without significant portal tract infiltration. In April 1970 she was readmitted because of a rise in serum bilirubin to 2·6 mg./100 ml. and of serum aspartate aminotransferase to 114 i.u./100 ml. She had no symptoms and the episode settled over 10 days, the provisional diagnosis being mild cholangitis. At the time of writing she is in the 18th month after transplantation, continues to be well and to work part-time (see Fig.). Her azathioprine dose is 100 mg. daily and the prednisolone has been reduced to 10 mg. day. Her serum bilirubin is 0·6 mg./100 ml., aspartate aminotransferase 63 i.u./100 ml., and alkaline phosphatase 18 K.A.u./100 ml.

Case OL 10

This patient, a man aged 56, had become jaundiced in Burma in 1943 and was first seen at King's College Hospital in 1963 following a haemorrhage from oesophageal varices. Investigations showed a compensated cirrhosis, and in January 1964 a portacaval anastomosis was performed. Shortly after this he noticed deterioration in memory and concentration. This became progressively more pronounced and in March 1966 he had an episode of frank portal-systemic encephalopathy with marked confusion, fetor, and flapping tremor. He was treated with protein restriction, neomycin,

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and later lactulose but with only temporary improvement. In January 1968 a colonic exclusion with caecorectal anastomosis was performed. For a few months he was improved, but by January 1969 he was unable to go out of his home. He had a pronounced ataxia of gait and also experienced momentary attacks of loss of consciousness which were followed by a considerable increase in confusion and hepatic flap. He also developed diabetes.

On 27 March 1969 orthotopic liver transplantation was performed. The donor was a 32-year-old man who had died as a result of a head injury. The total operating time was six and a half hours and the total ischaemia time 138 minutes. The removed liver showed advanced cirrhosis and, in addition, there were numerous small nodules scattered through the liver, which on microscopy showed the characteristic appearances of a multicentric hepatoma.

The postoperative course was uneventful and his mental state improved rapidly during the first few weeks. Serial electroencephalograms also showed striking improvement. Preoperatively the record was grossly abnormal, with low-voltage slow waves of theta frequency, but by the 11th day normal alpha rhythm was present. By the second month he had lost all signs of portal systemic encephalopathy and was able to receive a normal protein intake without neomycin or lactulose.

Immunosuppressive therapy consisted of prednisolone 60 mg. daily during the first week, reducing to 30 mg. thereafter, and azathioprine initially 50 mg., increasing to 125 mg. daily. During the fifth week he developed jaundice, which was thought to be due to mild rejection, the serum bilirubin rising to a maximum of 9·2 mg./100 ml. on the 44th day. He was given six daily injections of 20 ml. of antilymphocyte globulin (kindly supplied by Professor W. Brendel) and for a few weeks afterwards additional 100-mg. doses of prednisone ("pulse therapy"). With this, the liver function tests improved, the serum bilirubin falling to 0·8 mg./100 ml.

In the seventh month he was readmitted with jaundice, rigors, and fever. A diagnosis of cholangitis was made and he improved with ampicillin and without change in immunosuppressive therapy. A percutaneous liver biopsy, done in October 1969, showed a few small areas of hepatocellular necrosis with only slight portal tract infiltration. He then remained well at home, living a relatively normal existence. During the summer of 1969 he looked after his garden and built a greenhouse.

On 8 February 1970 he was readmitted acutely ill with hypotension due to a Gram-negative septicaemia. Blood cultures grew *Klebsiella* and *Citrobacter*. He improved initially with antibiotic therapy, but subsequently developed renal failure and died on 27 February.

Necropsy showed generalized peritonitis with breakdown of the anastomosis of the donor gall bladder to recipient common bile duct in one part, and a fistula extended downwards to the second part of the duodenum. The gall bladder wall was fibrosed and the common bile duct filled with fine granular calculi. The liver on histological examination showed some centrilobular necrosis of hepatocytes with moderate fibrosis of the portal tract and scanty infiltrate of plasma cells. The other main finding was a 2-cm. metastasis in the right adrenal with similar histology to the original hepatoma.

Discussion

Without liver grafting there can be no doubt that both these patients would have died in a few weeks. One patient had a severe chronic encephalopathy and the other was cachectic and deteriorating rapidly from hepatic malignancy. Both patients had malignant hepatoma, and the average prognosis of this condition is four to six months from the time of diagnosis (Lawrence *et al.*, 1966; Nelson *et al.*, 1966). Liver grafting enabled both patients to return to a normal existence and therefore provided valuable therapy. The long-term results of this treatment are unknown, but there are collateral reasons for guarded optimism. The liver is less aggressively rejected than most other tissues. In the pig this is especially evident; without any immunosuppressive therapy 3-month-old piglets have survived in good health more than two years after orthotopic liver grafting and have grown into normal adults. One sow gave birth to a litter of nine normal offspring 18 months after operation (Calne *et al.*, 1969).

Bile drainage via a cholecyst-choledochostomy (Calne, 1969) has proved satisfactory during the initial postoperative period and subsequently, though both patients had episodes of cholangitis. It is not surprising that Case OL 10, with a biliary fistula and a common bile duct full of calculi, should have experienced recurrent attacks of biliary infection during life and that finally one of these should lead to a fatal Gram-negative septicaemia. The development of calculi is of interest, for Bell *et al.* (1969) have shown that the cholestasis seen in the immunosuppressed homotransplanted liver in the dog is accompanied by an increased bile viscosity and diminished biliary output.

The selection of patients for orthotopic transplantation, and the advantages and disadvantages of the various conditions which are theoretically treatable, including cirrhosis, primary hepatoma, acute hepatic necrosis, and biliary atresia, are discussed in detail elsewhere (Williams, 1970). It is important to emphasize, however, that the possibility of metastatic recurrences with a primary hepatoma should not be a reason for excluding these patients. Prolonged and worth-while survival is possible, as shown by our two patients, and the same criteria apply to transplantation for malignant disease as for radical surgery and other varieties of growth. The excellent function of the grafts in these two patients was shown by the virtually normal liver function tests and histological appearances on biopsy. Measurements of the albumin synthesis rate using the ^{14}C carbonate method (kindly carried out by Dr. A. S. MacFarlane) have also given normal results.

The results of cadaveric renal transplantation continue to improve—more than 50% functional survival at two years has been achieved in several centres (Calne *et al.*, 1970)—our longest surviving patient does a full day's work plus overtime, nearly five years after grafting, and from other centres patients have lived longer than this with functioning cadaver kidneys. Normal life can be enjoyed, fertility can return in both sexes, and kidney transplants can support normal pregnancy and labour.

Unfortunately, the organization of liver transplantation is more difficult than that for the kidney, since the liver suffers irreversible damage if it is deprived of a circulation at 37°C. for more than 15 minutes. Within this period of time it is necessary to cool the liver via a cannula inserted into the superior mesenteric vein. Once cold, the liver can be removed and kept chilled in ice for at least two to three hours and probably up to five hours (Orr *et al.*, 1969) before serious damage occurs. Most satisfactory liver donors are patients on respirators who have severe head injury, or brain tumour, or haemorrhage in whom resuscitation has continued until irreversible cerebral damage has been apparent. The decision to abandon resuscitation—unrelated to any possible transplantation considerations—nevertheless allows time for the liver transplantation to be undertaken. The recipient can be prepared for surgery and the surgical instruments, personnel, and operating theatre staff can be alerted. When mechanical ventilation is stopped the circulation usually ceases shortly thereafter and brain death is revealed beyond any doubt. Liver cooling and hepatectomy are then begun.

When liver disease is severe enough to attempt liver grafting there is only a short period, usually a few weeks, before the patient will die or become unfit for anaesthesia. Indeed most patients referred to us for liver transplantation had died before a suitable liver became available. The only way in which this field can advance is for there to be more co-operation within the profession and a return of the goodwill and charity of the public towards organ transplantation, which suffered so severely following the unfortunate and often inaccurate publicity surrounding many of the cardiac transplantation operations.

In writing this paper we are the spokesmen of a combined group from Addenbrooke's Hospital and King's College Hospital, and to all who have been concerned in the care of these patients we express our thanks.

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Thromboembolic Complications in Myelomatosis

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Summary: Fourteen cases of myelomatosis associated with major thromboembolic complications are reported. Six patients died of pulmonary embolism, seven had deep-vein thrombosis as a presenting symptom, and three had evidence of amyloidosis. A preliminary estimate of the incidence of thromboembolism based on 376 patients admitted so far to the Medical Research Council's myelomatosis trial is about 3%, while pulmonary embolism accounted for about 3% of all deaths. Possibly a hypercoagulable state and the presence of amyloidosis may be important in the pathogenesis of this complication.

Introduction

While haemorrhage is common in myelomatosis, especially in the terminal stages, thromboembolism is not a well-recognized complication. Nevertheless, we have recently seen five patients suffering from deep-vein thrombosis, associated in four with pulmonary embolism, in three of whom a diagnosis of myelomatosis was made subsequent to the development of thromboembolism. Nine further cases of thrombosis have been found in the records of the Medical Research Council's myelomatosis trial.

Case Reports

Brief clinical and laboratory findings in the 14 patients are shown in the Table. Venous thrombosis or pulmonary embolism was the presenting feature of the illness in seven patients, and in these myelomatosis was diagnosed on the basis of laboratory investigations. In another four patients thrombosis occurred two months or less after diagnosis. Pulmonary embolism was the cause of death in six patients—three died five weeks or less after the diagnosis of myelomatosis was established, while in the other three pulmonary embolism caused death 6, 12, and 42 months after diagnosis. Thus five of the six fatalities from pulmonary embolism occurred in the first year after clinical recognition of the disorder. Twelve patients are among those admitted to the therapeutic trial in myelomatosis conducted by the Medical Research Council's Working Party on Leukaemia in Adults. By 15 March 1970, 376 patients had been entered to the trial, indicating a minimum incidence of thrombotic complications of 3·2%. This figure would be higher if any of the surviving patients were to develop thromboembolism. By December 1969, 192 patients had died, six of them (3·1%) from pulmonary embolism. Only 53 necropsies were performed, so it is possible that this figure is an underestimate. In seven patients (1·8%) the first presenting feature of myelomatosis was thromboembolism.

Discussion

There are only a few reports of thromboembolism complicating myelomatosis in the literature. In a clinicopathological study of myelomatosis Talerman (1969) found that massive pulmonary embolism was the cause of death in 3 out of 32 necropsies; he had not found this cause of death previously reported. Sanchez-Avalos *et al.* (1969), searching for this complication in a clinical survey, recorded episodes of pulmonary embolism in 3 out of 34 patients. Two other cases were mentioned by Lieberman *et al.* (1961), in one of which venous thrombosis had been present for nearly three years before the diagnosis of myelomatosis was established.

The mechanism of thrombosis in myelomatosis remains uncertain. Sanchez-Avalos *et al.* (1969) reported that certain laboratory findings were associated with thrombotic phenomena in myelomatosis—namely a shortening of the coagulation time in silicone tubes and an increase in the plasma fibrinogen concentration, suggesting the presence of a hypercoagulable state. An appreciable increase in the plasma concentration of fibrinogen (847 mg./100 ml.) and factor VIII (520% of standard normal) was found in one of our three patients (Case 3) in whom coagulation studies were made. High fibrinogen levels have been reported in myelomatosis, especially with IgG paraprotein (Viala *et al.*, 1963; Niléhn and Nilsson, 1966). Plasma fibrinogen estimations however, may not be accurate in this condition owing to conjugation of the paraprotein with fibrinogen or occlusion in the fibrin clot (Bang, 1967; Regoeczi, 1968; Sanchez-Avalos *et al.*, 1969). In either case measurement of fibrinogen as thrombin-clottable protein would overestimate the true value. An increase in factor VIII has been found in myelomatosis as well as in other types of hyperglobulinaemia (Pitney and Elliott, 1960; Propp and Dylong, 1965; Niléhn and Nilsson, 1966). Increases in plasma fibrinogen and factor VIII have also been reported in patients with carcinoma (Mider *et al.*, 1950; Amundsen *et al.*, 1963). Davis *et al.* (1969), however, found that raised fibrinogen and factor VIII occurred in a number of non-malignant disorders and were not specific for malignant disease.

Malignant diseases, especially carcinoma, predispose to thrombosis (Lieberman *et al.*, 1961; Miller *et al.*, 1967; Wiernik and Serpick, 1969). In some types of carcinoma, especially carcinoma of the pancreas, the incidence is very high. Different histological types of pancreatic carcinoma however, are associated with pronounced differences in the incidence of multiple thrombi (Lafler and Hinerman, 1961). It

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