

*Leading article*

## Present position of liver transplantation and its impact on hepatological practice

In developmental terms, orthotopic liver transplantation, an embryo in 1963, grew to come of age in the early 1980's,<sup>1</sup> can now be reasonably considered to have graduated from college with an upper second honours degree. The period of development has come to an end and liver transplantation is now well established as a therapeutic option for almost the entire range of acute and chronic liver diseases. The acceptance of this procedure, which not so long ago posed considerable surgical, anaesthetic and medical problems, in clinical practice is graphically shown by the rapid growth in the number of centres doing liver transplants, especially in the North American continent and Europe.<sup>2,3</sup> At present one year survival rates of 70–80% and higher are widely attained, with data suggesting that five year survival rates of 60–70% are likely.<sup>3</sup> Although the introduction of cyclosporine has had a major impact on liver transplantation, it is simplistic to interpret the improved survival rates as caused solely by this immunosuppressive agent. The doubling of the one-year survival rate which Starzl attributed to cyclosporine in his programme,<sup>4</sup> has been reproduced in the Cambridge/King's College Hospital joint series at a later stage, and it is likely that experience, improved selection of patients and timing of transplantation, refinements in surgical technique and advances in immunosuppression, contributed considerably to the upward trend.

Of the four broad indications for liver transplantation, end stage chronic liver disease is numerically the most important, accounting for 65% of patients in our programme. All causes are suitable (including alcoholic liver disease when the ability to abstain is established), and the main area of debate concerns the timing of transplantation. The improved overall survival rates have generated greater confidence in referring patients at an earlier stage for transplantation, when their chances of surviving the procedure are greatest, rather than in the final throes of their illness. Nevertheless, the procedure still carries a mortality and there properly remains a reluctance to refer patients for transplantation until the disease is unresponsive to appropriate medical treatment, with decreased quality of life, or with the appearance of major complications.

Of the cholestatic diseases, the natural history of primary biliary cirrhosis is the most predictable. Transplantation should be considered when the serum bilirubin exceeds 100  $\mu\text{mol/l}$ , or when portal hypertension results in recurrent bleeding from oesophageal varices despite efficient sclerotherapy. Primary sclerosing cholangitis is somewhat less predictable, because of the fluctuating course of the disease and there is the added consideration of cholangiocarcinoma complicating the later stages. Biliary atresia with persistent cholestasis despite a Kasai procedure is the commonest indication for transplantation in children and growth patterns, in addition to the standard parameters, need to be considered when assessing the need for transplantation. Patients with chronic active hepatitis, autoimmune and

viral, and cirrhosis, deserve consideration for transplantation when there is evidence of severe hepatocellular damage, manifested by poor synthetic function (prothrombin time  $>5$  s prolonged and albumin  $<30$  g/l), intractable ascites or encephalopathy, or when complications such as spontaneous bacterial peritonitis or variceal bleeding develop. The greatest difficulty is undoubtedly encountered in the assessment of cryptogenic and other forms of morphologically inactive cirrhosis. These patients are often capable of leading a normal life for substantial periods despite the presence of severe, but static liver dysfunction, until a rapid and relentless deterioration is provoked by complications making transplantation less successful. In these patients there is a need for serial quantitative assessments of the residual function of the liver, such as caffeine clearance or aminopyrine breath tests, which would help to time transplantation correctly. Excellent results have been obtained with liver transplantation for the Budd-Chiari syndrome, although some of these patients later develop overt myeloproliferative disorders that presumably predisposed to the original hepatic vein thrombosis and which will need control after surgery.

Orthotopic liver transplantation has more recently been used in the two main variants of acute liver failure: fulminant and late onset, or subacute hepatic failure.<sup>5-7</sup> Up to the present 30 such patients have been transplanted in the Cambridge/King's College Hospital series. Anticipated perioperative difficulties with coagulation and haemodynamics proved to be largely unfounded and the principal problem encountered has been availability of the donor organ at the optimal time. Early assessment of the likely prognosis is crucial in the selection of patients who are most likely to benefit from transplantation. We have found five variables to be especially useful. Poor prognosis is suggested by the presence of three of the following: aetiology is non-A, non-B hepatitis, halothane hepatitis or idiosyncratic drug reactions; age is  $<10$  or  $>40$  years; duration of jaundice before the onset of encephalopathy exceeds 7 days; serum bilirubin  $>300$   $\mu\text{mol/l}$ ; prothrombin time  $>50$  s. Such patients should be referred urgently for transplantation. The remainder, including those suffering from paracetamol overdose, are best treated with liver orientated intensive care. In the paracetamol group the results from intensive care are equivalent to those achieved with transplantation, unless there is a severe metabolic acidosis (pH  $<7.30$ ), when transplantation is likely to be very difficult because of associated hypotension and the pace of clinical deterioration.

Liver transplantation for primary hepatic cancer is bedevilled by the high rate of tumour recurrence, despite all efforts to detect extrahepatic spread at the time of transplantation.<sup>8,9</sup> The best patients are those with chronic liver disease who develop small tumours detected with routine screening by serum  $\alpha$ -fetoprotein estimations or ultrasound. In such circumstances transplantation offers a reasonable hope of a cure. Tumour recurrence rates exceed 65% in hepatocellular carcinoma and 75% in cholangiocarcinoma, but in some instances valuable palliation is obtained for several years.<sup>9</sup> The longest survivor in our programme was transplanted over 12 years ago for hepatocellular carcinoma in association with chronic hepatitis B and cirrhosis: he remains well and tumour free. The role of transplantation in the management of secondary hepatic malignancy needs further assessment: there is unquestionable benefit in the carcinoid syndrome, where other treatments for decreasing tumour size have failed.

Metabolic disorders comprise the fourth main indication for liver transplantation, not only in conditions where the liver is affected by inborn errors of metabolism, such as Wilson's disease, alpha-1-antitrypsin deficiency, or galactosaemia, but also when the liver is morphologically normal – for example in the Crigler-Najjar syndrome.<sup>10</sup> Similarly, combined organ transplantation may be undertaken to correct the metabolic defect and replace the damaged organ, for example kidney in primary hyperoxaluria<sup>11</sup> or heart in familial hypercholesterolaemia.<sup>12</sup>

The contraindications to transplantation are in a state of constant flux, as surgical and medical advances redefine absolute and relative contraindications. Portal vein thrombosis, HBeAg positivity, chronic hypoxaemia and oliguric renal failure were all at one time considered contraindications to transplantation, but this no longer prevails, even though such factors do add to the complexity of the overall management. This is well exemplified by a patient with primary biliary cirrhosis and primary pulmonary hypertension, a combination previously considered to exclude transplantation, who underwent combined liver, heart and lung transplantation<sup>13</sup> and is in excellent health more than one year later. The importance of age is also diminishing and liver transplantation has been successfully carried out in patients as young as a few weeks and as old as the mid-70s, although results are poorer in those aged over 60 years. Extrahepatic malignancy, active sepsis, active alcoholism and clinical AIDS are the presently accepted absolute contraindications, while other relative contraindications are considered in the context of individual patients.

Further improvement in results of transplantation can be expected. A recently developed modification of the Wisconsin preservation fluid is likely to greatly extend the time for which the liver graft can be stored between removal from the donor and transplantation into the recipient. Periods of up to 24 hours may be feasible, making organ procurement easier. This new development may result in less ischaemic damage and early experience suggests that the frequency of primary graft nonfunction is decreased by its use. Surgical techniques are being constantly refined, but problems with haemostasis and biliary reconstruction still remain.

In relation to graft rejection, new approaches to increase specificity and decrease toxicity of immunosuppressive agents are underway. Humoral therapy, particularly more specific monoclonal antibodies, is encouraging and should diminish reliance on high doses of corticosteroids to control acute rejection, a complication that develops in about 60% of patients in the early post-transplant phase. Chronic graft rejection, which develops in 10–15% of patients, is less amenable to medical management, although recent work in our programme has identified a role for HLA antigens and cytomegalovirus (CMV) infection in the immunopathogenesis of this complication,<sup>14,15</sup> raising the possibility of eliminating this problem by using appropriate donor/recipient graft matching and control of CMV infection.

Long term immunosuppression is maintained with various combinations of cyclosporine, prednisolone and azathioprine. Cyclosporine is an effective immunosuppressive drug with a lower incidence of infection and other problems encountered with high doses of corticosteroids. Benefits in the early months, however, are to some extent offset by unwanted effects during chronic administration, most notably hypertension and impairment of renal

function.<sup>16</sup> It is possible that these will be lessened by using lower doses of cyclosporine than initially given (10–17 mg/kg/day). In the Cambridge/King's College Hospital programme 'triple therapy' maintenance doses of cyclosporine 2–4 mg/kg/day, prednisolone 0.1–0.2 mg/kg/day and azathioprine 1 mg/kg/day are used. Early experience indicates that this regime gives good immunosuppression, but it is not yet clear if the objective in reducing side effects will be achieved.

Estimations of the potential requirements for liver transplantation range from four to 20 per million, suggesting a need for 200 to 1000 transplants annually in England and Wales. In 1984 2280 deaths were attributed to chronic liver disease, including 881 related to alcohol abuse. One thousand three hundred and forty two of these were under the age of 60 yr. In the same period 101 deaths were registered as due to hepatitis or acute liver failure, with 48 aged less than 60 yr. In 1985 deaths from chronic liver disease were 54.9 men and 46.0 women per million in England and 97.6 men and 68.1 women per million in Scotland. With the widening scope and better results of liver transplantation it is estimated that 1000 patients per year might need treatment. Of 216 liver transplants in the United Kingdom in 1987 most were done in the two programmes that at present have supraregional funding – Cambridge/King's College Hospital (111) and Queen Elizabeth Hospital, Birmingham (52). With the third centre in Leeds now approved, together with the planned expansion of the other two centres, it is likely that the numbers transplanted will rise rapidly. Availability of donor organs limits progress, however, and the number of organs offered for transplantation is too low. Urgent consideration of methods to increase donor organ procurement is needed. In addition to increasing awareness of medical personnel and the general public, such methods as 'required request' (as operated in the United States) and 'opting out' registers should be examined closely to determine if they are appropriate here. The onus is now firmly on politicians, medical leaders, and other interested bodies to create a structure that increases the availability of organs for donation, while respecting individual liberties and safeguarding the welfare of all patients.

The impact of liver transplantation on hepatology is moving beyond the management of end-stage disease and the five year survival rates of 65% are beginning to influence views as to what is the best longterm treatment for patients with chronic liver disease at different stages of the disease process. Indeed, most patients with liver disease should be considered potential candidates for transplantation, and should not be subjected to procedures that might prejudice its outcome without consideration of the broader implications. Previous complex biliary tract surgery, or construction of vascular shunts greatly increases the difficulty of liver transplantation and, while in some patients these operations are life saving, in many instances it may be more prudent to proceed to early transplantation.

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