THE INDICATIONS AND IMPLICATIONS OF LIVER TRANSPLANTATION

K.J. Simpson, O.J. Garden†*

INTRODUCTION

There has been much progress in the field of liver transplantation since the first human liver transplant was performed in 1963. With better immunosuppression, most notably the introduction of cyclosporin and more recently tacrolimus, and improvements in operative technique, post-operative care and patient selection, a dramatic improvement in survival following liver transplantation has been observed. This has resulted in increased numbers of liver transplant operations being performed throughout the world and an expansion and refinement in the indications for transplantation. Liver transplantation is now an established treatment for selected patients with either acute or chronic liver failure. In addition, a small number of patients with primary hepatoma or metastatic malignancy in the liver may now be candidates for transplantation. Occasionally liver transplantation is performed to improve a patient's quality of life, rather than treat liver failure, and thus to prolong life. This review will discuss each of these indications for liver transplantation before covering the ethical and financial implications of liver transplantation.

INDICATIONS FOR LIVER TRANSPLANTATION

A large number of hepatic disorders have been treated by liver transplantation (Table 1). The relative proportion of transplant operations performed for these different indications both in Scotland and the United Kingdom are shown in Figure 1. The indications for liver transplantation are broadly similar in Europe, North and South America, Saudi Arabia, Israel, Taiwan, China, Hong Kong and the Far East.[1-7] Endemic areas for hepatic infections such as hydatid disease and schistosomiasis rarely have hepatic complications of these infections as the prime indication for liver transplantation,[3] and therefore are not discussed further. Within Europe, over the last 20 years, a steady reduction in the numbers of liver transplants for primary malignant disease is noted with an increase in the numbers of those transplanted for complications of cirrhosis or acute liver failure.

In general, the indications for liver transplantation can be categorised into five main groups: acute liver failure; cirrhosis and chronic liver failure; hepatic malignancy; metabolic disorders; and transplantation to improve quality of life. In addition there are a group of transplanted patients who develop post-operative complications, which require re-transplantation. Inherent in the decision regarding whether a patient is a candidate for transplantation or not, is the accurate assessment of the patient's prognosis without transplantation and identification of any contra-indications. Unfortunately, with the exception of the cholestatic disorder, primary biliary cirrhosis and acute liver failure, accurate prognostication is somewhat lacking. Although some contra-indications to liver transplantation exist, with recent advances in the field, certain problems that would previously have been regarded as absolute are now only relative contra-indications, such as portal vein thrombosis (Table 2).

TABLE 1
The most common hepatic disorders assessed for liver transplantation.

- Viral hepatitis: hepatitis B, hepatitis C, nonA-nonB acute hepatitis.
- Alcoholic cirrhosis.
- Cholestatic liver diseases: primary biliary cirrhosis, primary sclerosing cholangitis.
- Autoimmune chronic active hepatitis.
- Cryptogenic cirrhosis.
- Hepatocellular carcinoma.
- Metabolic disorders: haemochromatosis, Wilson's disease.
- Acute (fulminant) hepatic failure.

TABLE 2
Contra-indications to liver transplantation (in both acute and chronic liver failure).

- HIV infection and AIDS.
- Extrahepatic malignancy (except 'early' skin cancers).
- Multifocal hepatocellular carcinoma.
- Uncontrolled extrahepatic infection.
- Advanced cardiac, respiratory or neurological disease.
- Active intravenous drug abuse.

ACUTE LIVER FAILURE

Several conditions (Table 3) lead to massive liver cell damage leading to acute liver failure manifested by coagulopathy, hypoglycaemia and encephalopathy. The relative frequencies of the different causes of acute liver failure vary in different parts of the world (Table 3). Although there has been much discussion regarding the definition of this condition, the original description by Trey and Davidson is still widely used: namely the development of hepatic encephalopathy within eight weeks of the onset of symptoms.[8] Cases of acute liver failure occurring between eight and 24 weeks after the onset of symptoms have been defined as late-onset hepatic failure.[9] Some patients with intensive medical management recover liver function and return to full health

**Consultant Physician, Scottish Liver Transplant Unit and Centre for Liver and Digestive Disorders, Royal Infirmary, Edinburgh*
†*Clinical Director, Scottish Liver Transplant Unit and University Department of Clinical and Surgical Sciences, Royal Infirmary, Edinburgh*

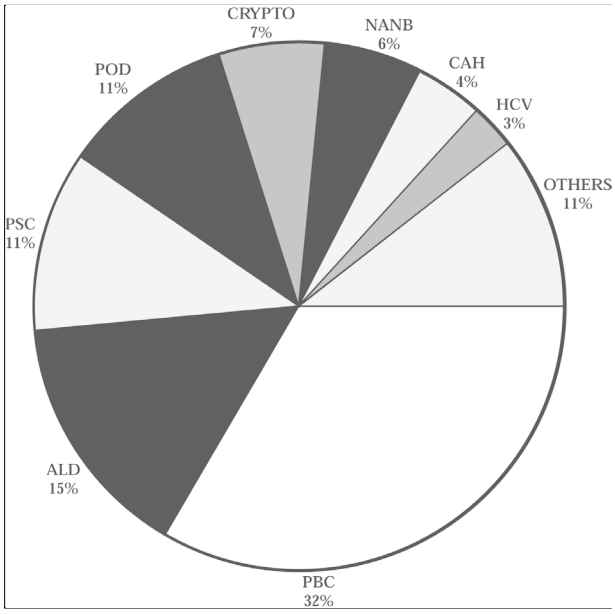

FIGURE 1A
Aetiology of liver disorders transplanted in the Scottish Liver Transplant Unit (November 1992 - December 1998, excludes retransplantation; total number = 208).

PBC = primary biliary cirrhosis, ALD = alcoholic liver disease, PSC = primary sclerosing cholangitis, POD = paracetamol-induced acute liver failure, CRYPTO = cryptogenic cirrhosis, NANB = nonA-nonB acute liver failure, CAH = autoimmune hepatitis, HCV = hepatitis C cirrhosis, Other = hepatitis B infection (three cases), drug reactions (four cases), Wilson's disease (two cases), alcohol and HCV (two cases), hepatoma (three cases), haemangio-endothelioma (one case), Caroli's syndrome/congenital hepatic fibrosis (one case), Secondary biliary cirrhosis (three cases), Budd-Chiari syndrome (two cases), hepatitis A acute liver failure (one case).

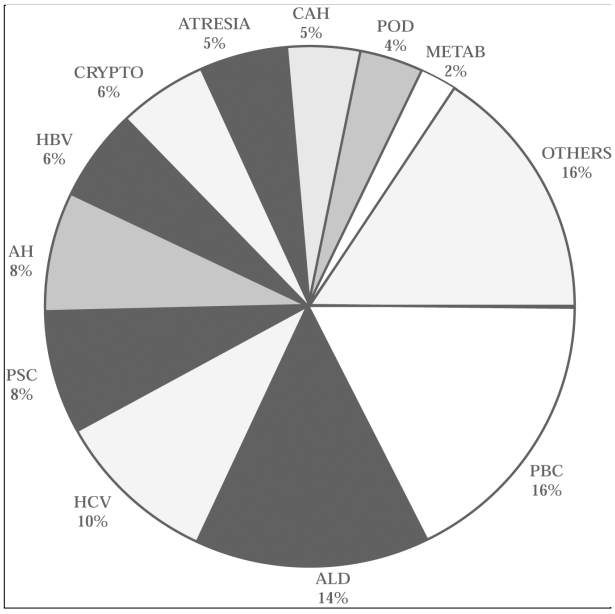

FIGURE 1B
Aetiology of liver disorders transplanted in the United Kingdom and Eire (November 1992 - December 1998, excludes retransplantation, total number = 3,019).

PBC = primary biliary cirrhosis, ALD = alcoholic liver disease, HCV = hepatitis C cirrhosis, PSC = primary sclerosing cholangitis, AH = acute hepatitis, HBV = hepatitis B, CRYPTO = cryptogenic cirrhosis, ATRESIA = biliary atresia, CAH = autoimmune hepatitis, POD = paracetamol-induced acute liver failure, METAB = metabolic liver disease, Other = alpha 1 antitrypsin deficiency, Budd-Chiari syndrome, secondary biliary cirrhosis, Wilson's disease, congenital biliary disease, nonA-nonB hepatitis, drug reactions, hepatitis A-induced acute liver failure, acute hepatitis B infection, hepatoma, cholangiocarcinoma, secondary liver tumour, polycystic liver disease, haemochromatosis.

without suffering chronic liver disease. However, a series of prognostic indicators developed by the Liver Unit at King's College Hospital, London, identifies a group of patients who have a predicted mortality of over 90% (Table 4). The prognostic indicators for liver transplantation in acute liver failure[10] are different in other parts of the world, such as France (Table 4).

Patients with acute liver failure who have these poor prognostic markers are considered candidates for

TABLE 3
Causes of acute (fulminant) hepatic failure.

- Paracetamol (acetaminophen) poisoning.
- Viral hepatitis: hepatitis A, B, D, E nonA-nonB hepatitis.
- Idiosyncratic drug reaction: rifampicin, isoniazid, halothane, non-steroidal anti-inflammatory drugs, anticonvulsants.
- Hepatic ischaemia.
- Budd-Chiari syndrome.
- Wilson's Disease.
- Acute fatty liver of pregnancy.
- Malignancy.

TABLE 4
Poor prognostic indicators (transplant criteria) in acute hepatic failure.

Paracetamol
Arterial pH <7.30
or
Prothrombin time >100 seconds and Grade III or IV coma and creatinine >300 μmol/L.

Non-paracetamol
United Kingdom
Any three of the following five factors:
- age <10 or >40 years,
- aetiology: drug induced or nonA-nonB hepatitis,
- prothrombin time >50 seconds,
- bilirubin >300 μmol/L,
- onset of hepatic encephalopathy >7 days after jaundice.

France
- Age <30 years and Factor V <20%.
- Age >30 years and Factor V <30%.

transplantation in the absence of any medical or psychiatric contra-indications. Despite a national consensus on the indications for liver transplantation in this condition, there are no national guidelines regarding contra-indications to transplantation. Absolute contra-indications to transplantation applied in the Scottish Liver Transplant Unit are shown in Table 5.

TABLE 5
Proposed contra-indications to liver transplantation in acute liver failure.

Medical (see Table 2)
- Untreated or progressive infection.
- Clinically apparent extrahepatic or metastatic malignancy.
- Progressive hypotension resistant to vasopressor support.
- Clinically significant ARDS (FiO_2 >0.8).
- Fixed and dilated pupils for >1 hour in the absence of thiopentone therapy.
- Severe coexistant cardiopulmonary disease.
- Acquired immunodeficiency syndrome.

Psychiatric
- Multiple episodes of self-harm (≥5) within an established pattern of behaviour, (especially if non-drug methods used).
- Consistently stated wish to die, in the absence of established mental illness, especially depression.
- Chronic refractory schizophrenia or other mental illness resistant to therapy.
- Incapacitating dementia or mental retardation.
- Active intravenous drug abuse.
- Active poly-drug use in a severe and chaotic fashion.
- Alcohol dependence or use of alcohol in a severe and chaotic fashion.
- An established pattern of past non-compliance with medical treatment.

Although these prognostic markers are indicators of poor prognosis, referral to a transplant centre should take place before these criteria have been reached. This allows maximum time for the transplant unit to assess the patient, preferably before the onset of significant hepatic encephalopathy, and to find a suitable donor if transplantation is considered necessary. In addition, patients with acute liver failure are potentially very unstable and can deteriorate during transfer. Indications for transferring patients with acute liver failure to a transplant centre are shown in Table 6.

TABLE 6
Indications for transfer of patients with acute liver failure to transplant units.

- Prothrombin time greater than the number of hours after the overdose.
- Prothrombin time greater than 50 seconds.
- Metabolic acidosis pH< 7.3.
- Hypoglycaemia.
- Hepatic encephalopathy.

CIRRHOSIS AND CHRONIC LIVER FAILURE.

Transplantation in patients with liver cirrhosis is not usually considered until the features of chronic liver failure or hepatic decompensation have developed. The Child-Pugh score (Table 7) developed several years ago continues to provide an estimation of prognosis in patients with cirrhosis.[11] Survival without transplantation in patients with good liver function (Child A category) is between 75% and 100% at three years. In contrast, patients with poor liver function (Child C) have a three-year survival between 20% and 45%. Other indicators of poor prognosis in patients with cirrhosis include diuretic-resistant ascites, spontaneous bacterial peritonitis or hepato-renal failure. Encephalopathy, especially if occurring spontaneously or with minimal precipitating factors, is also an indicator of poor prognosis. Malnourished patients and those with renal failure have particularly advanced liver disease with associated high operative mortality, and so it is advisable to transplant such patients before this stage is reached. Patients with associated liver and renal failure need careful assessment. The presence of significant intrinsic renal disease, which is more common in patients with end-stage cirrhosis, may require simultaneous renal transplantation because there is an immunological advantage to the patient receiving both organs from the same donor. However, renal failure consequent upon hepatic failure, the hepato-renal syndrome, will reverse following successful liver transplantation. With the notable exception of primary biliary cirrhosis, disease-specific prognostic indications are not available for other forms of chronic liver disease.

Primary biliary cirrhosis

Several prognostic models (Table 8) relying on multiple regression analysis have been developed for selection for hepatic transplantation in primary biliary cirrhosis (PBC). Such models often require complex mathematical

TABLE 7
Child-Pugh score.*

Score	1	2	3
Encephalopathy	none	grade 1-2	grade 3-4
Bilirubin (μmol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
Prothrombin time (seconds prolonged)	<4	4-6	>6
Ascites	none	mild	severe
Bilirubin in cholestatic liver disease (μmol/L)	<68	68-170	>170

*The individual values are added together to give the Pugh score. The Child classification divides the Pugh score into three groups, Child A <7, Child B 8,9, Child C ≥10. An increasing Pugh score is associated with increased mortality.

TABLE 8
Prognostic models developed for patients with chronic liver disease.

Primary biliary cirrhosis

- Mayo Clinic:
  R = 0.871 $\log_e$ bilirubin (mg/dL) + -2.53 $\log_e$ albumen (g/L) + 0.039 age (years) + 2.38 $\log_e$ prothrombin time (sec) + 0.859 (if oedema).

- European:
  R = 2.52 log10 bilirubin (μmol/L) = 0.0069 (age-20)/10 - 0.05 albumen (g/L) + 0.88 (if cirrhosis) + 0.68 (if central cholestasis) + 0.52 (if not treated with azothioprine).

Primary sclerosing cholangitis

- Mayo Clinic:
  R = 0.06 age (years) + 0.85 $\log_e$ minimum bilirubin (mg/dL) or 10 - 4.39 $\log_e$ minimum haemoglobin (g/dl) or 12 + 0.51 (biopsy stage) + 1.59 (indicator for inflammatory disease).

- King's College;
  R = 1.81 (hepatomegaly) + 0.88 (splenomegaly) + 2.66 $\log_{10}$ alkaline phosphatase + 0.58 (histological stage) + 0.04 age (years).

Alcoholic liver disease

- Beclair Model:
  R = 0.537 $\log_e$ bilirubin (μmol/L) -0.052 $\log_e$ albumen (g/L) + 0.048 age (years) + 0.469 (if encephalopathy).

computation for the prediction of survival,[12] however the modified Mayo model score can be calculated by inputting individual patient data at the Mayo Clinic's website. Use of the Child-Pugh classification, modified for primary biliary cirrhosis, is a simpler and generally available method of determining outcome in patients with PBC. However, most transplant centres consider patients to be candidates for transplantation if the bilirubin concentration consistently exceeds 100 μmol/L. This is based on classic studies showing such bilirubin concentrations are associated with an average life expectancy of only 18 months and a one-year mortality of over 50%.[13]

Primary sclerosing cholangitis

In common with primary biliary cirrhosis, several prognostic models[12] have been developed for estimating the prognosis in patients with primary sclerosing cholangitis (PSC, Table 8). The Mayo Clinic prognostic score can also be calculated by inputing individual patient data at the Mayo Clinic's web site. However, the Child-Pugh score is again a simple and relatively non-invasive way of determining prognosis in patients with cirrhosis secondary to PSC.[14] Increasing jaundice in this condition is not an automatic indication for transplantation; co-existing bacterial cholangitis may respond to antibiotic therapy or dilatation and temporary insertion of a biliary stent may effectively treat a single dominant extra-hepatic biliary stricture. However, the latter complication may be difficult to differentiate from cholangiocarcinoma, which is a contra-indication to transplantation as such patients have very poor survival.[15] Biliary tract cytology rarely shows malignant cells, and CT scanning may reveal mass lesions or multiple intrahepatic lesions in a small proportion of cases with multifocal cholangiocarcinoma. Occasionally laparoscopy, laparoscopic ultrasound or mini-laparotomy may be necessary to establish the diagnosis and stage the tumour.

Autoimmune chronic active hepatitis

Corticosteroid therapy is an effective therapy for the treatment of autoimmune chronic active hepatitis (AICAH). Patients are often converted onto azathioprine for long-term immunosuppression, to avoid the complications of long-term steroids in a group of patients that are often young women. However, in the Mayo clinic series 20% of patients deteriorated despite compliance with immunosuppressive therapy.[16] Such deterioration or the development of ascites, coagulopathy, hepatic encephalopathy or hypoalbuminaemia should prompt referral for liver transplant assessment. Patients presenting with decompensated liver disease secondary to untreated AICAH may respond to corticosteroid therapy, and a therapeutic trial of prednisolone therapy can produce marked clinical improvement. AICAH can recur post-transplantation but this seldom leads to significant clinical disease.[17] Rare cases of *de novo* autoimmune hepatitis have been described in children following liver transplantation for other indications; such cases respond to reductions in tacrolimus or cyclosporin levels, and increase in prednisolone dosage.[18]

Alcoholic liver disease

Alcohol-induced liver disease,[19] in common with other causes of cirrhosis, has been the subject of multiple logistic regression analysis with the development of several prognostic models (Table 8). However, the Child-Pugh score gives a fairly reliable estimate of prognosis in patients with alcohol-related liver disease. Although there has been much ethical debate regarding liver transplantation in this condition,[20] the one-year survival following liver transplantation for alcoholic liver disease is similar to that for other forms of cirrhosis.[21,22] A return to drinking alcohol (recidivism) seems to be uncommon in the first two years following transplantation. However, longer-term studies have suggested that most patients with alcoholic liver disease return to drinking.[23,24] Most transplant units prefer a period of abstinence for about six months before considering transplantation.[25] This demonstrates the patient's ability to abstain from alcohol and comply with medical treatment, and allows the opportunity for spontaneous hepatic, nutritional and general improvement. Occasionally such improvement may continue for 12-18 months after cessation of alcohol intake. Most transplant centres exclude patients who show features of alcohol dependence and thus are more likely to drink again. It is also important to exclude the presence of extra-hepatic alcohol-related disorders, such as brain damage or cardiomyopathy, which may contra-indicate transplantation.

Patients with severe acute alcoholic hepatitis may have a poor prognosis determined by Maddray's discriminant function or the Beclair model (Table 8). Such patients may benefit from corticosteroid therapy.[26] At present, few patients with alcoholic hepatitis are considered for transplantation because their post-operative survival is poor and the chances of recidivism are high.[1]

Hepatitis B infection

Following transplantation for post-hepatitic damage, hepatitis B almost invariably recurs in the grafted liver. This is characterised by an aggressive clinical course, with progression to cirrhosis within two years and the development of a distinct histological pattern termed fibrosing cholestatic hepatitis.[27] The risk of recurrence is highest in patients with active viral replication at the time of transplantation as manifested by the presence of hepatitis Be antigen or high titers of hepatitis B viral DNA in the serum. The risk progressively reduces in those who are hepatitis Be antibody-positive, those with hepatitis delta co-infection and those with fulminant hepatitis B.

Passive immunisation with high-dose intravenous hepatitis B immunoglobulin to maintain an antibody titre greater than 1:100 mIμ/ml significantly reduces the risk of recurrent hepatitis B following liver transplantation.[28] This allows liver transplantation to be considered for fulminant hepatitis B, co-infections of hepatitis B and hepatitis delta, and hepatitis B viral DNA negative, anti-HBe positive patients. Unfortunately this treatment is costly and may also have to be continued indefinitely.

The presence of hepatitis Be antigen, high titres of hepatitis B viral DNA or hepatitis Be antigen-deficient mutants have previously been considered contra-indications to transplantation because of high risks of recurrence (>90%). However, pre-transplant treatment with anti-viral drugs such as famciclovir or lamivudine, alone or in combination, may reduce hepatitis B viral DNA titres to such levels that transplantation may be possible. Prolonged treatment with either drug may be associated with the emergence of resistant stains of hepatitis B. Post-operatively such patients require to continue lamivudine and hepatitis B immunoglobulin prophylaxis long-term, and with the limited experience to date, the emergence of resistant viral strains has not been reported.

Hepatitis C infection

Patients with hepatitis C infection (HCV) are at risk of chronic hepatitis, cirrhosis and the subsequent development of hepatocellular carcinoma. Hepatitis C infection has become the most common indication for liver transplantation in the USA, and projected figures of the numbers of potential transplant recipients may swamp the donor supply. The prognosis of patients with cirrhosis secondary to HCV infection may be predicted using the Child-Pugh score. Screening such patients with liver ultrasound and serum alpha fetoprotein estimations may detect small hepatocellular cancers, which may be an indication for transplantation, even in the absence of decompensated liver disease. Hepatitis C inevitably reinfects the liver graft following transplantation.[29] However, in contrast with hepatitis B, this does not rapidly lead to significant graft dysfunction.

METABOLIC DISEASE

Haemochromatosis

Most patients with genetically-determined haemochromatosis present before significant liver disease has developed. Treatment with venesection will prevent the development of cirrhosis and subsequent risk of hepatocellular carcinoma. Diagnosis and screening for this disorder is likely to become more widely available with the identification of the genetic defect as a single base substitution.[30] Patients with haemochromatosis are transplanted when they develop chronic liver failure, and their prognosis is determined by the Child-Pugh score. Unfortunately post-operative survival may be less than in other forms of liver disease because of the associated cardiac dysfunction, increased risk of infection and the high frequency of hepatocellular carcinoma in the explanted liver.[31] Following liver transplantation, iron accumulation can continue within the liver, and phlebotomy may be required long-term.

Wilson's disease

Occasionally patients with Wilson's disease present with acute hepatic failure, and in this situation the patient's prognosis is assessed using the criteria described for non-paracetamol acute liver failure (Table 4). Acute liver failure may also occur in some patients who discontinue their copper chelation therapy, and such patients may also be considered as candidates for liver transplantation. Patients with Wilson's disease may also require transplantation for cirrhosis complicated by chronic liver failure.[32] Transplantation of the liver corrects the metabolic defect, with return of the serum caeruloplasmin and urinary copper excretion to normal. There have been some reports of liver transplantation leading to resolution of neurological Wilson's disease, unresponsive to medical therapy.

Miscellaneous metabolic diseases

Alpha-1-antitrypsin deficiency is a rare indication for liver transplantation, but may be indicated to treat progressive liver failure. Transplantation cures the metabolic defect with the plasma alpha-1-antitrypsin concentration returning to normal and the recipient taking on the donor phenotype.[33] Patients are, therefore, protected from any further development or worsening of any associated pulmonary disease.

With improving medical therapies, many patients with cystic fibrosis are surviving into adult life and therefore the associated liver disease is becoming a more important cause of death. Liver transplantation may be performed alone or in combination with heart/lung transplantation.[34] The multi-system nature of cystic fibrosis makes long-term survival of these patients more uncertain.

Many other metabolic diseases such as porphyria, urea cycle enzyme defects, galactosaemia and tyrosinosis have been successfully treated with transplantation.[35]

MALIGNANT DISEASE

Hepatocellular carcinoma

In the early days of liver transplantation, hepatocellular carcinoma was a relatively common indication for transplantation. Despite increasingly radical surgical resection, coupled with intraoperative chemotherapy, the results of treating large hepatocellular carcinomas have been disappointing. However, the fibrolamellar variant of hepatocellular carcinoma arises in non-cirrhotic liver tissue and the prognosis following transplantation is good, even for large tumours, with five-year survival up to 50%.[36] Liver transplantation for small hepatocellular carcinomas is currently considered on an individual patient basis. Patients are usually accepted for transplantation if they have small single tumours less than 5 cm in diameter, or 3 or less small (<3 cm) tumours in both lobes.[37] The use of pre-operative chemoembolisation to shrink larger tumours, prior to

subsequent transplantation, is controversial. Such patients require careful evaluation to exclude extrahepatic spread of the tumour, which would preclude transplantation. The recognition and acceptance of liver transplantation as a valid treatment option for small hepatocellular cancers, with the potential for long-term cure, has lead to discussion on the best mechanism for screening patients at risk. The most effective method appears to be annual or six-monthly ultrasound scanning by a skilled ultrasonographer and measurement of the serum alpha-fetoprotein.[38] Relatively small changes in the serum alpha-fetoprotein may herald the appearance of a hepatocellular carcinoma. Hepatocellular carcinoma may be confirmed by further imaging, if ultrasound is unrevealing, but one should avoid percutaneous biopsy of the tumour, which may lead to peritoneal dissemination of the tumour and thus contra-indicate transplantation.

Other tumours

Cholangiocarcinoma, which may complicate PSC, rapidly recurs after transplantation and therefore is considered a contra-indication to transplantation in most centres.[39]

Metastatic malignant disease of the liver is rarely considered an indication for transplantation except in the case of metastatic neuroendocrine tumours, such as carcinoid tumours, that have not responded to medical therapy or are unsuitable for surgical resection.[40]

Hepatic epithelioid haemangio-endothelioma is a rare slow-growing vascular tumour that can also be treated by liver transplantation.[41]

IMPLICATIONS OF LIVER TRANSPLANTATION

Donor issues

In association with immunological and surgical advances, the indications for liver transplantation have expanded in the last ten years. This is on a background of a contracting donor pool, and has resulted in increased waiting times and mortality rate while patients await transplantation. The situation is most pressing in paediatric transplantation, and has lead to the development of segmental or 'split-liver' transplantation.[42] During this operation a complete liver is divided, most frequently into two portions, utilising the segmental anatomy of the liver. Split-liver grafts are also used occasionally in small adult recipients, depending on the urgency of the patient's condition. In the United Kingdom, this operation is rarely used to provide living related liver donations. Living related donation is used much more frequently in renal transplantation, but is more commonly used for liver donation in certain countries such as Japan.[43] The limited number of infant and child donors has also led some workers to explore the possibility of using anencephalic infants as potential organ donors, with very limited success.[44] Others have used primate xenograft or extracorporeal circulation of blood through porcine livers in patients with acute liver failure.[45,46] These measures are used as a bridge to formal human liver transplantation in patients who are close to death.

More recently in the United Kingdom, in a drive to increase the number of donors available, the National Donor Registry has been developed. However, early experience with this scheme has been disappointing.[47] The use of non-heart beating cadaveric donors has also been discussed, but has not been generally accepted in the United Kingdom.[47] Semen donors in the United Kingdom are paid, and blood donors in other countries are also remunerated. However, the practice of payment to solid organ donors has been illegal in most countries since the early 1990s.[47]

Implications for patients with liver disease

As discussed above, most liver conditions are amenable to transplantation. Although the operation is associated with a certain mortality, this is directly related both to the aetiology of the liver failure and the patient's condition prior to transplantation. Improved mortality rates led to a recent consensus conference of American liver transplant physicians recommending that patients with liver cirrhosis be placed on a transplant list, if their expected mortality rate in the coming year was greater than 10%.[48] One of the most common reasons for rejecting patients for liver transplantation is that their condition is too advanced to expect them to survive the operation.[49] Therefore, doctors managing patients with liver disease must actively consider liver transplantation in all their patients. As well as improving operative mortality, undertaking liver transplantation earlier in their clinical course is associated with reduced complication rates, shorter post-operative hospital stay and reduced costs. This has to be balanced against the potential for both short- and long-term complications that may significantly impair a patient's quality of life. However, most studies have shown significant improvement in quality-of-life post-liver transplantation, with a number of patients returning to work or completing successful pregnancies.[50,51]

ETHICAL CONSIDERATIONS

Equity of distribution and access

Within the United Kingdom, the current system for distribution of donated organs is monitored centrally by the UK Transplant Support Service Authority (UK-TSSA). Each centre is responsible for maintaining their own transplant waiting list and establishing priorities within this. Patients may also be registered with UK-TSSA on a super-urgent list, where the patient is severely ill with acute liver failure or has developed hepatic artery thrombosis post-liver transplant and as such are not expected to survive longer than three days. Whereas in the elective setting, matching donor and recipient blood group and size is a consideration, these criteria may be ignored in the super-urgent setting. Similarly a marginal donor in whom the liver may be considered suboptimal may be used in the recipient with acute liver failure. Close co-operation between the transplant teams has established a system of zoning for organ retrieval, and there is also part-exchange of organs between centres to ensure optimal and efficient use of donated organs.

A similar system of allocation of donated organs exists in the USA. The USA is divided into several different zones. A liver is donated to the sickest patient in the local area, if no appropriate patients exist within the zone of the donated liver, then the organ is offered to other parts of the USA. However, this may result in sicker patients outwith the area of the donated organ not receiving a liver. This system of allocation favours the smaller liver transplant programs with shorter waiting lists, and also the transplant centres that are the only centre within a certain zone of allocation. In addition, well-informed patients, and those wealthy enough, are able to travel to these centres for assessment or even manage to get listed on several transplant centres' waiting lists (multiple listing). These inequalities

have lead to a recent proposal to have a national transplant waiting list, allocating donated livers to the sickest patients, rather than those closest to the donor. This has prompted much heated debate, and some States have even enacted laws prohibiting the cross-border transportation of donated organs.[52]

The current view of the consensus conference in the United States, as well as the General Medical Council in the United Kingdom, is that patients should be treated on the basis of medical need and not discriminated against on a basis of age, race, gender or socio-economic status. However, patients have to pass through many stages of assessment before actually receiving a transplant. Patients have to present themselves to medical attention, then be referred from their local hospital to the Transplant Centre for assessment, and a decision has to be taken as to whether or not the patient should be listed for transplantation. The patient then has to wait for a donor to become available, hopefully before they die of liver failure or its complications. At all of these steps the potential exists to introduce discrimination. Liver transplantation in the elderly (>65 years) appears to be as effective with regard to survival when compared to younger patients. In this country no specific age limit for transplantation has been set, but older patients may be rejected because of severe co-existent medical conditions that are age-related such as ischaemic heart disease. Some studies in the United States have also suggested that female patients and certain ethnic groups are less likely to be accepted for liver transplantation.[53,54]

Transplantation for alcoholic liver disease

One of the most perplexing ethical issues is transplantation for end-stage alcoholic liver disease. This disease is generally perceived as self-induced, affecting only 'down and outs' or 'skid-row' drinkers. However, only 20% of patients who drink heavily develop alcoholic cirrhosis and evidence is increasing that alcoholic liver disease is, in part, genetically determined.[55] Previous studies have shown that the survival of patients transplanted for alcoholic liver disease is similar to other groups.[21,22] In addition, there is a similar pattern of outcomes in terms of compliance and return to work in patients with alcoholic liver disease as compared to other groups.[56] Return to alcohol consumption is common in patients grafted for alcoholic liver disease, although this is rarely equivalent to pre-transplant volumes of alcohol.[23,24] Some dispute exists as to the relative susceptibility of the transplanted liver to the damaging effects of alcohol consumption, with significant alcoholic liver disease reported as frequent or uncommon in different studies.[57]

Although post-transplant acute hepato-cellular rejection may be less common in patients with alcoholic liver disease,[58] other studies have suggested increased morbidity in patients who return to drinking alcohol.[59] In a recent study from the United Kingdom, a patient with alcoholic cirrhosis was considered one of the least deserving of liver transplant recipients by both the general public and general practitioners.[60] In the Oregon Health Care study, transplantation for alcoholic liver disease was given a much lower priority than transplantation for other liver conditions, just above artificial *in-vitro* fertilisation and surgical treatment for uncomplicated haemorrhoids.[61]

Another potential source for discrimination is perceived non-compliance with medical treatment. Transplant patients have to undergo rigorous post-operative follow-up, often having to travel long distances to the Transplant Centre for routine visits. In addition, they have to comply with a strict regimen of medication that may have to continue for the rest of their lives. An inability to comply with or understand these demands can be a legitimate reason for denying a transplant because of the scarcity of donor organs and the potential mortality of recipients on the waiting list for these organs. In such situations, non-compliance is best assessed by objectively determining the patient's record of keeping medical appointments, taking prescribed drugs in the proper regimen, stopping substance abuse with professional assistance, and maintaining abstinence, and obtaining and following psychiatric therapy for diagnosed mental health problems.[62]

FINANCIAL AND HEALTH CARE IMPLICATIONS

When considered together, the assessment process, transplant operation with subsequent long-term follow-up and medication make liver transplantation an extremely expensive treatment option for patients with liver failure. Liver transplantation is the most expensive of solid organ transplants. In the UK, approximate costs of liver transplantation range between £32,000 and £50,000, and in the USA costs of up to $200,000 are quoted.[63] These figures do not include the continuing lifetime costs of follow-up and medication. In addition, indirect costs such as those associated with reduced output and performance, and the monetary, social and psychological costs to the patients and their families, have been poorly studied. Such high costs for the treatment of relatively few patients, perhaps associated with the general perception that all liver disease is secondary to alcohol, has resulted in the low prioritisation of liver transplantation in the Oregon Health Study in the USA and by public health directors in England and Wales. Furthermore, there are no alternatives that prolong survival and improve quality-of-life in patients with life-threatening acute or chronic liver failure, except liver transplantation. A dead patient is indeed a cheap patient! This contrasts with renal failure, for which long-term dialysis may prolong survival indefinitely. Ignoring the improvement in quality of life that a transplant affords patients with renal failure, the costs of transplantation compare favourably with long-term dialysis.

The costs of any individual liver transplant are dependent on a number of factors. Transplantation for hepatitis B is associated with the extra costs of HBIG therapy, which may have to be continued indefinitely; this adds £7,000-10,000 per year. The length of hospital stay is an important determining factor in the cost of an individual liver transplant. Therefore factors that lengthen hospital stay increase the costs, such as acute cellular rejection and its treatment, the use of marginal donors and the pre-transplant status of the patient. Liver transplantation for patients in ITU costs $211,711, compared with an average cost of $114,797 for a patient waiting at home. The former patients also have poorer post-transplant survival. Re-transplantation is also associated with increased costs that amount to more than the sum of two single transplant operations. This variation in the costs of individual transplant operations has lead to most purchasers paying a lump sum to cover each case, rather than individual reimbursement for individual liver transplants.

In the UK, most of the transplants are performed on UK residents covered by the NHS as far as costs are

concerned. In contrast, in the USA private medical insurance providers pay for approximately 80% of the liver transplants. Many such providers exist in the USA with differing coverage with regard to donor, surgical, anesthetic and continuing medication costs. Some policies have a total lifetime limit of a set figure such as $1,000,000. It is not uncommon for liver transplant patients in the USA to be faced with huge medical and pharmacy bills after their operation, because many of the medical insurance policies are inadequate to meet the financial burden of liver transplantation. Poorer patients are covered by the Health Care Financing Administration (HCFA) via the Medicaid or Medicare systems. However these systems will only pay for immunosuppressive drugs for three years post-transplant, a period considerably shorter that the longest surviving liver transplant recipient. The HCFA will not cover costs of liver transplantation for either acute or chronic hepatitis B or hepatic tumours. This is based on the poorer survival associated with these indications. The poor survival of patients with hepatitis B is due to the lack of availability of HBIG, which is not licensed by the FDA in the USA. In contrast, the rich or those with good private health insurance will be able to receive transplants for these indications. This apparent discrimination led to much debate in the USA following the high profile case of Mickey Mantle, a baseball 'Hall of Famer', who had liver cancer and received a liver transplant a few days after listing, but died only two months later.

In view of the high costs of liver transplantation, what are the benefits both for the patients and the community as a whole? Liver transplantation for any indication has not been the subject of randomised control trials. However, the survival of patients, following transplantation with either Child B or C cirrhosis, is significantly better than that predicted by mathematical modeling studies for a variety of disease-specific indications. This has been confirmed by a few case-matched studies. There is also an improvement in the patient's quality of life, although these improvements may not become evident until one year following liver transplantation and may never reach 'normal' levels of well-being reported by 'normal controls'. It is not uncommon for patients to return to work following transplantation, and successful pregnancies are possible.

A Dutch study[64] attempted to cost these benefits concluding that each life-year gained in survival was $23,800-$67,300 (1991 prices), and the cost of each quality adjusted life-year was $25,800-$67,300 (1991 prices).

CONCLUSIONS

Liver transplantation is now an accepted treatment for selected patients with acute and chronic liver failure. Some patients receive liver transplants to improve their quality-of-life which has been adversely affected by itch or fatigue. Both morbidity and mortality, as well as costs, are increased in patients with advanced liver failure. Therefore clinicians should actively consider liver transplantation in all their patients, even those who are out-patients or have Child class B cirrhosis, and referral is recommended if the conditions listed in Table 9 occur.

TABLE 9
Indications for consideration of liver transplantation in patients with chronic liver disease.

- Fatigue or intractable itch.
- The occurrence of spontaneous bacterial peritonitis.
- Intractable or drug-resistant ascites.
- Poorly controlled bleeding due to portal hypertension.
- Encephalopathy, especially if spontaneous.
- Malnutrition.
- Albumin <30 g/L.
- Prothrombin ratio >1.5.
- Bilirubin > 50 μmol/L (hepatic cirrhosis) or > 100 μmol/L (cholestatic liver disease).

ACKNOWLEDGEMENTS

KJS is supported by the Scottish Hospital Endowment Research Trust and the Scottish Liver Transplant Unit Endowment Trust. UK Transplant Support Service Authority prepared the statistics for Figure 1 from the National Transplant Database maintained on behalf of the UK transplant community. Dr George Masterton, Consultant Psychiatrist contributed the psychiatric contra-indications to liver transplantation in Table 5.

REFERENCES

1 Anon. Consensus statement on indications for liver transplantation. *Hepatology* 1994; **20:**635-85.
2 Lake JR. Changing indications for liver transplantation. *Gastroenterol Clin North Am* 1993; **22:**213-29.
3 Sebayel MA, Ramirez C, Kizilisik AT, Geldhof G *et al.* Four year experience with liver transplantation in Saudi Arabia. *Transplant Proc* 1998; **30(7):**3245-6
4 Shaharabani E, Mor E, Bar Nathan N *et al.* A 5-year experience in liver transplantation at Rabin Medical Center, Israel. *Transplant Proc* 1997; **29(6):**2642-3.
5 Liu PP, Chen CL, Chen YS *et al.* Experience with liver transplantation in Taiwan. *Transplant Proc* 1998; **30(7):**3178-9.
6 Kim ST, Lee KV, Park KW *et al.* Experience of liver transplantation. *Transplant Proc* 1998; **30:**3243-4.
7 Lo CM, Fau ST, Liu CL *et al.* Five year experience with development of a liver transplant programme in Hong Kong. *Transplant Proc* 1998; **30:**3247-8.
8 Trey C, Davidson CS. The management of fulminant hepatic failure. In: Poppa H, Schafer F (eds) *Progress in liver disease, vol III* New York:Grun and Strattan, 1970; 292-8.
9 Ellis AJ, Saleh M, Smith H, Portmann B *et al.* Late-onset hepatic failure - clinical-features, serology and outcome following transplantation. *Hepatology* 1995; **23:**363-72.
10 O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97:**439-45.
11 Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *B J Surgery* 1973; **60:**646-9.
12 Wiesner RH, Porayko MK, Dickson ER *et al.* Selection and timing of liver-transplantation in primary biliary-cirrhosis and primary sclerosing cholangitis. *Hepatology* 1992; **16:**1290-9.
13 Neuberger JM, Gunson BK, Buckels JAC, Elias E, McMaster P. Referral of patients with primary biliary-cirrhosis for liver transplantation. *Gut* 1990; **31:**1069-72.
14 Shetty K, Rybicki L, Carey WD. The Child-Pugh classification as a prognostic indicator for survival in primary sclerosing cholangitis. *Hepatology* 1997; **25:**1049-53.

[15] Abuelmagd KM, Selby R, Iwatsuki S *et al.* Cholangiocarcinoma and sclerosing cholangitis - clinical characteristics and effect on survival after liver-transplantation. *Transplantation Proc* 1993; **25:**1124-5.

[16] Czaja AJ, Rakela J, Ludwig J. Features reflective of early prognosis in corticosteroid-treated severe autoimmune chronic active hepatitis. *Gastroenterology* 1988; **95(2):**448-53.

[17] Neuberger J, Portmann B, Calne R, Williams R. Recurrence of autoimmune chronic active hepatitis following orthotopic liver grafting. *Transplantation* 1984; **37(4):**363-5.

[18] Kerkark N, Hadzic N, Davies ET *et al.* *De-novo* autoimmune hepatitis after liver transplantation. *Lancet* 1998; **351:**409-13.

[19] Poynard T, Barthelemy P, Fratte S *et al.* Evaluation of efficacy of liver-transplantation in alcoholic cirrhosis by a case-control study and simulated controls. *Lancet* 1994; **344:**502-7.

[20] Moss AH, Siegler M. Should alcoholics compete equally for liver-transplantation. *JAMA* 1991; **265:**1295-8.

[21] Belle SH, Kimberly CB, Detre KM. Liver transplantation for alcoholic liver disease in the United States: 1988 to 1995. *Liver Transpl Surg* 1997; **3:**212-9.

[22] Periera SP, Williams R. Liver transplantation for alcoholic liver disease at King's College Hospital: survival and quality of life. *Liver Transpl Surg* 1997; **3:**245-50.

[23] Tang H, Boulton R, Gunson B, Hubscher S, Neuberger J. Patterns of alcohol consumption after liver transplantation. *Gut* 1998; **43:**140-5.

[24] Howard L, Fahy T, Wong P *et al.* Psychiatric outcome in alcoholic liver-transplant patients. *QJM* 1994; **87:**731-6.

[25] Everhart JE, Beresford TP. Liver transplantation for alcoholic liver disease: a survey of transplantation programs in the United States. *Liver Transpl Surg* 1997; **3:**220-6.

[26] Mathurin P, Duchatelle V, Ramond MJS *et al.* Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. *Gastroenterology* 1996; **110:**1847-53.

[27] Davies SE, Portmann BC, O'Grady JG *et al.* Hepatic histological-findings after transplantation for chronic hepatitis b virus-infection, including a unique pattern of fibrosing cholestatic hepatitis. *Hepatology* 1991; **13:**150-7.

[28] Samuel D, Muller R, Alexander G *et al.* Liver-transplantation in European patients with the hepatitis-B surface-antigen. *N Engl J Med* 1993; **329:**1842-7.

[29] Gane EJ, Naoumov NV, Williams R. Long-term outcome of hepatitis C infection after liver transplantation. *N Engl J Med* 1996; **335:**522-3.

[30] Feder JN, Gnirke A, Thomas W*et al.* A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996; **13:**399-408.

[31] Farrell FJ, Nguyen M, Woodley S *et al.* Outcome of liver transplantation in patients with hemochromatosis. *Hepatology* 1994; **20:**404-10.

[32] Schilsky ML, Scheinberg IH, Sternlieb I. Liver-transplantation for Wilson's disease - indications and outcome. *Hepatology* 1994; **19:**583-7.

[33] Elzouki AN, Lindgren S, Nilsson S *et al.* Severe alpha(1) antitrypsin deficiency (PiZ homozygosity) with membranoproliferative glomerulonephritis and nephrotic syndrome, reversible after orthotopic liver transplantation. *Hepatology* 1997; **26:**1403-7.

[34] Couetil JPA, Soubrane O, Houssin DP *et al.* Combined heart lung-liver, double lung-liver, and isolated liver transplantation for cystic fibrosis in children. *Transpl Int* 1997; **10:**33-9.

[35] Todo S, Starzl TE, Tzakis A *et al.* Orthotopic liver-transplantation for urea cycle enzyme deficiency. *Hepatology* 1992; **15:**419-22.

[36] Ringe B, Wittekind C, Weimann A. Results of hepatic resection and transplantation for fibrolamellar carcinoma. *Surg Gynecol Obstet* 1992; **175:**299-305.

[37] McPeake J, Williams R. Liver-transplantation for hepatocellular carcinoma. *Gut* 1995; **36:**644-6.

[38] Collier J, Sherman M. Screening for hepatocellular carcinoma. *Hepatology* 1998; **27:**273-8.

[39] Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery* 1991; **110:**726-35.

[40] O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease - results in 93 consecutive patients. *Ann Surg* 1988; **207:**373-9.

[41] Marino IR, Todo S, Tzakis AG *et al.* Treatment of hepatic epithelioid hemangioendothelioma with liver-transplantation. *Cancer* 1988; **62:**2079-84.

[42] Thistlethwaite JR, Emond JC, Woodle ES *et al.* Increased utilization of organ donors - transplantation of 2 recipients from single donor livers. *Transplant Proc* 1990; **22:**1485-6.

[43] Strong RW, Lynch SV, Ong TH *et al.* Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990; **322:**1505-7.

[44] Peabody JL, Emery JR, Ashwal S. Experience with anencephalic infants as prospective organ donors. *N Engl J Med* 1989; **321:**344-50.

[45] Starzl TE, Fung J, Tzakis A *et al.* Baboon-to-human liver transplantation. *Lancet* 1993; **341:**65-71.

[46] Chari RS, Collins BH, Magee JC *et al.* Brief report: treatment of hepatic failure with *ex vivo* pig-liver perfusion followed by liver transplantation. *N Engl J Med* 1994; **331(4):**234-7.

[47] Pereira SP, Williams R. Limits to liver transplantation in the UK. *Gut* 1998; **42:**883-5.

[48] Lucey MS, Brown KA, Everson GT *et al.* Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg* 1997; **3:**628-37.

[49] Neuberger J. When should patients be referred for liver transplantation. *BMJ* 1987; **295:**565-6.

[50] Gross CR, Malinchoc M, Kim WR *et al.* Quality of life before and after liver transplantation for cholestatic liver disease. *Hepatology* 1999; **29(2):**356-64.

[51] Rayes N, Neuhaus R, David M *et al.* Pregnancies following liver transplantation - how safe are they? A report of 19 case under cyclosporine A and tacrolimus. *Clin Transplant* 1998; **12(5):**396-400.

[52] Ubel PA, Caplan AL. Geographic favoritism in liver transplantation - unfortunate or unfair? *N Engl J Med* 1998; **339:**1322-5.

[53] Belle SH, Detre KM. Report from the Pitt-UNOS Liver Transplant Registry. *Transplant Proc* 1993; **25(1):**1137-42.

[54] Zettermana RK, Belle SH, Hoofnagle JH *et al.* Age and liver transplantation: a report of the Liver Transplantation Database. *Transplantation* 1998; **66(4):**500-6.

[55] Bassendine MF, Day CP. The inheritance of alcoholic liver disease. *Baillieres Clin Gastroenterol* 1998; **12(2):**317-35.

[56] Snyder S, Drooker M. A psychiatric perspective on liver transplantation for patients with alcoholism and alcoholic liver disease. *Curr Opin Organ Transpl* 1998; **3(1):**63-7.

[57] Lee RG. Recurrence of alcoholic liver disease after liver transplantation. *Liver Transpl Surg* 1997; **3:**292-5.

[58] Vanthiel DH, Bonet H, Gavaler J, Wright HI. Effect of alcohol use on allograft-rejection rates after liver-transplantation for alcoholic liver-disease. *Alcohol -Clin Exp Res* 1995; **19:**1151-5.

[59] Coffman KL. The question of screening alcoholic liver transplant candidates. *Curr Opin Organ Transpl* 1998; **3:**68-71.

[60] Neuberger J, Adams D, MacMaster P *et al.* Assessing priorities for allocation of donor liver grafts: survey of public and clinicians. *BMJ* 1998; **317:**172-5.

[61] Dixon J, Welch HG. Priority setting - lessons from Oregon. *Lancet* 1991; **337:**891-4.

[62] Wolcott DL. Organ-transplantation psychiatry. *Psychosomatics* 1993; **34:**112-3.

[63] O'Grady JG. Clinical economics review: liver transplantation. *Aliment Pharmacol Ther* 1997; **11:**445-51.

[64] Bonsel GJ, Klompmaker IJ, Essinkbot ML *et al.* Cost effectiveness analysis of the Dutch liver-transplantation program. *Transplantation Proc* 1990; **22:**1481-4.