74% of the survivors of liver transplantation for alcoholic liver disease are able to work and contribute to society as a result of having had the transplant procedure.

Probably the most surprising statistic concerning liver transplantation for alcoholic liver disease is the finding that 89.5% of the transplant survivors have remained alcohol-abstinent.[12] Of those that have resumed drinking, the majority drink only moderately (three or fewer drinks per week) as determined by self-report and corroborated by their significant other and their primary-care physicians. This alcohol abstinence following successful liver transplantation appears to be the rule rather than the exception if appropriate selection criteria are utilized for the selection of such individuals for transplantation.

The factors that appear to identify those alcoholics most likely to benefit and remain abstinent after successful liver transplantation are (1) the support of a significant other, be it a spouse, friend, or relative; (2) an acceptance of alcohol as the cause for their prior liver disease; (3) active involvement in and completion of a 4- to 6-week alcohol treatment program and abstinence for 3 to 6 months prior to transplantation; and (4) an existing job or an adequate education that allows for subsequent employment and, consequently, a redirection of interests away from those associated with alcohol use toward other forms of recreation or interest.[13–15]

Based on the above experience with liver transplantation for alcoholic liver disease, it would appear that the need for transplantation exists for this group. A high survival rate is possible accompanied by a high rate of subsequent employment and a surprisingly low rate of alcohol abuse recidivism. These facts would appear to justify the continued application of liver transplantation for individuals with advanced alcoholic liver disease who, without such therapy, would either die or become invalids because of their disease.

VIRAL LIVER DISEASE

Liver transplantation is a therapeutic option for patients with either fulminant hepatic failure or end-stage liver disease (cirrhosis) occurring with or without hepatocellular cancer due to viral hepatitis (Tables 2 and 3). As was the case for alcoholic liver disease, the prevalence of viral liver disease is substantial, and the need for some type of therapy, be it medical or surgical, is obvious (Table 1).

To date, with the exception of the controversial use of prostaglandins in patients with fulminant hepatic failure, no specific medical therapy exists, and liver transplantation is the only realistic therapeutic option currently available.[16] Compared with historical controls, liver transplantation for individuals with fulminant hepatic failure increases the survival rate 11-fold. When compared to individuals given maximal medical therapy with intent to transplant, liver transplantation increases the chance for survival threefold.[17]

Fulminant hepatitis attributable to type A or B hepatitis

Table 2. Annual Incidence of Viral Hepatitis and Purported Need for Transplantation

Disease Type	Cases per Year
Type A hepatitis	
Annual incidence	1,200,000
Fulminant cases	1,200
Type B hepatitis	
Annual incidence	300,000
Fulminant cases (0.1%)	300
Chronic cases (5%)	15,000
Type C hepatitis	
Annual incidence	175,000
Fulminant cases (0.1%)	175
Chronic cases (25–50%)	43,750

typically occurs at the two extremes of life. Specifically, in children it occurs in those under 10 years of age, and in adults it typically occurs in those older than 50. As a result, the potential for a long life following recovery from these two types of fulminant hepatitis is only limited by the older age of about half the total cases (the adults older than 50 years of age).

Moreover, recurrent disease can occur following liver transplantation for fulminant hepatitis due to the A, B, or C viruses.[18–20] The data currently available relative to the issue of disease recurrence following fulminant type C hepatitis as opposed to types A and B have only been clinical, but they are nonetheless widely accepted.[1–3] A unique complication of both types B and C fulminant hepatitis that can occur with either spontaneous recovery from the hepatitis or transplantation and that limits long-term survival is marrow aplasia involving one or more of the stem-cell lines present within the marrow.[21]

Worldwide, chronic viral hepatitis leading to decompensated cirrhosis is due either to type B or C hepatitis and is the single most frequent indication for liver transplantation. As was the case with alcoholic liver disease, most of the patients with chronic type B hepatitis who are considered for liver transplantation are in their mid-40s and should therefore have the potential for a long life following successful liver transplantation.[20,22] The major impedi-

Table 3. Indications for Liver Transplantation in Cases of Viral Hepatitis

Type A hepatitis	Rare cases of fulminant hepatitis
Type B hepatitis	Fulminant and chronic liver disease
	Hepatoma
Type B+D hepatitis	Same as for type B
	Fulminant hepatitis is more likely
Type C hepatitis	Same as for types A and B
Other NANB hepatitis	Similar to type C
Unusual types (Herpes, CMV, EBV, adenovirus, and others)	Usually fulminant hepatitis in an immunocompromised host

ment to achieving this goal of a long life following successful transplantation for type B hepatitis (and probably also for type C hepatitis) has been the high rate of disease recurrence, reported to be almost 100% for those with type B hepatitis and as high as 10% to 25% for those with type C hepatitis. Preliminary data suggest that the long-term survival of transplant recipients with chronic viral hepatitis may approach that in patients with other chronic hepatocellular diseases with the use of alpha-interferon[23] and possibly with repeated administrations of either hepatitis B immune globulin (HBIG) or one or another of the monoclonal antibodies raised against the HBsAg. These agents have an activity many orders of magnitude greater than that present in commercial lots of HBIG.[20,24–26] Even without such therapies, a 50% to 60% survival rate to 5 years can be expected, despite disease recurrence with liver transplantation for chronic viral hepatitis. Thus, it would appear that sufficient numbers of patients survive and return to a normal, active life to justify the continued performance of the procedure.[27,28] With an additional 5 or more years of life, those who become reinfected may live until an effective antiviral agent can be discovered and therefore be made available to treat them without the need for retransplantation. The results with such retransplantations, however, have been less satisfactory than those obtained with first grafts for chronic hepatitis.[20]

Based upon the above data, it would appear that substantial numbers of patients could benefit from liver transplantation for either acute or chronic liver disease. The survival rate of such patients may be lower than that achieved for other diseases but is sufficiently great to justify transplantation. Moreover, the quality of life of transplant survivors who were transplanted for viral hepatitis is dramatically improved and appears not to be significantly different from that of the normal population.

HEPATIC MALIGNANCY

Hepatocellular carcinoma (Table 4) is an uncommon, but not rare, form of cancer with an annual estimated incidence of 13,600 cases within the United States.[29] When considering this figure, one has to recognize that the United States is a low-incidence area, and more populous countries such as China, South Africa, and others have an incidence that exceeds 20 cases per 100,000 population, making it one of the more frequent types of cancer worldwide. The major etiologic factor for hepatic cancer is HBV infection, especially early onset or infant/childhood disease that occurs as a consequence of vertical transmis-

sion from mother to child. Hepatoma is also a rather common, untoward consequence of chronic liver disease, particularly cirrhosis and a number of heritable metabolic liver diseases.

The optimal therapy for hepatocellular carcinoma is partial or subtotal hepatectomy. Unfortunately, these procedures can only be accomplished in individuals with normal residual livers and typically those with single tumors involving a single hepatic lobe.[30,31] Even in the best of hands, such surgery carries an operative mortality that ranges from 5% to 30%.[32] These figures have to be counterbalanced by the fact that fewer than 50% of the cases explored without intent to transplant are resectable, and that fewer than 20% of the cases explored have their tumors fully resected.[33] Obviously the only hope for those with large tumors involving more than one lobe of the liver, those that are located centrally near the porta, those that occur in cirrhosis, and those that, until recently, have been treated with incomplete tumor removal, is a total hepatectomy with liver transplantation. Figure 1 shows the actuarial survival after liver transplantation for hepatitis B carriers with and without liver cell cancer compared to that of over 1000 individuals transplanted for other causes. It is true, as noted earlier, that patients who are HBsAg-positive at the time of transplantation have a survival rate that is reduced by approximately 20% from 2 to 5 years after transplantation as compared with all other recipients. It can also be seen from this figure that those who have a hepatoma and are HBsAg-positive at the time of transplantation have a 20% reduction in long-term survival from 3 to 5 years following transplantation. Thus, the presence of a hepatoma clearly reduces the long-term prognosis. This is not to say that the situation is hopeless.

When looked at another way, these same data are quite hopeful. After 3 years, it seems that 30% of the patients transplanted for hepatocellular carcinoma are cured of their disease. These cases represent cures in individuals who could not be treated with a smaller resection, who are

Table 4. Hepatobiliary Cancer

Annual incidence: 13,600 cases (US)
HBV is responsible for 80% of cases worldwide
HBsAg-positive individuals have a 200- to 300-fold increased risk
Age at time of infection determines carrier risk
   ≥85% if ≤10 years
   ≤10% if ≥20 years
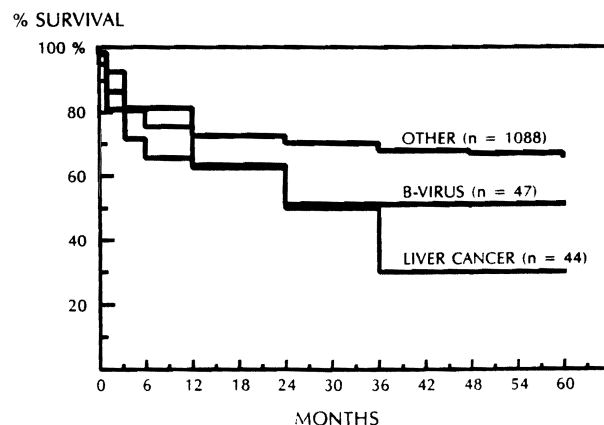
% SURVIVAL

Fig 1. Actuarial survival after liver transplantation for hepatitis B carriers and liver cancer compared to other indications.

HBsAg-positive, and who had no hope of survival with current modes of chemotherapy, with or without adjuvant chemotherapy.[34]

It should be noted further that transplant recipients who have an incidental tumor, that is, one whose largest diameter is less than 5 cm and typically is encapsulated and shows no evidence for vascular invasion upon histologic examination of the resected specimen, can be cured with a 90% survival rate at 3 years or more after transplantation. As expected, the removal of such cases from the larger group of all cases transplanted for hepatocellular carcinoma reduces the rate of success achieved in the remaining cases. The data available from Europe appear to corroborate the data available from Pittsburgh concerning these issues.[8,35]

The reported experience with fibrolamellar carcinoma[36-38] and epithelial hemangioendothelioma[39-41] is somewhat better than that observed with other types of hepatic cancer. Conversely, the prognosis with cholangiolar carcinoma has been considerably worse.[5,9,42]

The improvements that may occur with the addition of adjuvant chemotherapy, immunotherapy, and an aggressive attack upon micrometastasis identified during the anhepatic phase of the procedure using radiolabelled monoclonal antibodies directed at oncofetal hepatocyte surface antigens remain to be determined, but they are expected to improve current results.

Thus, the fact that (1) transplantation can cure as many as 25% to 30% of patients that would otherwise die without transplantation; that (2) disease-free intervals of 2 to 3 years can be achieved, providing those destined to experience disease recurrence an extension of high-quality life; and that (3) no competitive medical or radiotherapy options currently exist, suggest rather strongly that liver transplantation ought to be and will continue to be offered to individuals with hepatocellular carcinoma. The data also suggest that as techniques for cancer surveillance such as quarterly alpha-fetoprotein and descarboxyprothrombin and semiannual ultrasound examinations become routine, more hepatic cancers will be identified while they are "incidental" lesions, when the prognosis with liver transplantation is markedly improved. As a result, the overall prognosis of individuals transplanted for hepatic cancer should improve remarkably.

SUMMARY

In closing, it is important to note that the indications for liver transplantation are not static but rather are remarkably dynamic and capable of change over time. Thus yesterday's major indications can become relative contraindications, while yesterday's absolute contraindications have become today's nuisances. The goal for physicians who care for individuals with problems such as alcoholic liver disease, viral hepatitis, and hepatic cancer should be to develop new strategies of care that will ultimately eliminate these diseases as problems, rather

than eliminating individuals with such health problems from currently available health options. In other words, physicians who accept the responsibility for a patient's life should be searching for the best form of therapy available for their patient rather than examining the reasons that exist for limiting one's choice in health care.

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