While treating the medical problems caused by alcoholism is not new (Beresford, 1979), few other circumstances have focused the issues surrounding the care of alcohol-dependent people as have the dilemmas of whether to provide an alcoholic with a "new" liver, when to do so, and how to construct follow-up care.

A decade ago the possibility of an alcoholic receiving a new liver appeared remote. A consensus conference at the National Institute of Health in the United States, for example, stated that although liver transplantation was becoming an increasingly viable clinical procedure, it should be offered to alcoholics only in rare circumstances (Anonymous, 1983). While this statement was intended to restrict the use of liver transplantation in alcoholic liver disease, it was the first official consideration of the possibility of alcoholics receiving "new" livers. The authors of that document went on to warn that only alcoholics who were likely to remain abstinent should be given a liver graft. As we will discuss below, the distribution of liver grafts to alcohol-dependent (AD) people with liver failure has grown beyond the National Institute of Health panel's vision but the concern with post-transplant abstinence has persisted.

A few years after the National Institute of Health consensus pronouncement, the transplantation group at the University of Pittsburgh published data from a series of alcoholics who had received a liver graft: 1-year survival characteristics did not differentiate them from non-alcoholic recipients and they appeared to be maintaining an abstinent state (Starzl et al., 1988). This prompted Starzl's comment that liver transplantation was a cure for alcoholism. Few in the alcoholism/addictions treatment community would agree with his exuberant conclusion: clinical cases are legion in which patients have undergone extensive, often painful procedures only to return to uncontrolled drinking at some later date. At the same time, Starzl's comment implied that the propensity to drink in an uncontrolled fashion had something to do with liver physiology or with an interaction between the liver and the brain. Most current biological research in the field of alcoholism suggests that the mechanisms that may account for tolerance, withdrawal and loss of control of alcohol use are probably confined to the brain alone. At least, such has been the working assumption to this point.

At about the same time, a Michigan court established the legal precedent that alcoholism alone did not contraindicate liver transplantation (Beresford et al., 1990). The judge admonished the medical profession against requiring, as a condition of the transplant, preoperative lengths of abstinence that were greater than the likely natural course of the end-stage liver disease. Recognizing the dilemma caused by the scarcity of livers suitable for transplantation, the court challenged both the transplant and the alcoholism research communities to provide a reasonable set of criteria upon which to select alcoholics for liver transplantation.

In response to this circumstance and fueled by two medical advances—the introduction of cyclosporine-A and improved surgical techniques which, taken together, rendered liver transplant a highly survivable procedure—we began a study of the selection of alcoholic patients (Beresford et al., 1990). We quickly noted a series of observations that required further inquiry. First, for example, it was evident that most of the people being referred for liver transplant and who qualified for alcohol dependence by standard diagnostic criteria were relatively young: the average age was approximately 44 years. By
contrast, in the United States, cirrhosis deaths due to alcohol use reach a peak prevalence in the seventh decade of life (Grant, DeBakey & Zobeck, 1991).

At the same time, alcoholic women were over-represented among referrals: the ratio was approximately two AD males for every AD female, as compared to the four-to-one ratio seen in general population statistics for alcoholism (Schuckit, 1991). This meant that approximately 60% more women were being referred than might have been expected. While this fact is not surprising to those familiar with studies demonstrating a predilection towards liver injury among women, it runs contrary to the popular stereotype of the chronic alcoholic who is usually pictured as a middle-aged or elderly male. Stereotypes can have a powerful influence on families who must decide on an organ donation to a regional transplant program.

We also noticed that the length of pre-evaluation abstinence for AD candidates, generally characterized as greater or less than 6 months, appeared to have little association with those factors that research in alcoholism had recognized as the best prognostic indicators of long-term abstinence or its lack. In our view, these indicators appeared to be: (1) a diagnosis of alcohol dependence by standard criteria, rather than by an assumption based on a probable cause for liver failure or by clinical intuition, (2) an active and unambivalent acceptance of this diagnosis by the liver transplant candidate, and as often as possible by their family, (3) an indication of a socially stable environment, and (4) the presence of two or more of the four prognostic factors for long-term abstinence observed by George Vaillant. The last category includes (a) a rehabilitation relationship with another person, (b) one or more "substitute dependencies", or activities that structure time otherwise spent in drinking, (c) a source of improved hope or self esteem, and (d) a certain, untoward consequence of drinking (Vaillant, 1983). We reported our experience with this approach in an early description of a sample of 32 presumed alcoholic candidates for transplant for liver transplantation (Beresford et al., 1990).

As this patient series enlarged over a number of years, further data from 269 transplant candidates accrued. We have presented this in detail in another forum (Lucey, Merion & Beresford, 1994). The predilection both for relatively younger people and for women has remained. At the same time, it became clear that only three of every four candidates referred to our program as alcoholics in fact met standard criteria for alcohol dependence. The remaining candidates were split almost equally between a diagnosis of alcohol abuse (defined as evidence of a tolerance to alcoholism with no evidence of withdrawal symptoms, of loss of control or of social difficulties due to drinking) or no substance use diagnosis whatever. Conversely, we found previously unrecognized alcohol dependence in putatively non-alcoholic patients referred for liver transplant consideration.

In our program, a careful clinical assessment of prognostic factors for future abstinence resulted in a disqualification of approximately one of every six alcoholic candidates because their likelihood after transplantation for a resumption of sustained and uncontrolled drinking appeared high. A follow-up analysis of 99 alcoholic candidates for liver transplantation found that alcoholic recipients were likely to remain alive for 2 years in approximately 80% of cases. In contrast, the estimated actuarial survival of alcoholic candidates denied transplantation because of their psychiatric evaluation was significantly less, reaching zero at 2 years. (Lucey et al., 1992).

Some answers began to appear on the clinical meaning of pre-operative abstinence for greater or less than 6 months: a resource utilization study done by our group found no differences, based on length of preoperative sobriety, in such measures as the number of complications post-operatively, the number of days spent in the intensive care unit, or in hospital stay after the operation (McCurry et al., 1992).

The most salient question, however, had to do with the likelihood of remaining abstinent after having received a new liver graft. When we addressed this in a follow-up study, we found that the likelihood of 1-year abstinence was in the range of 90% among alcoholic recipients (Beresford et al., 1992). Contrary to expectation, we also found a relatively high rate of alcohol exposure among non-alcoholic recipients post-operatively: 18 of 39 (46%) patients had used any alcohol since the transplant and 11 of 39 (28%) had used alcohol within 30 days of the follow-up interview. This occurred despite the fact that both AD and non-AD patient groups had been warned specifically against alcohol use because of its potentially toxic effects on the
Table 1. Multi-center data on alcoholic liver transplant recipients

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<td>91</td>
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Table 1. Multi-center data on alcoholic liver transplant recipients

After the publication of our early experience, other programs began evaluating alcoholic patients with respect to drinking risk and probable long-term prognosis. While many of these patient series are still under way, sufficient experience across centers has now been accumulated (see Table 1) to suggest that a first-year abstinence rate in the range of 90% is not unusual and is probably the norm for highly selected AD patients. (Coffman, 1992; Everson, 1992; Gish et al., 1993; Osorio et al., 1993; Tripp, Clemons & Stuart, 1992)

Further experience with the selection process has added different methods of assessing which candidates are at high risk for alcoholic relapse and which are not. One recently published series, for example, described an assessment based on the quantity and frequency of alcohol use and asserted that a contract, signed by the alcoholic candidate, is a valuable adjunct to discriminating between high- and low-risk candidates (Gish et al., 1993). Another group has provided a mathematical calculation, based on a survey of alcoholic patients in the American Veterans Administration system, that provides a coefficient claiming to predict high-risk relapse (Yates et al., 1993). While these methods require further evaluation before they can be applied generally, most transplant programs now attempt to recognize high-relapse-risk drinkers based on an assessment of empirical clinical data. In most programmes, high-relapse-risk AD candidates make up a minority of alcoholics referred for liver transplantation.

Conversely, our experience has been that very-low-relapse-risk AD patients, those who are likely to remain abstinent for long periods of time, are also recognizable. In Table 2, for example, we list the frequencies of Vaillant's prognostic factors among a series of AD liver transplant candidates. Alongside are the actual selection rates for liver transplant. Those with all four of Vaillant's prognostic factors have a high rate of selection for liver transplant, equaling that seen for candidates suffering from non-alcoholic liver diseases such as primary biliary cirrhosis or sclerosing cholangitis. Those with one or none of Vaillant's prognostic factors had a very much lower rate of selection, about a one in seven chance. The largest group, and the most difficult to assess clinically, fell between these extremes: people with two or three of Vaillant's prognostic factors. The chance of proceeding to liver transplant among this group was approximately one in three. One may reasonably ask whether Vaillant's factors viewed pre-operatively have any bearing on post-operative sobriety since, as discussed below, abstinence rates during the first year remain high. Because of confounding treatment variables an assessment of this question can only be done after the first post-operative

Table 2. Vaillant's prognostic factors and the frequency of listing for transplant (n = 190 AD patients)

<table>
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<th>Listed</th>
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<tr>
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<td>14</td>
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year using large numbers of alcoholic liver transplant recipients. These data do not exist at the present time.

The prognostic approaches used so far, including our own, represent extrapolations from observations made on AD subjects in other settings and for other purposes. We do not know, for example, which of those factors previously thought related to long-term abstinence are relevant people who receive a liver graft and, if so, to what degree. Ordinarily, in the study of clinical therapeutics, a randomly assigned, controlled, double-blind trial of liver transplantation for alcohol-dependent subjects would be the optimal way to decide on the true risk of post-transplant relapse. Several factors obviate a trial of this nature, however.

The first is the lack of an alternative treatment, a requirement for any randomized study. It is well documented that people with end-stage liver disease who do not receive liver transplant will perish within a relatively brief time. Unlike the situation in kidney transplantation, there is no hepatic equivalent to long-term dialysis, at least not at present. This alternative may ultimately result as extra-corporeal artificial liver devices that have been used to prolong life for a matter of a few days become more effective.

A second problem is that physicians involved in the care of patients with end-stage liver disease lack what has been termed "equipoise": a state of indifference regarding two treatment choices, a prerequisite for an ethical, randomized trial. Since selection for liver transplant inevitably means that a doctor believes that liver transplantation is the most appropriate treatment for a particular patient, it follows that the transplant physician cannot ethically allocate a selected patient to a non-transplant treatment protocol. This is driven, in part, by a third factor: the very small supply of livers suitable for transplantation relative to the very large demand for them. One may easily compare the efficacy of a standard and a new antibiotic when there is enough of both to go around. This is not the case in liver transplantation. Waiting lists are now long and deaths occur solely because of supply and demand.

The next best alternative for study, in our view, is a longitudinal examination of outcome among AD patients selected clinically for liver transplant. In such a study, a cohort of alcohol-dependent persons could be identified, characterized and followed closely for a minimum of 3 years with respect to specific measures: the occurrence of alcohol relapse, hospitalization because of alcohol relapse, graft health, medical compliance and the presence of Vaillant's prognostic factors over the long term. Data from longitudinal study will shed light on the applicability of a series of factors, including the traditionally troublesome one of length of pre-operative abstinence. Similarly, a study of this nature would be able to document the actual rates of relapse over the long term, frequencies that most seasoned alcohol clinicians would expect to rise as the intensity of the experience of the transplant operation and of post-operative care attenuates.

This intuitive prediction of relapse among AD recipients has recently received empirical support from our patient series (Lucey et al., 1994). A follow-up assessment of 46 AD cases, averaging 3 years' post-transplant survival, demonstrated that 18 (39%) admitted to one or more occasion of at least some alcohol use while the remaining 28 remained abstinent. Five (11%) of the patients returned to regular, uncontrolled drinking that led to hospitalization. Three late deaths occurred among long-term survivors due respectively to recurrent hepatitis B infection, unexplained hypoglycemia and presumed rejection in an actively drinking patient who had stopped immunosuppression. Long-term survivors had an average of five liver biopsies: no significant differences in the frequency of the histological features of liver injury separated alcohol users from abstainers. Only one long-term survivor, who was actively drinking, presented typical features of alcoholic steatohepatitis at biopsy. The most common form of liver damage was non-alcoholic hepatitis. Although alcoholic liver disease was unusual even among those five patients who had resumed heavy drinking, four of the five experienced severe, non-hepatic complications of alcohol abuse after transplantation. These included recurrent pancreatitis, pneumonia, cellulitis, intoxication, delirium tremens and cessation of immunosuppressive therapy mentioned above. While alcoholic drinking post-transplant may not lead to early alcoholic liver damage, it does appear to be associated with significant morbidity. These data are among the first to offer empirical support for the contention that alcoholic relapses are bad for liver transplant recipients.
In our 1-year follow-up report (Beresford et al., 1992), we discussed a possible explanation for the high rate of first-year abstinence: the transplant team’s providing each recipient with all of Vaillant’s factors for good prognosis merely as a consequence of the transplant and normal follow-up care. One crucial question for study is whether or not similar provisions of support, brought to bear over the long-term, can succeed in maintaining the high rate of abstinence seen in the first year.

The controversy surrounding the provision of scarce resources to alcoholics, at the expense of other potential candidates for the same resources, raises larger issues concerning what health care resources of any type should be devoted to the care of alcohol-dependent people and at what expense (Atterbury, 1986; Benjamin & Turcotte, 1994; Cohen, Benjamin & Transplant Health Policy Center, 1991; Flavin, Niven & Kelsey, 1988; Loewy, 1987; Makela & Room, 1985; Moss & Siegler, 1991; Schwartzman, 1989). Answering these questions in abstract terms leads to a thicket of biases and philosophical viewpoints, some of which are more a response to direct, and often negative, experiences with alcoholics. The best counterweight in this, as in other instances of clinical controversy, is the pursuit of empirical research.

In our view, the time has come both for systematic study of the natural course and long-term outcome of providing alcoholic patients with a transplanted liver and for investigation of clinical methods that might extend or improve upon the frequencies of abstinence among AD liver graft recipients. Our approach, and indeed our bias from the beginning in this line of investigation, has been that the facts gleaned from empirical observation will serve as the best guides in offering alcoholics this life-saving procedure. We hope that, through careful study of the clinical course of alcoholic patients after orthotopic liver transplantation, we may gain insights into the mechanisms that underlie alcoholism and alcoholic liver disease.

THOMAS P. BERESFORD & MICHAEL R. LUCEY

References


Beresford, T. P. (1979) Alcohol consultation and general hospital psychiatry, General Hospital Psychiatry, 2, pp. 293-300.


Everson, G. T. (1992) Summary of hepatic transplantation for alcoholic liver disease, University of Colorado Medical Center, pers. comm.


injury in alcoholics after liver transplantation—a long term follow-up study (abstract), Gastroenterology, 106(4, Pt.2) P.A935


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