

## Current Status of Liver Transplantation

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### Summary

Liver transplantation has become the treatment of choice for a wide range of end-stage liver disease. As outcomes have improved, so the demand for this therapy has increasingly exceeded the availability of donor organs. Access to liver transplantation is controlled such that donor organs are generally allocated to the patients who are likely to benefit most, although if all patients who might benefit were placed on the waiting list, the donor shortage would be greatly increased.

Recurrence of the original liver disease is emerging as an important issue. Fewer patients are transplanted for liver tumors, as earlier results showed a very high rate of recurrence. In recent years there has been a change in the underlying conditions of patients on the waiting list, and a preponderance of patients now present with hepatitis C and alcoholic cirrhosis.

Increasingly, transplant units are looking to sources of donor organs that would previously have been deemed unsuitable—such marginal donors include non-heart-beating donors (NHBDs). Results from controlled NHBDs—those cases in which cardiac arrest is predicted—suggest that this is a good source of viable organs.

Splitting a donor liver to provide two grafts has successfully enabled the transplantation of a child and an adult from one organ. The transplantation of two adults from a single organ remains a greater challenge.

Transplantation from living donors has been practiced increasingly over the last decade, although anxieties have been expressed over donor safety. In many countries this now represents a significant contribution to overall liver transplant activity.

**Key Words:** Liver; transplantation; donor; allocation; indications.

### 1. Historical Perspective

The first human liver transplant was performed on March 1, 1963, at the University of Colorado on a 3-yr-old boy suffering with biliary atresia (*1*). He died before the operation was completed; it was not until 1967 that the first

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meaningful survival was reported (2). Between 1967 and 1980, 170 liver transplants were performed at the University of Colorado, and between 1968 and 1983, 138 transplants took place in Cambridge, England (2), with 1-yr survival rates of approx 30%. With the emergence of cyclosporine, pioneered by Borel and Calne, as well as gradual refinements of various technical aspects, particularly bile duct reconstruction and coagulation support, outcome figures improved.

In 1983, a National Institutes of Health (NIH) Consensus Conference concluded that liver transplantation was now a therapeutic option for patients with end-stage liver disease, rather than an experimental procedure (3). This led to a rapid expansion of the number of patients referred for liver transplantation worldwide. Five years after the NIH conference, 616 patients awaited liver transplants in the United States. Ten years later, this number had increased to 12,056.

Since the early 1980s, there have been significant advances in all aspects of liver transplantation, including recipient selection, donor management, operative technique, immunosuppression, and postoperative management of liver recipients. These changes, which have marked the evolution from an experimental technique to established and routine therapy, have resulted in enormous improvements in outcome. The overall 1-yr survival for adults and pediatric orthotopic liver transplants is now expected to be in excess of 85%, with 5- and 10-yr survival in excess of 70 and 60%, respectively (4–7). Partly as a consequence of this improved outcome, the selection criteria have broadened, leading to changes in the demographics of the patient population.

## **2. Current Indications for Liver Transplantation**

The goal of liver transplantation is not only to prolong life, but also to improve the quality of life. The selection of patients to achieve these goals and the ideal time at which to intervene during the course of chronic liver disease remain among the greatest challenges for the transplant team. The current indications for liver transplantation can be categorized as follows: advanced chronic liver disease, fulminant hepatic failure, inherited metabolic liver disease, and liver tumors.

Controversy exists over transplantation for alcoholic liver disease, hepatitis B, hepatitis C, and hepatic malignancy because of the risk of recurrent disease and consequent reduced long-term survival. There has been much ethical debate in relation to the use of a scarce resource in both patients with self-inflicted diseases and conditions with a high probability of recurrence. Neuberger and colleagues clearly demonstrated the difficulties faced in attempting to allocate such a scarce resource (8). This study showed that the priorities of the public differed from those of the medical profession. The former placed greater emphasis on factors such as age of recipient, whereas doctors felt that

outcome and value to society were a greater priority. Patients who displayed traits consistent with antisocial behavior (e.g., alcoholism) were given a low level of importance by all. In general, the indications for liver transplantation can be defined as either an intolerable quality of life (because of the liver disease) or an anticipated length of life of less than 1 yr because of liver failure.

### 3. Organ-Allocation Policies

Various schemes have evolved to allocate organs with some reference to urgency. In the United States, the Model for End-Stage Liver Disease (MELD) score, based on serum creatinine, bilirubin, and international normalized ratio (INR), was developed initially during a retrospective study at the Mayo Clinic of patients undergoing transhepatic portosystemic shunts (TIPS). It was subsequently validated as a determinant of short-term prognosis in patients with chronic liver disease (9) and utilized as a disease severity index. In February 2002, the MELD score was implemented by the United Network for Organ Sharing (UNOS) as a criterion for organ allocation to adult patients with chronic liver disease followed the ruling of the Department of Health that allocation be conducted according to medical urgency. Priority is still given to status 1 patients (fulminant hepatic failure or early graft failure following transplantation requiring emergency re-transplantation); these remain a local and regional priority. After these patients, livers are offered to patients based upon their probability of candidate death derived from MELD scores. With a MELD score of 6 or less, the time on the waiting list is also used as a prioritization factor (10). Early reports indicate that this allocation system based on medical severity may reduce the number of deaths on the waiting list (11).

In the United Kingdom, four fundamental concepts underpin the allocation policy, as agreed at the Edinburgh colloquium in 1996 (12). First, guidelines need to be drawn up and agreed on by all those involved. Second, the main criteria for selection must be based on quality of life and anticipated life expectancy. Third, patients selected for transplantation should have a more than a 50% probability of being alive 5 yr after the transplant. Finally, livers are allocated to give the maximum outcome (in preference to every potential recipient having equal share of the donor pool by right). Thus, it is generally agreed that organ allocation should be based on utilitarian rather than deontological principles.

In UK practice, certain patients (those with either fulminant liver failure or primary nonfunction of a transplant—the equivalent of UNOS status 1) have national priority (these patients are deemed “super-urgent”). Thereafter, livers are offered first to the retrieving unit and then, if there is no suitable recipient locally, around the rest of the country on a continually rolling priority based on the balance of net export at each individual center. Thus, livers are allocated to

the most urgent patients on an individual basis (i.e., *ad hominem*), but otherwise all livers are allocated to the transplant unit (rather than to the individual patient). At a local level, individual patient prioritization is usually established at a multidisciplinary meeting. These difficult decisions are based on the principles outlined above, with general co-morbidity of the recipient, length of time on the waiting list, as well as disease progression all taken into account. If a patient's condition deteriorates while on the list, it may be necessary to consider removing him or her from the active waiting list. Effective communication not only between members of the medical team but also with the patient and his or her family is clearly essential at every level of the process.

In addition to blood group matching and, to some extent, size matching, the selection of the recipient for a particular donor organ may also be affected by the quality of the liver on offer. In the interests of obtaining the maximum benefit for the maximum number of patients, there is a strong argument to utilize organs from the better donors in the sicker recipients—the patients who are least able to tolerate a poorly functioning transplant in the immediate post-operative period. Healthier recipients are more able to cope with the period of poor initial graft function that can be associated with the use of a marginal liver (*see below*). This is now a generally accepted principle in the interests of obtaining the maximum benefit from the limited donor supply, but one that clearly poses ethical issues on occasions.

#### **4. Hepatitis C/HIV Infection**

There has been a clear shift in indications for transplantation in the last 15 yr, with a continued increase in non-cholestatic liver diseases predominantly made up of hepatitis C and alcoholic liver disease. In the United States, the proportion of recipients with hepatitis C virus (HCV) infection increased from 12 to 37% between 1990 and 2000, with a similar increase in the number and proportion of liver transplant candidates registered with hepatitis C on the waiting list (**13**). According to the UNOS, in 2001 there were 9783 patients with hepatitis C awaiting a cadaveric liver transplant. Combined infection with hepatitis B or C and HIV (contracted together through either sexual or intravenous routes) has led to a cohort of such patients with chronic liver failure being considered for transplantation. Reservations have been voiced because of the potential for reemergence of hepatitis in CD4-deficient recipients, as well as the use of a scarce resource in an individual with a preexisting life-limiting disease. However, with continual improvements in anti-retroviral medication in HIV (the use of protease inhibitors in combination with non-nucleoside reverse-transcriptase inhibitors), there is now a greatly improved life expectancy with this condition. This allows many patients coinfecting with HIV and hepatitis B/C to be considered for liver transplantation with reasonable prospects for survival.

A recent report on HCV-infected liver transplant recipients estimated the risk of developing recurrent cirrhosis to be as high as 44% at 5 yr posttransplant (**14**). Berenguer et al. reported data from the UNOS registry demonstrating that 5-yr graft survival in recipients transplanted for hepatitis C was 56.8%, the worst of all indications with the exception of malignancy (**14**). Antiviral agents (interferon, including pegylated interferons, ribavirin, or combinations) have a low rate of success because of poor patient tolerance, side effects, or a limited and/or transient response.

In contrast, significant progress has been achieved in the outcome of hepatitis B virus (HBV)-infected liver recipients with the use of current HBV antiviral agents. Han and colleagues reported negative hepatitis B surface antigen serology in 98.3% of patients after transplantation using intramuscular anti-hepatitis B immunoglobulin and lamivudine (**15**).

## 5. Tumors

Another major demographic shift is the reduction in the proportion of patients transplanted for primary liver cancer. This diagnosis is clearly associated with poor outcome because of recurrent disease. In the European Liver Transplant Registry (ELTR) data, the 1-, 5-, and 9-yr patient survivals for patients with cirrhosis (79, 69, and 62%) are significantly better than for patients treated for primary liver cancer (67, 40, and 26%). With improvements in imaging technology, as well as the adoption of defined selection policies, the proportion of livers being transplanted for cancer is falling.

## 6. Retransplantation

In recent years there has been a significant decrease in the number of retransplants performed. This reflects improvements in every step of the transplant process, including choice of donors, preservation fluids, surgical techniques, and, perhaps most important, postoperative recipient management and immunosuppressive protocols. This issue was addressed by Clemente et al. (**16**) in a large retrospective analysis covering more than a decade. They demonstrated a shift in the major cause of retransplantation from chronic rejection to primary graft failure, with 5-yr actuarial survival rates dependent on the cause of graft failure (45.5% for chronic rejection and 19.4% for primary failure) (**16**). Graft loss caused by rejection is now uncommon after liver transplantation. The incidence of chronic rejection in 1048 liver recipients followed for a mean period of more than 6 yr was only 3% (**17**). In a randomized trial comparing cyclosporine with tacrolimus after liver transplantation (the Tacrolimus vs Microemulsified Cyclosporin [TMC] study), the incidence of chronic rejection was only 0.3% in the tacrolimus group (**18**). Another study concluded that chronic rejection does not occur in the pediatric liver recipi-

ent population as long as baseline immunosuppression with tacrolimus is maintained (19).

## 7. Immunosuppression

The mainstay of post-liver-transplant immunosuppression is triple therapy with a calcineurin inhibitor (usually tacrolimus), together with an anti-proliferative agent (mycophenolate or azathioprine) and a corticosteroid (prednisolone). Increasingly, clinicians are tailoring the immunosuppressive regimen to the individual recipient. For example, faster withdrawal of corticosteroids has been shown to be efficacious in recipients transplanted for hepatitis B, where the drug is known to increase viral replication (20). In contrast, prolonged low-dose steroid use in autoimmune hepatitis has been shown to reduce disease recurrence in the graft (21).

Particularly since publication of the TMC study in October 2002, the large majority of liver units have preferentially used tacrolimus over cyclosporine as a first-line calcineurin inhibitor (18). This randomized prospective multicenter study of 606 patients demonstrated a significantly better graft and patient survival at 1 yr in patients on tacrolimus. The combined primary endpoint of death, retransplantation, or treatment failure (owing to rejection) was reached in 21% patients on the tacrolimus arm and 32% in the cyclosporine arm of the trial—a significant difference.

Tolerance remains the goal of the transplant physician. There is evidence that some patients are able to have immunosuppression withdrawn and yet maintain adequate graft function. Starzl's group in Pittsburgh have proposed that dissemination of donor leukocytes (including pluripotent stem cells) occurs from allografts inducing donor/recipient nonreactivity. A series of 95 recipients was reported in which weaning from immunosuppression was attempted (22). These patients were all more than 5 yr from transplant and had stable graft function. At the time of the report, 20% were drug free up to 4.5 yr later, and 39% remained in the weaning process. Twenty-six percent of patients required reinstitution of their immunosuppression for biopsy-proven or presumed acute rejection. Chronic rejection was not seen. This group has also described specific genetic polymorphisms of tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-10 in children that have been successfully weaned from immunosuppression after liver transplantation (23).

Other tolerance-induction strategies have been attempted in animals, including total body irradiation, costimulation blockade, development of chimerism, and lymphocyte depletion using a variety of monoclonal and polyclonal antibodies. Buhler and colleagues recently published a case report of combined human leukocyte antigen (HLA)-matched donor bone marrow and renal allotransplantation. This is the first example of an intentional and clinically appli-

cable approach to inducing renal allograft tolerance achieving potent and sustained antitumor effects in patients with multiple myeloma (24).

## **8. Donors**

The biggest obstacle to the continued expansion of liver transplantation is the increasing gap between waiting lists and organ availability. If localized primary liver tumors, alcoholic liver disease, and allograft failure are accepted as indications, the demand for liver transplants has been calculated to be 25 per million population (25). Using current donor criteria, no more than 80% of all donor livers can be used (25); thus, depending on donor incidence, between 30 and 80% of the patient demand can be met. In 2001, 1978 potential liver recipients died on the waiting list in the United States without receiving a graft (UNOS database).

On first consideration, the prospects for the future are not encouraging. Donor numbers have decreased because of a progressive (and welcome) fall in the two leading causes of brain death in the United Kingdom: head injury from road traffic accidents and intracranial hemorrhage (26). Between 1989 and 1992, the annual number of donors in the United Kingdom resulting from road traffic accidents fell from 279 to 194, a decrease of 30%. The situation is further complicated by changes in neurosurgical practice. Improvements in imaging and shortage of intensive care beds have resulted in a more restrictive policy in the transfer of patients to regional neurosurgical units: patients with a very poor prognosis can now be identified at an early stage. For this reason many patients who would previously have been assessed in a neurosurgical intensive care unit are no longer identified as potential donors (27).

A number of strategies are evolving to address the current situation. These include the use of organs from marginal donors (those outside the criteria previously used in respect to age, co-morbid condition, and cardiovascular stability), organs from NHBDs, the more extensive use of liver splitting (to obtain two transplants from one donor liver), and the transplantation of organs from living donors. Each of these potential solutions raises specific clinical and ethical issues.

## **9. Marginal Donors**

What constitutes a "marginal donor" remains controversial, and different transplant units have developed their own arbitrary policies to determine whether a liver is used or discarded based on broadly accepted guidelines. A selection of 10 major studies in the last decade on this subject includes no less than 32 separate parameters in the various definitions. These include preexisting liver damage (steatosis, obesity, alcohol, deranged liver function tests), adverse lifestyle (drug abuse, homosexual practice), age, hemodynamic instability (hypotension,



inotrope use, cardiac arrest, NHBDs), risks of sepsis and malignancy, and others (length of stay on intensive therapy unit [ITU], malnutrition, hypernatremia).

Widening the acceptance criteria in an effort to expand the donor pool has become a necessity. The use of livers from marginal donors has been shown in several studies to lead to an increased risk of primary graft dysfunction (28–31). This term encompasses both catastrophic primary nonfunction, resulting in death or retransplantation in the first week, or impaired primary function manifest as a coagulation disturbance and increased transaminase levels and resulting in prolonged ITU stay and increased requirement for renal support (and greatly increased cost).

Both primary nonfunction and impaired primary function represent the clinical manifestations of cumulative injury derived from the period of brain death within the donor, subsequent warm/cold ischemia during preservation, and reperfusion at the time of transplantation.

A recent study from Birmingham suggested that the two most important independent donor variables that correlate with graft dysfunction are macrosteatosis (>30% on histopathological analysis) and donor age (32). In the study the outcome with such marginal organs could be dramatically improved if cold ischemia time was restricted to no more than 12 h. Strasberg et al. reaffirmed this association by describing cold preservation time, steatosis, and donor age as the only three parameters with a proven relationship to early graft outcome, the others having an uncertain relationship that required further evaluation (33).

## **10. Reduced-Size Liver Transplantation**

Size reduction of an adult liver was implemented initially to overcome the need for size-matched grafts in pediatric recipients. The technique was introduced clinically in 1981, and the first successful transplant of part of a liver was reported by Bismuth and Houssin, who transplanted the left lobe from an adult to a child in 1984 (34). Further experience at several centers suggested that the use of the left lateral segment (segments II and III) taken from an adult donor would provide an ideal-sized graft for a small child and that the results were comparable to whole size-matched grafts (35). An additional refinement, reported from both Europe and Australia, was the retention of the recipient vena cava, to which the venous outflow (the left hepatic vein) of the graft was anastomosed (36,37). This allowed even larger donor-to-recipient size mismatches as well as retaining a right hemi-liver with intact vena cava. This enabled the concept of liver splitting and, subsequently, living donation.

### **10.1. Liver Reduction**

Liver reduction involves transplantation of part of the liver, the remaining liver being discarded. It is a solution to size discrepancy, but does not affect the



overall availability of donor organs. Liver transplantation from reduced livers (as opposed to split livers) is now usually restricted to left liver grafts (segments I–IV), usually including the donor cava, and left lateral segmental grafts (segments II–III), excluding the vena cava. Generally, if a right lobe graft would fit, then the entire liver would be suitable. The technique has been developed further by the transplantation of a single hepatic segment—either segment II or segment III (38).

Patient and graft survival is equivalent to, and in some circumstances better than, survival after full-size grafting (39). Rates of arterial thrombosis are lower when a pediatric recipient receives a reduced adult graft rather than a cadaveric whole pediatric graft, presumably because of the larger caliber of the donor vessel (40). Conversely, the presence of a cut surface increases the rate of bleeding and bile leaks in the reduced grafts. The development of liver reduction has made possible a reduction in pretransplant deaths in small children from 25% in 1989 to less than 10% today (41). This technique also led directly to the surgical techniques necessary for liver splitting and living donor transplants.

## 11. Split Liver Transplantation

Split liver transplantation, first reported by Pichlmayr et al. in 1988 (42), has the advantage of providing not only organs suitable for small children, but also additional transplants suitable for small adults. Usually, the adult would receive the right-liver graft including segment IV with the inferior vena cava attached and a child the left lateral segment. Segment I (the caudate lobe) is either preserved or discarded, depending on local preference.

Transplants have also been performed of two adult recipients using a single split liver. In these cases, segment IV is retained with the left lobe. The main technical challenge is to provide an adequate mass of liver tissue to both recipients: the left lobe (typically 40% of the liver mass) is sufficient only for a recipient of small body mass. Postoperative liver function can be predicted based on the transplanted liver mass as a proportion of the weight of the recipient. A proportion of 1% (transplantation of a 700-g liver lobe into a 70-kg patient) is considered a safe limit.

Although usually performed as an *ex vivo* procedure (the operation is performed on the explanted, cooled liver), the splitting procedure can also be performed *in situ* during the donor-procurement procedure. This has the advantages of less preservation injury (shorter cold ischemia time) and improved hemostasis of the cut surface (25). *Ex vivo* splitting is also associated with a higher rate of biliary complications (22% vs 27%) compared with whole-organ (4%) or *in situ* split grafts (0% vs 3%) (43). However, the logistics are complex because of the considerably prolonged donor operation and the necessity of a

very experienced retrieval team. It places enormous additional strain on the already stretched resources of liver-retrieval teams, other transplant teams, and donor hospitals. The *ex situ* technique is therefore generally employed, with the procedure performed once the liver has been returned to the transplanting center.

The early experience of liver splitting involved application of the new procedure in high-risk patients, often as a desperate measure; this was reflected in a high morbidity rate (44). Between January 1987 and June 1999 a total of 1036 split grafts (mostly *ex situ*) was transplanted in 898 patients. In adults, the 1-yr patient and graft survival rates were 68 and 60%, respectively. In children (<15 yr), the corresponding figures were 75 and 59%. Survival rates were significantly better in centers that had performed more than 40 split transplants, suggesting a significant learning curve (European Liver Transplant Registry. Custodian: R Adam, Villejuif, France).

## 12. Living-Related Transplantation (LRT)

One of the most challenging and controversial developments devised as a means of reducing waiting list deaths is the use of partial liver grafts from living donors. The first clinical success was reported in 1989 (45), and since that time the technique has been adopted in many centers with great success. Initially, the major proponents were the Japanese liver units where legal and cultural issues render cadaveric donation rare.

The use of living donors has enormous potential advantages in terms of organ quality (absence of the adverse effects of brain death, short cold ischemia time), which reduce the risk of early dysfunction. Also, it enables the transplant to be carried out as a planned procedure at a time optimal to the patient and suitable for the donor and the transplant team. However, although increasingly widely performed not only in Japan, but also in North America and Europe, living donor liver transplantation has yet to make a major impact in the United Kingdom. This reflects unresolved anxieties about donor safety as well as the basic ethical dilemma of putting a healthy individual's life at risk. Living donation must meet three major ethical requirements if it is to succeed: (1) a convincing need for the technique, (2) acceptable risk and benefit to the participants, and (3) a satisfactory process for ensuring adequate informed consent and protection of the donor. It is yet to be seen whether this technique will become widely practiced in Britain.

## 13. NHBDs

The use of organs from NHBDs is increasingly seen as an important solution to the discrepancy between the supply and demand for donor livers. This is accentuated by the changes in neurosurgical practice (described above)

whereby patients with catastrophic cerebral injury are identified at an early stage and allowed to die following withdrawal of medical support. These patients, therefore, are usually not diagnosed as brain dead, and death occurs and is defined by cardiac arrest. Because cardiac arrest in these donors is predicted, it is possible to prepare the transplant team and to await the moment of death. Such donors are, therefore, termed “controlled” NHBDs. Other situations are unpredictable (e.g., the cardiac arrest that occurs outside the hospital or in the emergency department), usually preceded by an unsuccessful attempt at cardiac resuscitation. The logistics of organ retrieval in such cases are more complex. These organ donors are termed “uncontrolled” NHBDs.

Many ethical issues are involved in retrieval of organs from NHBDs. The points of potential conflict of interest (between care of the donor and recipient) include intervention prior to declaration of death and the duration of mandatory no-touch period after cardiac arrest before organ retrieval. The clinical and moral requirements governing NHBD cadaveric organ-procurement policy can be summarized as follows: (1) organs can only be taken from donors who are dead; (2) the care of the living must never be compromised in favor of potential recipients; and (3) informed consent must be obtained prior to retrieval.

In HBDs death is defined by neurological criteria, whereas in NHBDs death is declared only after cardiac arrest. Thus, a fundamental difference between HBDs and NHBDs is that, until the moment after cardiac arrest, the NHBD is alive. The rationale for the mandatory “hands-off period” is to delay any intervention until such time as any central neurological activity, present before cardiac arrest, will have ceased beyond doubt.

The time between cardiac arrest and the start of the organ-retrieval process varies in different institutions: intervals ranging from no waiting to 10 min have been reported. The first international workshop in Maastricht, Netherlands, held in 1995 recommended that a 10-min period after cardiopulmonary arrest be allowed before intervention by the transplant team. However, there is evidence that the 10-min no-intervention period contributes to an increased incidence of primary nonfunction and delayed graft function.

Clinical experience with NHBD liver transplantation is limited (46–48). Under controlled circumstances, with shorter warm ischemia times, the results are acceptable (49). In an uncontrolled setting, when cardiac arrest occurs outside the operating room, results have been poor with a high rate of primary nonfunction (47). Otero and colleagues reported a primary nonfunction rate of 20% in 20 grafts from Maastricht category 2 (uncontrolled) NHBDs (50); the corresponding primary nonfunction rate in 40 HBDs was 2%. Most of the successful cases reported from this group utilized continuous in vivo perfusion with cardiopulmonary bypass or chest compressions with oxygenation. It is likely that this provides some recovery of cellular energy stores prior to cold storage.

## 14. Auxiliary Liver Transplantation

There are two situations in which it is logical to transplant a donor liver but to preserve part of the patient's own liver: transplantation for fulminant liver failure and transplantation for metabolic liver disease.

In many patients with fulminant liver failure, regeneration of hepatocytes leads to recovery and avoids the need for transplantation—the operation is indicated in those patients who are unlikely to survive long enough for adequate regeneration to occur. The objective in auxiliary liver transplantation is to transplant enough healthy functioning liver tissue to bridge the patient over the period of acute liver failure while allowing the native liver time to recover.

In patients with certain metabolic disorders, liver transplantation has been recommended in order to provide one liver-specific enzyme—the function of the liver is otherwise normal. It may be possible to provide adequate levels of enzyme function by transplanting part of a donor liver (34). Examples of such metabolic defects include Crigler–Najjar syndrome type I (51), ornithine transcarbamylase deficiency (52), and propionic acidemia (53).

The advantages of auxiliary transplantation in these circumstances are clear—the patient is largely spared the risks normally associated with graft failure due to rejection and other causes. Importantly, in the case of fulminant liver failure, if the native liver recovers, immunosuppression can be gradually withdrawn, sparing the patients all the long-term morbidity of immunosuppression, including infection, malignancy, and nephropathy.

Currently most groups performing auxiliary partial orthotopic liver transplants (APOLTs) use right, left, or left lateral splits/reduced grafts. Technical problems include compression of major venous vessels into and out of the graft, inadequate portal flow into the donor graft and subsequent thrombosis, inadequate graft size, and toxic liver syndrome in patients with acute failure. These problems have largely been overcome, and satisfactory results have been reported (54); auxiliary transplantation is being considered by a number of centers as a potential adjunct to orthotopic transplant (55). Experience with immunosuppression withdrawal is limited; however, the collected European experience found that 65% of patients surviving more than 1 yr with a successful auxiliary liver transplant were free of immunosuppression (54). In this series the overall 1-yr patient survival rate of 62% in auxiliary liver transplantation was similar to that for orthotopic liver transplantation (61%).

## 15. Xenotransplantation

The use of animals, particularly pigs, as an organ source presents a very attractive alternative to human organs. Pigs can be bred and raised under very clean and controlled conditions. The anatomy and physiology is similar to human counterparts, and the waiting list could be cleared with huge expansion

of the potential donor pool. Before this can become a clinical reality, however, problems relating to immunological, microbiological, and physiological barriers need to be overcome.

In 1992 and 1993, two orthotopic xenotransplantations were performed, placing baboon livers into patients with liver failure secondary to hepatitis B infection. These patients survived 70 and 26 d (56). The livers worked, but not normally, with levels of proteins including albumin remaining in the normal range for baboons and not humans.

No long-term pig-to-primate liver transplants have been performed, although porcine livers transgenic for human complement regulatory proteins have functioned successfully in the short term. Patients with acute liver failure have been supported for a few hours to days with extracorporeal liver perfusion (ECLP) while a human donor liver is sought (57). These procedures have indicated the pig liver to be functional in the short term, with improvements in clinical status and reduction of blood ammonia and lactic acid levels. Whether genetic engineering would be able to “humanize” a pig liver adequately remains to be seen. The major porcine complement factors are only 70% homologous with human factors, and pig and human albumin 65% homologous, discrepancies that may be exaggerated in cascade or regulatory systems.

Pigs and humans represent discordant species, and xenografts from one to the other would be expected to undergo hyperacute rejection because of the presence of preformed antibodies to the  $\alpha$ -gal epitope on vascular endothelium leading to activation of the classical complement pathway. Transgenic techniques have been developed to prevent the hyperacute response. These include the production of pigs transgenic for a human complement regulatory proteins—the introduction of a single human complement regulator gene has been shown to abolish the immediate, complement-mediated hyperacute xenograft rejection. However, induced antibodies and subsequent cellular mechanisms are not controlled by this means (58).

Having controlled the immediate effect of complement activation caused by preformed antibodies, a xenograft is at risk of damage from induced antibodies (delayed xenograft rejection). This has proved difficult to control using conventional immunosuppressive drugs. McGregor and colleagues recently reported that by combining the use of organs that express human decay accelerating factor (hDAF) with the administration of a soluble Gal glyco-conjugate and other immunosuppressive agents, the survival of pig hearts in baboons is extended to a median of 76 d (59). The recent generation of pigs that do not express the main target antigen (60) ( $\alpha$ 1,3-galactosyltransferase gene-knockout pigs [GT-KO]) might prevent the antibody response.

Safety issues include concern about transmission of exogenous viral infections, such as cytomegalovirus, from donor pig to recipient. Early weaning and

subsequent isolation can lead to an absence of virus in these piglets. The presence of endogenous retroviruses in all pig cells has also led to concern. Oldmixon et al. showed that certain pigs lack the capacity to transmit porcine endogenous retrovirus to human cells in vitro (61).

However, even if the safety and immunological barriers to porcine xenotransplantation were overcome, there are real doubts as to the potential value of liver xenotransplantation. Although probably useful in the short-term treatment of liver failure (as a liver-assist device), it is widely agreed that there would be large-scale incompatibilities involving many enzyme systems within the pig liver and proteins synthesized by the liver. It is unlikely, therefore, that the pig liver will prove to be a good substitute for the human liver in clinical transplantation, at least without major genetic engineering.

## 16. The Future

The practice of liver transplantation has become a victim of its own success, with an inexorable rise in patients waiting for surgery and a donor pool that remains static. The future must involve improved utilization of potential organ donors—current initiatives within the British transplant community are addressing this. Optimization of donors including improvements in nutrition as well as possible techniques for ameliorating reperfusion injury are being investigated, as are improvements in preservation techniques and viability assessment (including normothermic extracorporeal perfusion). Living donor transplantation remains a controversial technique, but one that could go a long way to redressing the shortage of donors. Improvements in immunosuppression have had a major effect on the survival of liver-transplant patients, a trend that is likely to continue. A clinically applicable means of achieving immunological tolerance would radically reduce the short- and long-term risks of liver transplantation. Although clearly desirable, this would have the effect of expanding still further the population of patients for whom transplantation is the preferred treatment.

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