Transplantation is one of the greatest achievements of modern medicine. In AD 2000, liver transplantation is well established as the definitive treatment for irreversible acute and chronic liver disease, and progress continues both in scientific investigation and in clinical practice. The care of liver transplant patients, once the domain of transplant centers, has more recently been integrated into the community-based practice of medicine. The two major challenges currently facing liver transplantation are the large and increasing disparity between the numbers of available cadaver donor organs and of qualified patients listed and waiting for transplantation and the management of recurrent disease after liver transplantation, particularly recurrent chronic hepatitis C. Future issues concerning liver transplantation will probably center on the effective use of available cadaver donor organs, including re-evaluation of selection criteria to strike a balance between medical need and the chance of a successful outcome, and on the development of new technologies to expand liver transplantation, such as cadaver split-liver transplantation, adult-to-adult living related and unrelated liver transplantation, xenotransplantation, hepatocyte transplantation, and liver-directed gene therapy. This article reviews the chronology of liver transplantation, presents the current status of transplantation, and offers speculation regarding the future directions of liver transplantation.
LIVER TRANSPLANTATION: THE PAST

Experimental Liver Transplantation

The first experimental attempts at liver transplantation, in dogs, were initiated 45 years ago, in 1955, by Welch of Albany, New York, who described the insertion of an auxiliary liver engrafted heterotopically in either the pelvis or right paravertebral gutter (Table 1) [68].

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1955</td>
<td>First experimental liver transplantation using an auxiliary technique (Welch)</td>
</tr>
<tr>
<td>1956</td>
<td>First experimental orthotopic liver transplantation (Cannon)</td>
</tr>
<tr>
<td>1963</td>
<td>Use of azathioprine and prednisone for immunosuppression</td>
</tr>
<tr>
<td>1963</td>
<td>First human liver transplantations (Starzl)</td>
</tr>
<tr>
<td>1966</td>
<td>Introduction of antilymphocyte globulin</td>
</tr>
<tr>
<td>1967</td>
<td>First 1-year survival after human liver transplantation (Starzl)</td>
</tr>
<tr>
<td>1980</td>
<td>Introduction of cyclosporine for immunosuppression</td>
</tr>
<tr>
<td>1983</td>
<td>NIH Consensus Development Conference on liver transplantation</td>
</tr>
<tr>
<td>1987</td>
<td>Use of University of Wisconsin solution for improved organ preservation</td>
</tr>
<tr>
<td>1989</td>
<td>Introduction of tacrolimus for immunosuppression</td>
</tr>
</tbody>
</table>

The portal vein was anastomosed to the inferior vena cava and the hepatic artery to the aorta or iliac artery, and no immunosuppression was used. The first experimental liver replacement, that is, orthotopic liver transplantation, was reported by Cannon at the University of California at Los Angeles in 1956, but none of those dogs survived. [11] Cannon had speculated that the liver might play a role in rejection and that a replaced liver should not contribute to its own destruction.

In 1958, liver transplantation was established as a primary research focus at Peter Bent Brigham Hospital in Boston, Massachusetts, under the direction of Moore, [39] [40] and Northwestern University in Chicago, Illinois, under the direction of Starzl. [55] [56] The focus of research in Boston was the immunology of liver transplantation; in Chicago, it was liver regeneration and hepatotrophic growth factors. Initial successes were hampered by the technical challenges in the performance of liver transplantation in dogs and the inevitable development of allograft rejection. Two technical improvements ultimately provided better survival rates; adequate preservation of the graft with portal infusion of chilled lactated Ringer's solution leading to core cooling, [55] and decompression by bypassing the obstructed recipient splanchnic and systemic venous beds during the anhepatic phase when the native liver was being removed and donor liver grafted in its place. [40] [55]

The original saline preservative solutions were replaced by improved solutions. The Collins solution allowed safe preservation for 5 to 6 hours [2] [66] and later the University of Wisconsin solution extended the preservation time 18 to 24 hours. [28] [29] [60] As experience with human orthotopic liver transplantation evolved, venous bypasses were used less often and now are seldom employed. [54]

Early Development of Immunosuppression

The development of the field of immunosuppression was critically important in liver transplantation. The first attempts at liver transplantation had been performed without immunosuppression, and thus no long-term organ engraftment was possible. In 1944, Medawar showed that graft rejection is an immunological event that has both specificity and memory. [36] [37] The initial attempts to suppress the immune system to ameliorate rejection used corticosteroid
therapy or total-body irradiation. In the late 1950s and early 1960s 6-mercaptopurine and azathioprine were introduced as immunosuppressants (Table 2).[^53]

In animal experiments and in early human cadaver kidney transplantation, it was learned that single-agent immunosuppression only rarely controlled rejection but that the combination of prednisone and azathioprine effectively prevented rejection and allowed successful renal transplantation. It also became evident that large boluses of corticosteroids could be used to reverse episodes of acute allograft rejection. These two observations by Starzl and colleagues at the University of Colorado made clinical transplantation possible and opened the way for human liver transplantation.[^53]

**Human Liver Transplantation**

The first attempted human liver transplantation was reported in 1963 by Starzl.[^58] The recipient was a 3-year-old boy with biliary atresia who had had multiple previous operations and died of blood loss during surgery because of uncontrollable coagulopathy. Two other liver transplantations were carried out in the same year, but the recipients died after 22 and 7 days, respectively.[^53][^58] In the next year, isolated attempts at human liver transplantation were unsuccessful in Boston[^37] and in Paris.[^16] These first seven human liver transplant operations achieved patient survivals ranging from zero to 23 days.[^53]

The first truly successful human liver transplantation was performed in 1967 by Starzl at the University of Colorado. The recipient was an 18-month-old child with a hepatocellular carcinoma who survived more than 1 year before succumbing to recurrent tumor.[^53] Six other patients underwent liver transplantation in 1967 and 1968, with a maximum survival of 30 months. During the next 12 years, approximately one liver transplantation per month was performed at the University of Colorado, and the 1-year mortality rate was greater than 50%. The long-term survival of liver transplant recipients remained at 30%.[^54] On a more encouraging note, 30 of the first 170 patients (18%) in the consecutive series of liver transplants at the University of Colorado from 1963 through 1979 lived more than 10 years.[^53] The usual immunosuppressive regimen was prednisone, azathioprine, and polyclonal antilymphocyte globulin.[^54]

During this period, Calne of Cambridge University and the hepatologist Williams of King’s College Hospital in London began clinical trials in liver transplantation.[^10] Their first patient also exsanguinated, but success soon followed. Other liver transplantation teams were established in Hanover, Germany, in 1972, under the direction of Pichlmayr, and in Paris in 1974, under Bismuth. By 1980, it had been shown that liver transplantation could be accomplished, but the relatively high mortality rate seemed to indicate that the procedure was not practical.

**TABLE 2 -- HISTORY OF IMMUNOSUPPRESSIVE DRUG REGIMENS**

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>1963</td>
<td>Azathioprine plus corticosteroids</td>
</tr>
<tr>
<td>1966</td>
<td>Polyclonal antibodies; antilymphocyte globulin as an adjunct</td>
</tr>
<tr>
<td>1970</td>
<td>Cyclophosphamide substituted for azathioprine</td>
</tr>
<tr>
<td>1978</td>
<td>Cyclosporine use in humans</td>
</tr>
<tr>
<td>1980</td>
<td>Cyclosporine plus corticosteroids</td>
</tr>
<tr>
<td>1981</td>
<td>Development of monoclonal antibodies</td>
</tr>
<tr>
<td>1989</td>
<td>Tacrolimus plus corticosteroids</td>
</tr>
<tr>
<td>1990s</td>
<td>Development of newer agents (e.g., mycophenolate mofetil, rapamycin)</td>
</tr>
</tbody>
</table>
Development of Cyclosporine and Tacrolimus

The evolution of liver transplantation from an experimental operation applied to a few individuals to routine surgery with excellent graft and patient survival rates resulted from several advances, but the development of cyclosporine has been credited with the ultimate success and wide acceptance of liver transplantation. The initial experimental and clinical effectiveness of cyclosporine in transplantation was demonstrated by Calne and colleagues in 1978 and 1979. 

Cyclosporine was the first selective method of immunosuppression, and its use increased the survival rate of liver transplant recipients from approximately 30% to more than 70%. 

The development of cyclosporine in the late 1970s and early 1980s led to the acceptance of liver transplantation for routine patient care by the National Institutes of Health Consensus Development Conference in 1983 and to the opening of many new transplant centers.

With the initial use of tacrolimus (FK506) at the University of Pittsburgh, the 1-year graft and patient survival rates increased further. Later direct comparison between cyclosporine and tacrolimus in controlled trials, however, produced equivalent results that were quite good with either agent used as the basis of a multiple-drug immunosuppressive regimen. Although the merits of cyclosporine versus tacrolimus continue to be debated, there is a clinical advantage in having available two good agents that can be substituted as clinical circumstances dictate.

Another advance in immunosuppression was the development of monoclonal antibodies, particularly muromonab-CD3 that is used to control steroid-resistant rejection and is occasionally used for induction of immunosuppression in the setting of renal insufficiency. Muromonab-CD3 has now essentially replaced the earlier antilymphocyte and antithymocyte globulins, which could never be standardized. Other agents, such as mycophenolate mofetil and rapamycin, are being tested in clinical trials to determine their roles in liver transplantation.

Additional Developments in Liver Transplantation

The initial technical achievement of liver replacement and the development of improved immunosuppressive regimens were accompanied by many other advances that led to the current 1-year patient survival rates of 85% to 90% after liver transplantation for most conditions (Table 3). Animal experiments were inadequate preparation for liver transplantation in sick patients with portal hypertension and severe coagulopathy, many of whom had prior right upper quadrant surgery with adhesions. The management of hemodynamic and metabolic problems that may arise during surgery by anesthesiologists who specialize in liver transplantation, the use of modern blood component and coagulation factor replacement therapy, and improved surgical methods to control operative bleeding have all improved the outcome of liver transplantation. The massive blood loss that routinely characterized earlier operations has been replaced by minimal blood loss, and as many as 30% of liver transplantations can be performed without blood transfusion. The introduction of venovenous bypass, which was important in the early experience of surgeons with liver transplantation, facilitated the development of new programs by supporting hemodynamics during the anhepatic phase.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-Year</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>91</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>89</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>86</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>86</td>
</tr>
</tbody>
</table>

TABLE 3 -- SURVIVAL AFTER ADULT LIVER TRANSPLANTATION BY DIAGNOSIS
<table>
<thead>
<tr>
<th>Condition</th>
<th>Data</th>
<th>1987</th>
<th>1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic liver disease</td>
<td>85</td>
<td>76</td>
<td>63</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>84</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>83</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td>Malignancy</td>
<td>72</td>
<td>43</td>
<td>34</td>
</tr>
</tbody>
</table>


Biliary complications were a major source of morbidity and mortality in early liver transplants, with as many as 50% of patients developing one or more biliary complications. A primary duct-to-duct anastomosis can now be performed without T-tubes or stents, a development which has reduced the biliary complication rate to 5% to 10%. The use of radiologic and endoscopic diagnostic and therapeutic procedures has also facilitated the management of biliary complications with lower rates of morbidity.

Other important advances include better understanding and diagnosis of acute and chronic allograft rejection and improved prevention and treatment of infections that occur in the immunosuppressed transplant recipient. The routine use of posttransplantation allograft liver biopsies has allowed more accurate diagnosis of acute rejection and identification of other pathologic processes that can cause early allograft dysfunction. Prophylactic regimens for early bacterial infection after liver transplantation and for late cytomegalovirus, fungal, and Pneumocystis infections are now routine and have substantially reduced morbidity and mortality from these infections.

**LIVER TRANSPLANTATION: THE PRESENT**

The first 3 decades of liver transplantation witnessed great successes in the development of surgical techniques and improvement in immunosuppressive regimens. These successes are accompanied by a new set of problems. In particular, the growing disparity between the availability of cadaver donor livers and the number of potential transplant recipients on the waiting lists in the United States and other countries has led to increased deaths among persons on the waiting list and sicker patients coming to transplantation. An increasing number of transplant patients have chronic hepatitis C virus (HCV) infection, and recurrent hepatitis C is an important cause of morbidity and mortality that may reduce the long-term utility of liver grafting. Newer approaches to solving these problems are under way, but no comprehensive solution is in sight.

**Donor Shortage**

The number of liver transplantations performed in 1996, 1997, and 1998 in the United States was relatively stable, at slightly more than 4000 transplantations annually. Currently, however, there are more than 12,000 potential liver transplant candidates on the United Network for Organ Sharing (UNOS) waiting list in the United States, and therefore, a lower percentage of the patients with chronic liver disease who might benefit from liver transplantation can actually undergo the procedure. This growing discrepancy between the available donor organs and the need for transplantation has led to scrutiny of the traditional selection and listing criteria for liver transplantation.

The supply of donor livers is insufficient to meet the current and future need for liver transplantation, and organ donation has remained relatively stagnant, with only minor increases in retrieval rates in recent years in spite of many efforts to increase donation. The growing disparity between the number of liver transplantations that can be performed each year and the
number of patients on the waiting list is reaching crisis proportions in the United States. Although the number of donors and liver transplantations increased 2.4-fold between 1988 and 1997, the number of patients on the liver transplantation list increased 15.6-fold, and the number of deaths increased 5.8-fold during the same period. This situation will only worsen in the coming years. Analysis of data from the past 5 years to predict the status of liver transplantation in the year 2000, assuming no major changes in organ availability or performance of transplantation, reveals an even greater crisis at the turn of the century with 20,000 or more patients awaiting a liver transplantation.

**United Network for Organ Sharing**

The disparity between the number of cadaver organs and candidates for liver transplantation has led to re-evaluation of UNOS allocation and distribution policies for livers and has spurred a nationwide debate among transplantation professionals, potential recipients, and the federal government. Distribution policies determine the geographical areas within which livers are allocated, and allocation policies determine which patients within a geographical area will receive the available livers. The historical allocation scheme has dictated that the sickest patients who have waited the longest receive transplantation first. In the recent past, there have been modifications and redefinition of UNOS status based on disease severity, but the basic principle, as shown in the box, still holds.

| UNOS Liver Status For Patients 18 Years of Age According to Disease Severity |
|---------------------------------|-------------------------------------------|
| Status 1                        | Fulminant liver failure with life expectancy <7 days, including FHF, primary graft nonfunction, hepatic artery thrombosis, and acute decompensated Wilson's disease |
| Status 2A                       | Hospitalized in ICU for chronic liver failure with life expectancy <7 days, with a Child-Pugh score of 10 and one of the following: unresponsive active variceal hemorrhage, hepatoportal syndrome, refractory ascites/hepatic hydrothorax, or stage 3 or 4 hepatic encephalopathy |
| Status 2B                       | Requiring continuous medical care, with a Child-Pugh score of 10, or a Child-Pugh score 7 and one of the following: unresponsive active variceal hemorrhage, hepatoportal syndrome, spontaneous bacterial peritonitis, or refractory ascites/hepatic hydrothorax; presence of an hepatocellular carcinoma. |
| Status 3                        | Requiring continuous medical care, with a Child-Pugh score of 7, but not meeting criteria for status 2B |
| Status 7                        | Temporarily inactive |


FHF = fulminant hepatic failure

The UNOS distribution scheme as of mid-1999 dictates that patients at transplant programs served by a local organ procurement organization (OPO) have the first priority for livers obtained by that OPO. Because of this local use of livers, the waiting times for liver transplantation differ considerably for patients listed in different regions in the United States. This local policy means that a patient in one OPO who is not in immediate danger of dying may receive a transplantation before a sicker patient in another OPO in a nearby geographic area. This reality has led to discussion about widening the liver distribution area for...
patients who are listed as status 1, but computer simulation modeling by UNOS showed that wider sharing, that is, a single national waiting list, would allow urgency (often termed justice) to prevail over medical utility. Utility factors focus on maximizing the overall benefits of transplantation to society, that is, giving priority to the patient who maximizes the chances of a successful outcome by having the least risk of dying after transplantation. Urgency, or justice, recognizes the needs of the individual transplant patient by giving priority to the sickest patient, who has the greatest risk of dying before transplantation. The argument made against current UNOS policies is that the geographically restricted distribution scheme overrides prioritization based on medical urgency in favor of utility and is unfair to transplant candidates in most need of liver replacement. [23] This argument proposes a national waiting list to equalize access to liver transplantation, that is, a patient-driven rather than a local or center-driven allocation scheme. Finally, the transplantation community is becoming cognizant of cost-outcome analyses and the reality of managed care, which has transferred financial risk from insurers to providers. [20] High-risk patients represent a significant liability to transplantation centers in the managed care marketplace. Appropriate and reasonable patient selection may become an important consideration in allocation policies.

**Uniform Listing Criteria for Chronic Liver Disease**

At a recent consensus conference at the National Institutes of Health organized by the American Society of Transplantation and the American Association for the Study of Liver Diseases, uniform minimal listing criteria were developed for general application to patients with miscellaneous chronic liver diseases. [33] These criteria are

I. Immediate need for liver transplantation

II. Estimated 1-year survival 90%

III. Child-Pugh score 7 (Child-Pugh class B or C)

IV. Portal hypertensive bleeding or a single episode of spontaneous bacterial peritonitis, irrespective of Child-Pugh score

These criteria were established using the general principle that any patient listed should have an expected 1-year survival with general supportive care of 90% or less, which is less than expected with liver transplantation. Large studies of the natural history of patients with compensated cirrhosis resulting from miscellaneous causes [25] [46] or chronic hepatitis C [21] have shown that survival is relatively good until decompensation, when 5-year survival rates fall to approximately 50%. Thus, the indication for listing for liver transplantation should not be simply the presence of cirrhosis, without decompensation, that is, Child-Pugh class A, but should be the development of decompensation, for example, Child-Pugh class B or C.

**Solutions to the Organ Shortage**

The current approaches to the organ shortage include increased efforts to achieve higher rates of organ procurement, expanded use of marginal donors, and surgical alternatives such as cadaver split-liver and adult living donor related and unrelated liver transplantation. Xenotransplantation may become an option in the future.

There has been a concerted effort to increase organ donation, and in some countries small gains have been made in the past years. In the United States, there was 5.6% increase in cadaver donors in 1998, the first substantial increase since 1995. [61] The organ donation rate in the United States is approximately 20/1 million population, compared with Spain, the leading Western nation, with donor rates of 25/1 million and Italy, the worst Western country, with a rate of less than 10/1 million.
The expanded use of marginal donors in recent years has included implanting donor livers from older individuals, use of grafts with substantial fatty change, and engrafting donor grafts from patients with mild chronic hepatitis C into recipients with hepatitis C or from patients with a positive hepatitis B core antibody (anti-HBc) into recipients with hepatitis B, and, occasionally, into other recipients. This experience is too limited for long-term outcome to be compared with patients receiving grafts from uninfected donors, but it is known that anti-HBc-positive grafts frequently transmit hepatitis B virus (HBV), and recipients without HBV infection are, therefore, at risk and should receive prophylaxis in the form of lamivudine or hepatitis B immune globulin. The short-term and medium-term outcome of transplanting HCV-positive grafts into patients with chronic hepatitis C seems to be good. Although increasing donor age is associated with poor graft function, the organ shortage seems to justify use of these grafts, and the overall percentage of donors over the age of 50 years has increased substantially. It seems that the judgment of the harvesting surgeon as to whether the donor liver is good, fair, or poor is also an important factor affecting graft survival. There were no differences in the 3-month graft survival rates using livers from younger donors judged good versus those considered fair or poor, but there was a significantly lower survival rate using fair or poor grafts from donors aged 50 years or older (61% versus 92% for organs classified as good). It has been suggested that donor/recipient gender matching should also be considered. Because livers from women transplanted into men generally have a poorer outcome, transplantation of grafts from older women into men may be even more likely to result to in poor graft function.

Split-liver transplantation, after unsatisfactory initial results, has undergone a resurgence during the past 2 to 3 years. This procedure essentially achieves two liver transplantations from a single cadaver liver, with the right lobe usually implanted into an adult recipient and the left lobe or left lateral segment transplanted into a child. The organ used in split-liver transplantation can obviously be shared between two institutions or used at a single transplant center. Living-donor liver transplantation for adults, using a right hepatic lobe, is also being performed more often, and good results are being reported from centers in the United States and Japan. The Japanese center has also had good outcomes using living-donor liver transplantation for high-urgency patients.

**Recurrence of Disease After Liver Transplantation**

Chronic hepatitis C has become the most common cause of end-stage liver disease requiring liver transplantation and accounts for 25% to 40% of all transplantations in some centers. Hepatitis C viral infection may also be present in patients with alcoholic liver disease and in patients undergoing liver transplantation who are classified as having cryptogenic cirrhosis. Most patients have had HCV infection for several decades before the onset of liver failure. After liver transplantation, HCV reinfection occurs in almost all patients. Most of these patients subsequently develop chronic hepatitis, and a few progress to cirrhosis. Fortunately, the infection appears to be benign in 80% to 85% of patients on short-term and medium-term follow-up, and survival rates are comparable with patients receiving transplantation for nonviral chronic liver diseases. It has been shown, however, that transplant recipients with recurrent hepatitis C have poorer quality of life, greater depression, and higher psychologic distress than those without HCV infection. Whether progressive chronic hepatitis and cirrhosis will occur in most patients with longer follow-up remains uncertain but is possible.

Numerous host and viral factors have been implicated in the development of severe recurrent hepatitis C, suggesting that the process is multifactorial. The overlapping histologic features of HCV infection and allograft rejection, which include portal and parenchymal mononuclear cell infiltrates, fatty change, swollen hepatocytes with necrosis, and occasional bile duct damage, make distinction between these two entities difficult at times.
The best treatment of recurrent HCV infection after liver transplantation remains uncertain. It seems that neither interferon nor ribavirin alone is beneficial, but the combination of both agents shows promise. In one study, 18 of 21 patients tolerated therapy, and 24% of patients experienced a virologic sustained response with improved aminotransferase levels and liver biopsy histologic scores. Whether maintenance therapy can be discontinued in patients who have a sustained virologic response remains unknown. Studies are in progress to determine if preemptive therapy early after liver transplantation will alter the posttransplantation infection rate or the severity of recurrent hepatitis C.

Other diseases can recur after liver transplantation, including HBV infection, alcoholic liver disease, and immunologic liver diseases, such as primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. The strategies for diagnosing or preventing these entities are well established, unlike the management challenges presented by recurrent hepatitis C.

**LIVER TRANSPLANTATION: THE FUTURE**

In the immediate future, developments in liver transplantation will probably extend from the developments of the past few years, enlarging the efforts to increase organ donation, further expanding split-liver and adult living related and unrelated liver transplantation, and optimizing the use of the existing donor pool by adjusting allocation and distribution policies and refining selection criteria. Possible clinical developments in the near future include xenotransplantation, hepatocyte transplantation, and liver-directed gene therapy.

**Xenotransplantation**

If xenotransplantation can be made safe and affordable, it may solve many of the current problems of access to liver transplantation. Xenotransplantation is the engraftment of organs obtained from one species into another species. Xenografting is not a new concept, but it has resurfaced with the availability of more potent immunosuppressive agents and the critical shortage of human cadaver organs. Most investigators are now focusing on the pig as a potential donor based on appropriate size, unlimited supply, ability to be genetically engineered, and the more easily controlled risk of zoonotic infection. The immunologic hurdles to xenotransplantation are hyperacute rejection, acute vascular rejection, and cellular rejection. Another important consideration in xenotransplantation is the potential transmission of infectious agents from the graft to the recipient. It has been suggested that the movement to xenotransplantation will occur as a step-by-step process, beginning with limited clinical trials, using xenotransplantation initially as a bridge to human cadaver transplantation, then implanting porcine xenografts in patients who cannot obtain a human graft, and finally using xenotransplantation as an alternative to allotransplantation. Before this sequence can unfold, many critical ethical issues must be addressed.

**Hepatocyte Transplantation and Liver-Directed Gene Therapy**

Liver cell transplantation is being developed to treat acute and chronic liver failure and inherited metabolic disorders. Liver cells can be isolated from a number of species, including humans, and then cultured or cryopreserved for future use. Cultured cells can be directly transplanted from allogeneic donors (a process that requires immunosuppression) or transplanted back into an individual after being surgically harvested and transduced in culture with a therapeutic gene for either a defective or absent protein. In the latter case, immunosuppression is not required. Liver-directed gene therapy can be used to replace a missing gene, express a gene that is not normally expressed in the liver, interfere with gene expression,
disrupt an offending gene, or repair a mutated gene. Hepatocyte transplantation has already been successfully used to treat some inherited disorders, and both nonviral and viral vectors are being developed for gene therapy targeted at the liver. Both technologies will probably develop into more practical therapies.

It is hoped that in the future the need for liver transplantation will be reduced if effective medical treatments, some of which may employ gene-direct therapy, can be discovered to treat the full spectrum of metabolic, viral, and immunologic liver diseases. The late 1990s have already witnessed some advances in the treatment of chronic hepatitis C and chronic hepatitis B, and the next few years should bring improved treatments for many liver diseases that have historically progressed inevitably to cirrhosis and liver failure, with the resultant need for liver transplantation.

**SUMMARY**

During the past 3 decades, liver transplantation has achieved such acceptance that more than 12,000 qualified recipients are listed for liver transplantation in the United States, but unfortunately just over 4000 cadaver donor organs are available each year. Thus, given the increasing disparity between the number of potential recipients and available cadaver organs, the current challenge in liver transplantation is to optimize the outcome of liver transplantation from this limited resource. Currently under way is re-evaluation of selection criteria to use these 4000 cadaver liver grafts most effectively by striking the proper balance between medical urgency and utility. In parallel with this re-evaluation, there is ongoing expansion of cadaver split-liver transplantation and adult living related and unrelated liver transplantation. Hoped-for but as yet unachieved developments in liver transplantation are xenotransplantation, hepatocyte transplantation, and liver-directed gene therapy. Liver transplantation has come a long way from the initial, unsuccessful human transplantations in 1963, but many challenges remain.

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