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GUEST EDITORIAL

LIVER TRANSPLANTATION TODAY

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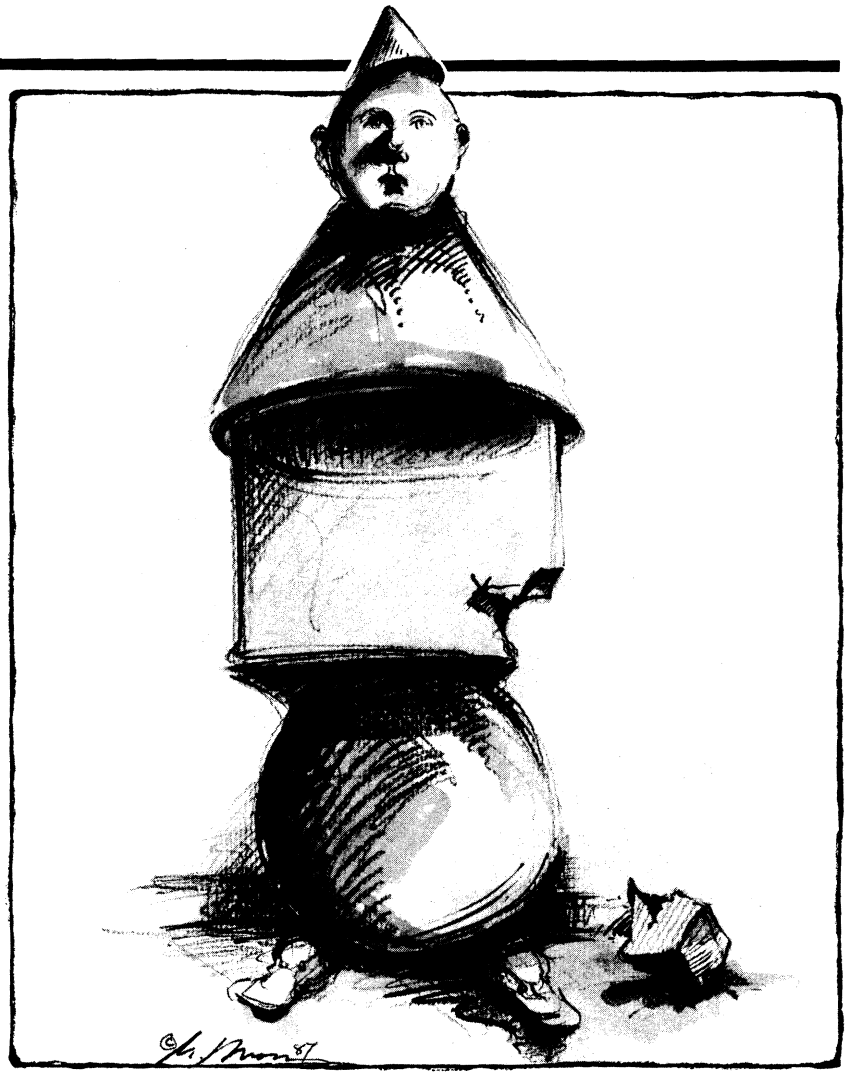

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Clinical organ transplantation had its beginnings in 1902 with the report of an experimental organ heterotransplant (kidney) by Ullmann.[1] Liver transplantation was conceived later, apparently by Welch[2] in the early 1950s, as a heterotopic procedure, leaving the diseased organ in situ. Orthotopic liver transplantation in animals was first reported in 1956 by Cannon, but without the details, title, or identification of the animal used.[3]

Two research programs in liver transplantation were independently established in 1958 in Boston and Chicago. Clinical application was first performed in Denver in March 1963; azathioprine (Imuran) and steroids were used for immunosuppression.[4]

Because of poor initial results, a moratorium was voluntarily placed on human liver transplantation for four years while further laboratory work continued. After the four years, clinical trials were resumed in Denver and in Cambridge, England (by Calne), with a one-year survival rate of about 33% in both locations.[5]

In the beginning, liver transplantation was performed without the use of intraoperative venous bypasses. Blood loss was excessive, renal failure was common, and vascular anastomoses had to be done so quickly that teaching the procedure was almost impossible. As the central components of the procedure were refined, survival improved to modest levels.

As time passed, more people

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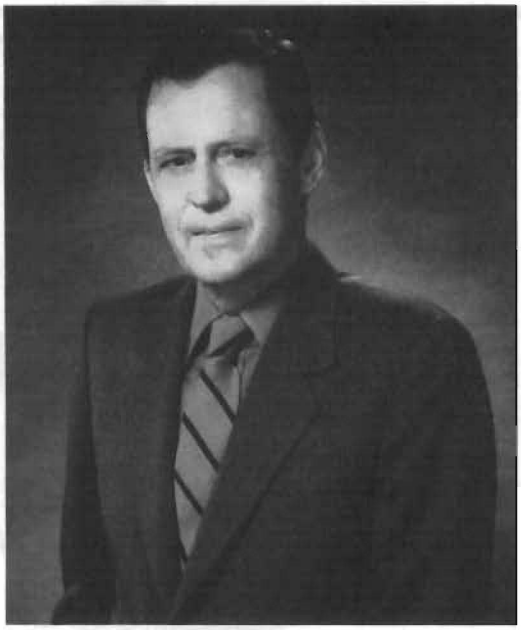
An international organ transplant forum, to be held in Pittsburgh in September 1987, will honor Dr Starzl for his 25-year contribution to the field of organ transplantation.



were referred for liver transplantation, but the availability of the operation was highly restricted. Liver transplantation was not an approved treatment for end-stage liver disease and was not covered by health insurance carriers, making the cost prohibitive.

One of the greatest breakthroughs in liver transplantation occurred in 1978 with the introduction of cyclosporine (Sandimmune). First tested in England by Calne[6] and shortly thereafter in the United States, cyclosporine represents one of the largest advances in transplantation surgery to date. Survival rates after liver transplantation improved to their current overall level of 69% and 55% at one and five years, respectively. This improvement in survival has greatly increased the acceptance of this procedure as a treatment method.

In the mid-1980s, use of the venous bypass, first with heparinization and later without, remarkably improved the practicality of liver transplantation.[5,7] Blood loss declined dramatically as did the incidence of renal failure. More important, perhaps, was that with the use of the bypass system, the procedure could be taught, and the surgical technique could be disseminated to other medical centers.

As results with liver transplantation improved, more patients began to be referred in a premoribund state, which increased their chances of surviving the operation. As stated earlier, use of the heparin-free bypass system drastically reduced the requirement for blood products as well as the total operating time.

As public awareness of the applicability of the procedure grew, pressure for acceptance of orthotopic liver transplantation as a viable treatment for end-stage liver failure grew appropriately. In 1983 at the National Institutes of Health Consensus Development Conference on Liver Transplantation,[8] the fruition of these labors was realized with the pronouncement that liver transplantation was no longer considered an experimental procedure but a service operation for patients with irreversible liver failure. After this announcement, many insurance companies began reimbursement for hepatic replacement, thus extending to many this second chance for life.

As is inevitable when a procedure becomes economically profitable, its use greatly increased. This was fortunate in that the number of centers doing the transplants was not adequate to meet the demand. However, many medical centers started liver transplantation programs with few or no formally trained physi-

Table 1. Liver transplantation centers in the United States, with the number of operations performed in 1986 (including retransplantation)

City	Center*	No. of operations
Pittsburgh	University of Pittsburgh	344
Boston	Area cooperative	80
Omaha	University of Nebraska	58
Los Angeles	University of California	52
Rochester, MN	Mayo Clinic	47
Dallas	Baylor University	37
Minneapolis	University of Minnesota	32
Dallas	Children's Hospital	27

*Additional centers in Georgia, California, New York, Utah, Michigan, Illinois, North Carolina, Virginia, Maryland, and Florida.

cians or surgeons. Although patients must bear the "learning curve" in the infancy of any procedure, this was not the case with liver transplantation, since the techniques had been refined and instruction was available to those who desired it.

Liver transplantation today

There are currently many new liver transplantation centers across the United States, with plans for a number of others to open. The number of transplants performed increases yearly, but demand still far outweighs the number of organs available. Even though the refinement of the flexible procurement method[9] allows nearly all of the transplantable organs to be procured from a common donor, it still has not produced the number of organs needed annually.

The busiest centers in the United States today, with the number of transplants performed in 1986 (including retransplantation), are shown in table 1.

Candidates and results

Candidates for orthotopic liver transplantation can be divided into several broad categories. Results of their operation usually depend on the diagnosis. While this list by no means constitutes all indications for transplantation, it does represent the most common current ones.

VIRAL CIRRHOSIS—Chronic active hepatitis is currently the most common indication for orthotopic liver transplantation in adults. Because these patients usually have severe portal hypertension and a small shrunken liver,

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transplantation is often technically quite difficult. One-year survival rate is 67.2% but drops to 50.9% at three years. These patients commonly have coexisting risk factors due to general poor health, making their long-term survival somewhat lower than average. If the causative virus was hepatitis B, recurrence has been the rule, and a number of such recipients have come to retransplantation.

ALCOHOLIC CIRRHOSIS—Alcoholic cirrhosis is considered separately from nonalcoholic cirrhosis because the number of cases requiring transplantation is small. The recipients often are in even poorer medical condition than patients with viral cirrhosis. Technically the operation is no harder to perform than that in other cirrhotic patients, but candidates must be selected with the greatest of care because recidivism is so prevalent among self-abuse groups. It is desirable for the patient to demonstrate abstinence from alcohol before being considered for transplantation.

PRIMARY BILIARY CIRRHOSIS—A disease commonly affecting middle-aged women, primary biliary cirrhosis is the second most frequent indication for liver transplantation in adults. The technical aspects of the operation are relatively easy, and the one- and five-year actuarial survival rates are both 68.4%. The disease is believed to have an autoimmune etiology, with 85% to 90% of patients demonstrating antimitochondrial antibodies.[10] Immunosuppressant drugs, such as steroids, azathioprine, chlorambucil (Leukoran), and cyclosporine, have all been tried without much success.[11] To date no cases have recurred after transplantation in our center, even though antimitochondrial antibody tests remain positive after transplantation in about 90% of cases.[12] Neuberger and associates[13] of Cambridge, England, have reported recurrences in the era before the availability of cyclosporine.

SCLEROSING CHOLANGITIS—Sclerosing cholangitis is a disease primarily of young men and is often associated with other disease entities, particularly inflammatory bowel disease. Like primary biliary cirrhosis it is considered most likely an autoimmune disorder, also without significant response to immunosuppressants. Unfortunately, many of these patients have had previous operations in the hepatic hilum, and often they are not referred until all attempts at medical and surgical intervention have been exhausted. These patients commonly present after multiple bouts of cholangitis, and many have cholangiocarcinomas coexisting with cirrhosis, making it too late for transplantation to effect a cure. The operation is moderately difficult, but survival is currently 75.5% at one year and 57% at three years. Posttransplantation recurrence of sclerosing cholangitis has not been reported.[14]

TUMORS—The first orthotopic liver transplantations were done in patients with unresectable tumor. It was thought that these patients would do well with transplantation, since portal hypertension and its complications were usually absent. While short-term survival has been excellent, long-term survival has been poor.[15]

Hepatoma is currently the most common primary liver tumor considered for transplantation. Patients found to have incidental liver malignancy at the time of transplantation for other causes have not had recurrence, but the same is not true when malignancy was the reason for liver replacement. The recurrence rate has been at least 50% at one year; few of these patients are long-term survivors. The exception to this is the subgroup of patients with fibrolamellar hepatoma, who have a one-year recurrence rate of 14.3% (1 in 7). The eventual recurrence rate in this subgroup is still quite high, but transplantation offers excellent palliation, even to those who are not ultimately cured.

DUCT CELL CARCINOMA—Acceptance of these tumor patients for transplantation is not routine because long-term survival

has been essentially zero. If the diagnosis is known preoperatively, patients should undergo radiation therapy. If the tumor is discovered incidentally in the hepatectomy specimen, postoperative irradiation is recommended. Transplantation is still attempted for an occasional patient with the preoperative diagnosis of highly localized duct cell carcinoma, but the carcinoma must be high in the ductal system with no evidence of extrahepatic spread.

INBORN ERRORS OF METABOLISM—This group encompasses both children and adults and includes such diseases as alpha$_1$-antitrypsin deficiency, hepatocellular degeneration (Wilson's disease), cystic fibrosis, hemochromatosis, tyrosinemia, glycogen storage disease, hemophilia, and hypercholesterolemia. The operation is relatively easy, and results have been good, particularly in children, in whom the one- and five-year survival rate is 73.8%.

BILIARY ATRESIA—Biliary atresia is by far the most common indication for orthotopic liver transplantation in children. Most of these children have had right upper quadrant surgery, usually a portoenterostomy (Kasai procedure) but occasionally a portosystemic shunt. While this has greatly increased morbidity, it has not negatively influenced survival to a statistically significant extent.[16] Portoenterostomy may still be appropriate for tiny children for whom donors are difficult to find, but repeated revisions and stomal creation are no longer justified. The difficulty of the operation depends directly on previous right upper quadrant procedures. Actuarial survival is 68.4% at one year and 66.7% at five years. Because only small doses of prednisone are necessary, the children with biliary atresia who undergo transplantation have essentially normal growth and development.[17]

What's new in liver transplantation?

Major new advances in technique will be rare, since the surgical technique in liver transplantation has been highly refined. The field of immunosuppression, however, is relatively new and therefore open for major and almost continuous breakthroughs. Several areas of immune modulation are currently under investigation or have recently finished clinical trials and should be considered by their separate mode of action or end result.

Disease recurrence

Alpha interferon, an immune substance manufactured by leukocytes, is currently being investigated as an inhibiting agent for hepatitis B. In the first phase of study the drug is being given preoperatively to patients in an attempt to rid the body of virus. It is also being perfused into the donor liver at the time of harvesting with the hope of making the liver more resistant to recurrence. If results prove to be encouraging, clinical trials will probably be extended to patients whose disease has recurred postoperatively.

Prevention of acute rejection

Monoclonal anti-T-lymphocyte antibody, or muromonab-CD3 (Orthoclone OKT3), has just recently been released for widespread clinical use for the treatment of steroid-resistant rejection in cyclosporine-treated patients. Results have been excellent (70% to 80% success rate), with few major side effects.[18]

Currently under investigation for the prevention of hyperacute rejection is platelet-activating factor receptor antagonist, both alone and in combination with prostaglandins. We have been able to show that in xenograft renal transplantation (pig to dog), these drugs in combination demonstrate significant abrogation of a very rapid and violent form of hyperacute rejection. It is hoped that the use of these drugs will prove extremely useful in preventing the much less severe forms of rejection seen in the clinical setting.[19]

Long-term immunosuppression

The final area of current investigation is with new long-term immunosuppressive drugs. FR 900506 (MW822) was isolated from *Streptomyces tsukukacusis*, and 15-deoxyspergualin (MW 467) was isolated from spergualin taken from *Bacillus latersporus*. Both drugs have been shown to prolong cardiac and skin allograft survival in rodents.

In *in vitro* studies, FR 900506 has been found to exert its immunosuppressive effect by inhibiting T lymphocyte proliferation through inhibition of interleukin-2 release. Interestingly, however, this inhibition is far stronger (on the order of 10^3) than cyclosporine.

15-Deoxyspergualin has no effect on lymphocytes but has been found to act as a suppressor of the monocyte system, a novel mode of drug action in transplantation immunology.

Summary and conclusions

In summary, liver transplantation has truly come of age. To put things in perspective, the recipient waiting list at the University of Pittsburgh never includes fewer than 200 suitable candidates, and it continues to grow in spite of the fact that we are now doing essentially one transplant per day. There are many excellent transplant centers throughout the United States and Europe, the only limiting factor being the supply of donors.

Orthotopic liver transplantation is now covered by most major health insurance carriers, and some form of government coverage is anticipated for the indigent. As the supply of donors increases with aggressive education programs, the need for transplantation centers will also increase. However, this should not be uncontrolled growth. Mandatory training in transplantation surgery will surely be required as a prerequisite to the establishment of transplant centers in the future.

The field of organ transplantation is the newest and most dynamic in medicine today. The results are encouraging and acceptable and offer the only hope to many persons dying of end-stage organ failure. With improvements in immune modulation at hand, organ transplantation will soon become a commonplace procedure offering a completely normal life expectancy. PGM

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References

1. **Hamilton D.** Kidney transplantation: a history. In: Morris PJ, ed. Kidney transplantation: principles and practice. 2d ed. New York: Grune & Stratton, 1984:1-12
2. **Welch CS.** A note on transplantation of the whole liver in dogs. Transplant Bull 1955;2:54
3. **Gordon RD, Iwatsuki S, Esquivel CO, et al.** Liver transplantation. In: Cerilli J, ed. Organ transplantation and replacement. Philadelphia: Lippincott (in press)
4. **Starzl TE, Marchioro TL, Von Kaulla KN, et al.** Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963;117(Dec):659-76
5. **Starzl TE, Iwatsuki S, Van Thiel DH, et al.** Evolution of liver transplantation. Hepatology 1982;2(5): 614-36
6. **Calne RY, White DJ, Thiru S, et al.** Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978;2(8104-5):1323-7
7. **Shaw BW Jr, Martin DJ, Marquez JM, et al.** Venous bypass in clinical liver transplantation. Ann Surg 1984;200(4):524-34
8. **National Institutes of Health.** Consensus development conference statement: liver transplantation—Jun 20-23, 1983. Hepatology 1984;4(1 Suppl):107-10S
9. **Starzl TE, Hakala TR, Shaw BW Jr, et al.** A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 1984;158(3):223-30
10. **Kapelman B, Schaffner F.** The natural history of primary biliary cirrhosis. Semin Liver Dis 1981;1(4): 273-81
11. **Schaffner F.** Primary biliary cirrhosis. In: Berk JE, Haubrich WS, Kalser MH, et al, eds. Bockus gastroenterology. 4th ed. Philadelphia: WB Saunders, 1985:3150-76
12. **Esquivel CO, Bernardos A, Demetris AJ, et al.** Liver transplantation for primary biliary cirrhosis in 76 patients during the cyclosporine era. (In press)
13. **Neuberger J, Portmann B, Macdougall BR, et al.** Recurrence of primary biliary cirrhosis after liver transplantation. N Engl J Med 1982;306(1):1-4
14. **Marsh JW, Iwatsuki S, Makowka L, et al.** Orthotopic liver transplantation for primary sclerosing cholangitis. (In press)
15. **Iwatsuki S, Starzl TE.** Liver transplantation in the treatment of cancer. In: Ishak, Okuda, eds. Neoplasms of the liver. 2d ed. (In press)
16. **Cuervas-Mons V, Rimola A, Van Thiel DH, et al.** Does previous abdominal surgery alter the outcome of pediatric patients subjected to orthotopic liver transplantation? Gastroenterology 1986;90(4):853-7
17. **Urbach AH, Gartner JC Jr, Malatack JJ, et al.** Linear growth following pediatric liver transplantation. Am J Dis Child (in press)
18. **Fung JJ, Demetris AJ, Porter KA, et al.** Use of OKT-3 with cyclosporine and steroids for reversal of acute kidney and liver allograft rejection. Nephron (in press)
19. **Makowka L, Miller C, ChapChap P, et al.** Management of hyperacute rejection by modification of the platelet response. (In press)