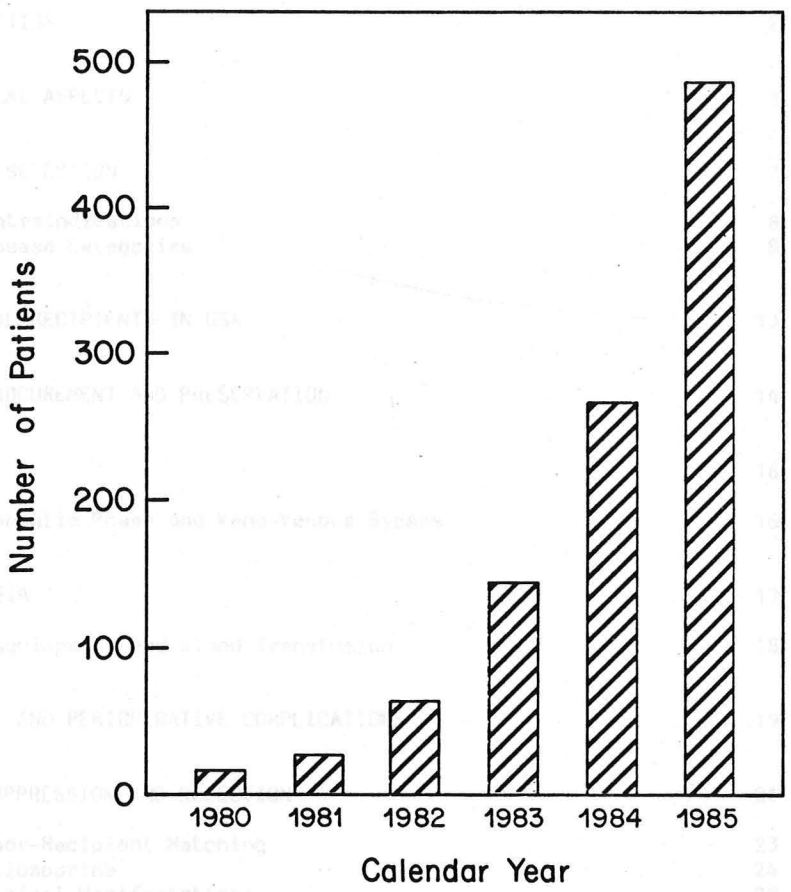
HEPATIC TRANSPLANTATION



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INTRODUCTION

Inherited and acquired liver diseases in both pediatric and adult populations are often progressive despite conventional management, thereby resulting in significant morbidity and early mortality. Specific therapy is rarely available and there is no alternative such as an artificial liver support system for those with advanced disease. Therefore, over the past 20 years, efforts to prolong survival of patients with irreversible liver disease have concentrated on human orthotopic liver transplantation.

The success of this experimental approach has improved outcome to such an extent that in June 1983 the National Institutes of Health convened a Consensus Development Conference to resolve current issues related to the status of experimental liver transplantation. They concluded that "Liver transplantation is a promising alternative to current therapy in the management of the late phase of several forms of liver disease" and "that liver transplantation.....deserves broader application" (1).

The conclusions of the NIH Consensus Development Conference were based on the eventual outcome of many patients who had undergone liver transplantation. The patient illustrated in the following case history demonstrates the desired result.

M.H. 11/12/38

1962 - Abnormal liver function tests, diagnosed as possible hepatitis
1970 - Complaints of intermittent fatigue, malaise and right upper quadrant pain; hepatosplenomegaly noted.
1971 - Cholestatic liver function tests, normal extrahepatic biliary tract at laparotomy. Wedge biopsy of the liver was consistent with primary biliary cirrhosis. Anti-mitochondrial antibody positive. Liver function tests: bilirubin 1.9 mg/dl, AP 936 IU, SGOT 140 IU, albumin 4.7 g/dl.
1975 - Massive variceal hemorrhage requiring surgical decompression (mesocaval H-graft). Post-operatively liver function deteriorated but stabilized. LFTs: bilirubin 2.7 - 20.3, AP 560 - 910, SGOT 77 - 220, albumin 3.1.
1979 - Gradual onset of encephalopathy, lassitude and depression responding to protein restriction, lactulose and neomycin. LFTs: bilirubin 14.0, AP 675, SGOT 268, albumin 3.1.
1980 - Recurrent bleeding and infections occurring with progressive weakness and debility, confining patient to bed for majority of time. LFTs: bilirubin 15.9, AP 340, SGOT 234, albumin 1.9.
April: Orthotopic liver transplantation carried out at Colorado General Hospital by Dr. Thomas Starzl. Immunosuppression with cyclosporine and prednisone.
May: Drainage of intra-abdominal fluid collection. Gradual improvement in strength and well-being.
1981 - LFTs: bilirubin 0.3, AP 255, SGOT 53, albumin 4.1
1985 - Well, on cyclosporine 500 mg/day and prednisone 10 mg/day; creatinine 1.5-1.7 mg/dl, BUN 20-30 mg/dl. LFTs: bilirubin 0.3, AP 86, SGPT 28, albumin 4.4.

This case history clearly demonstrates that orthotopic liver transplantation is able to provide a viable alternative therapy for the late phase of chronic liver disease.

HISTORICAL ASPECTS

Heterotopic Transplantation

Experimental liver transplantation began in the 1950s with heterotopic grafts; an extra liver was engrafted in an abnormal situation (2,3). Since the original report in 1955, there have been a variety of techniques used for grafting of a liver in a heterotopic site, with or without removal of the recipient liver (non-auxiliary or auxiliary graft, respectively). From these experiments came understanding of the role of hepatotrophic factors for maintenance of liver function. Atrophy of the grafted liver occurred unless the portal vein of the graft was supplied with blood from the splanchnic bed. Furthermore, the importance of adequate hepatic arterial blood supply to the liver, in addition to portal venous blood, was realized.

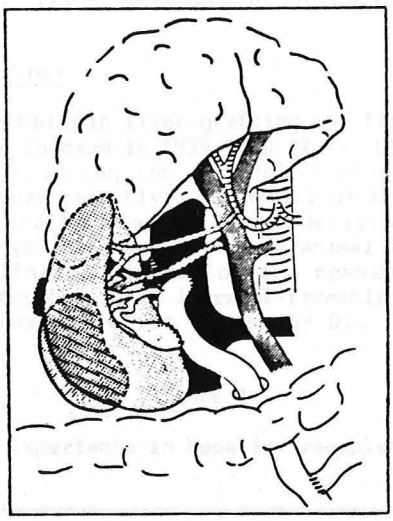


Fig. 1—The surgical procedure.

The liver graft is placed below the right lobe of the recipient's liver. The suprahepatic portion of the inferior vena cava of the graft is sutured. The infrahepatic portion, the portal vein, and the hepatic artery of the graft are anastomosed end-to-side to the suprarenal infrahepatic part of the inferior vena cava, the portal vein, and hepatic artery of the recipient, respectively. The common bileduct and gallbladder of the graft are anastomosed to a jejunal Roux-en-Y loop.

From: Houssin et al, Lancet 1:990-993, 1980.

The major problem with heterotopic liver transplantation was, and continues to be, technical. There is insufficient room in the abdomen for a second liver, even when the recipient's own liver is small and shrunken with cirrhosis. In addition, the many anastomoses required limit the choice of graft site. Successful heterotopic liver transplantation in man has been rare (2 long-term survivors in more than 50 attempts). Fortner and coworkers reported a patient who survived for 5 years with a functioning heterotopic liver graft (4). An alternative and successful approach was used by Houssin and colleagues (5). They transplanted a liver, obtained from a 5 year old child, into the right subhepatic space of a patient in coma with hepatic encephalopathy from hepatitis B surface antigen-positive chronic liver disease. The patient has survived for more than 2 years. Of interest, they found no evidence of infection of the graft with hepatitis B virus in follow-up (5).

In the future, heterotopic transplantation of part of a recipient liver may be technically possible. The advantages of this approach are reduced morbidity and mortality during surgery without recipient hepatectomy and the potential availability of functioning hepatic tissue if the graft fails or is technically unsuitable. However, with the recent success of orthotopic liver transplantation, further attempts at heterotopic grafting are less likely.

Orthotopic Transplantation

Experimental orthotopic liver grafting was first carried out in dogs, by teams in Boston and Chicago in 1959-1960 (2,3). Other investigators have used a pig model in studying the surgical, technical and other aspects of transplantation (3). More recently a rat model of hepatic transplantation has been used in order to examine the underlying mechanisms of graft survival or rejection (6). The background in animal liver transplantation, together with the clinical success of the combination of prednisone and azathioprine for immunosuppression in renal transplantation led to the first orthotopic liver transplantation in man by Dr. Thomas Starzl at Denver, Colorado in 1963.

TABLE I

Early Experience in Hepatic Transplantation

Year	n	% surviving 1 year
before 1967	6	0
1967 - 1969	19	26
1969 - 1971	25	24
1971 - 1973	25	32
1974 - 1976	36	33

From: Starzl et al, Gastroenterology 77:375-386, 1979.

The early attempts did not result in survival for longer than 23 days (2). However, in 1967 a 19 month old child with a hepatocellular carcinoma successfully underwent orthotopic hepatic transplantation and survived for more than a year before succumbing to recurrent malignancy (2). Over the ensuing years, this original success by Starzl's group was repeated, however, the one year survival rate remained at approximately 30% after 111 consecutive transplant operations in more than 12 years (7-9). Similarly, a second transplant program, largely limited to adults, was established in the United Kingdom by Dr. Roger Williams and the surgeon Mr. Roy Calne (10,11). They also had few long-term survivors (6/43 patients living more than one year) before 1976 (10).

TABLE II

Survival after Orthotopic Liver Transplantation

Country	Year	n	% surviving 1 year
USA*	1963-1976	111	28
	1977-1979	60	33
UK**	1968-1976	43	14
	1977-1979	42	38

*From: Starzl et al, Gastroenterology 77:375-386, 1979; Starzl et al, Arch Surg 116:1342-1343, 1981.
**From: Calne and Williams, Br Med J I:471-476, 1977; Calne et al, Br Med J 283:115-118, 1981.

Between 1976 and 1980, surgical techniques and patient selection criteria were improved and one year survival reached 50% in the 30 patients transplanted by Starzl in an 18 month period of 1976-1978 (9). However, this fell again to 26% (6/23 surviving 1 year) in 1978-1979 (12). Not until after the introduction in 1980 of cyclosporine for transplantation immunosuppression was there sustained successful orthotopic liver transplantation with 1 year survivals of 50% or better (13). In 1981, Starzl reported that an astounding 83% (10/12) of patients who survived surgery and received cyclosporine A and prednisone were living after eight to 14 1/2 months; another patient lived for a year before dying of recurrence of cholangiocarcinoma (13). A further 2 patients had died during surgery for an overall 1 year survival of 79% (11/14).

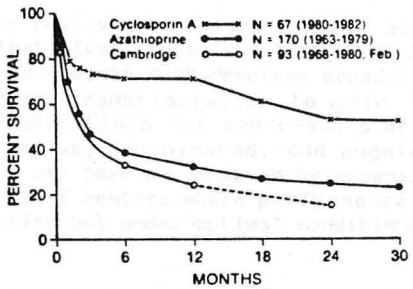


Fig.2- The actuarial survival of patients treated with cyclosporin A and low-dose steroids compared to the actual 1-year survival obtained under conventional immunosuppression by us (azathioprine) and the workers at Cambridge. The data for the Cambridge curve were obtained from published reports (53, 122).

From: Starzl et al, Hepatology 2:614-636, 1982.

In contrast, Calne and Williams reported substantial nephrotoxicity in early trials of cyclosporine A immunosuppression (14) and 3 cases of lymphoma in patients treated for liver or renal allograft immunosuppression (14). These results improved with technical modifications resulting in fewer biliary tract complications. More recently, encouraging results of hepatic transplantation have been reported from two additional European centers (15,16). In Groningen, The Netherlands, preliminary reports indicated an actuarial 1-and 2-year survival of 60%, using azathioprine and prednisone for immunosuppression (16). Thus, the relative contributions of improved immunosuppression, better surgical techniques and more rigorous patient selection criteria have not been resolved.

The significant improvement in the prognosis of liver transplantation with survival for the first year being better than 60%, led many patients and parents of children with liver disease to seek transplantation. The problem of covering the cost of the procedure arose since it had been declared experimental by the Health Care Financing Administration and was supported for the most part during development by the Clinical Research Center granting agency of the NIH. The NIH therefore assembled a panel of experts to consider various aspects of liver transplantation in June 1983. They issued a National Institutes of Health Consensus Development Conference Statement after reviewing data pertaining to 540 human orthotopic liver transplantations carried out in four medical centers in the United States and Western Europe (1).

The conclusions of the panel were:

"After extensive review and consideration of all available data, this panel concludes that liver transplantation is a therapeutic modality for endstage liver disease that deserves broader application. However, in order for liver transplantation to gain its full therapeutic potential, the indications for and results of the procedure must be object of comprehensive, coordinated, and ongoing evaluation in the years ahead. This can best be achieved by expansion of this technology to a limited number of centers where performance of liver transplantation can be carried out under optimal conditions."

The outcome of this report has been a rapid growth in both the number of centers carrying out liver transplantation and in the number of patients transplanted. The most active program is that of Starzl who has been at the University of Pittsburgh Health Center since 1981. Together, the two programs in Dallas, at Baylor University Medical Center and Children's Medical Center/Southwestern Medical School constitute the second most active center in the USA.

TABLE III

Growth of Hepatic Transplantation
1980 - 1985

Year	No. of Centers	No. of Patients Transplanted
1980	1	14 (14)
1981	1	26 (26)
1982	3	70 (62)
1983	6	117 (75)
1984	20	262 (135)
1985	28	412 (205)

The numbers in parentheses refer to patients transplanted by Starzl and colleagues.

PATIENT SELECTION

Orthotopic liver transplantation is an alternative choice of therapy in patients with irreversible, progressive chronic liver disease when no alternative forms of therapy are available and when there are no contraindications to transplantation. In addition, patients must be able to accept the procedure and understand its nature and costs. Most candidates for orthotopic transplantation have a life expectancy of six months or less.

Contraindications:

Absolute contraindications for orthotopic liver transplantation include portal vein thrombosis, although reports of successful interposition grafting with donor iliac or other vein (17) may render this a relative contraindication in the future. Severe hypoxemia with P_aO_2 <50 mmHg due to right-to-left intrapulmonary shunts is also a contraindication since these shunts do not close postoperatively for periods up to several weeks (18), thereby increasing mortality. Sepsis and malignancy outside the hepato-biliary system are also absolute contraindications to transplant surgery. Whereas active alcoholism is an absolute contraindication, liver disease due to prior alcohol consumption in an abstinent (>6 months) patient is a relative contraindication in view of potential extra-hepatic disease and non-compliance. Similarly, advanced cardiopulmonary or renal disease limits transplant potential.

Although a pragmatic upper limit of 55 years has been suggested by a number of programs, older patients with no other contraindications may be considered for liver transplantation. Similarly, HBsAG positivity which increases the likelihood of recurrence, particularly if HBeAg is also positive, is a relative contraindication and a number of patients with HBsAg-positive liver disease have been transplanted. Intrahepatic or biliary sepsis increases the risk of perioperative mortality and careful evaluation is required. Finally, prior surgery, particularly of the right upper quadrant, increases the risks from orthotopic transplantation.

Disease Categories for Hepatic Transplantation

The major disease categories for which hepatic transplantation is indicated include the following:

1. Malignancy - Hepatocellular carcinoma
   Cholangiocarcinoma

2. Hepatitis - massive hepatic necrosis (viral or non-viral)

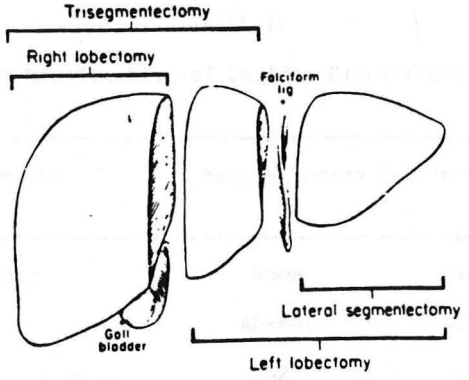
3. Chronic liver disease and cirrhosis
   - chronic hepatitis
   - cirrhosis (non-alcoholic)
   - alcoholic cirrhosis (abstinent)
   - biliary cirrhosis (1° or 2°)
   - sclerosing cholangitis
   - Budd-Chiari syndrome

4. Metabolic disorders - Wilson's disease
   - hemochromatosis
   - alpha-1 antitrypsin deficiency
   - miscellaneous

5. "Congenital" disorders - Biliary Atresia
   - Miscellaneous

1. Malignancy

Hepatocellular carcinoma is only treatable by surgical resection or orthotopic liver transplantation (19). In 600 consecutive patients with hepatocellular carcinoma in Japan, the median survival of untreated patients was 1.6 months and for medically treated patients the median survival was 2.8 months (19). In contrast, patients treated by surgical resection had a median survival of 19.6 months. Unresectability thus represents an adverse prognostic indicator and orthotopic liver transplantation is an alternative therapy if unresectability is on the basis of underlying cirrhosis or multicentricity. However, median survival of 41 patients with hepatocellular carcinoma transplanted at 4 centers since January 1980 was 8.1 months and only 37% survived longer than 1 year (20). The few long-term survivors encourage further attempts to cure this disease by transplantation. Cholangiocarcinoma has also been treated by transplantation, however, recurrence and death within 12 months has been the usual course. The disease category of malignancy constituted 25.7% (139/540) of patients undergoing orthotopic liver transplantation at 4 centers from 1963-1983 (20).



Main types of hepatic surgical resection.

Figure 3

From: Williams and Melia, Clin Radiol 31:1-11, 1980

2. Hepatitis

Occasional patients with acute or subacute massive hepatic necrosis or fulminant hepatic failure from Wilson's disease have undergone hepatic transplantation. In general, transplantation for acute or fulminant liver disease should be limited to patients at a site capable of transplantation at recognition of the disease. With subacute liver disease, specific indications for transplantation include bilirubin >25 mg/dl and presence of other factors listed below for chronic liver diseases.

3. Chronic Liver Disease and Cirrhosis

Patients with chronic liver disease and cirrhosis constitute the major category for adult hepatic transplantation. Disease specific indications for transplantation include one of the following: bilirubin >20 mg/dl, albumin <1.8 g/dl, encephalopathy unresponsive to protein restriction (<40 g/d), neomycin and lactulose therapy. In addition, transplantation surgery must be performed before preterminal variceal bleeding, irreversible hepatorenal syndrome, irreversible brain injury or uncorrectable coagulopathy occur. Hepatorenal syndrome per se is not a contraindication since there has been documented reversal of this functional renal failure following orthotopic liver transplantation (21). Vascular instability associated with anasarca, ascites and pleural effusions, catabolic states and irreversible metabolic bone injury also prevent transplantation. No standardized selection criteria have been established for patients with chronic liver disease. Occasional studies have used Pugh's modification of Child's classification (Table IV) (22). Uniformity of criteria or use of such a system would also allow comparison of the results from different centers. Chronic liver disease and cirrhosis accounted for 49.6% (268/540) of patients transplanted at four centers between 1963 and 1983 (20).

TABLE IV

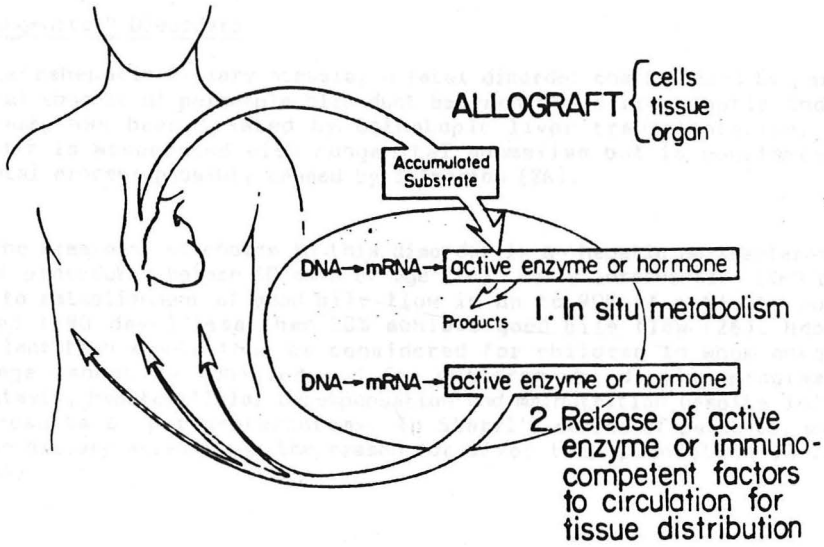
Pugh Modification of Child's Classification

Clinical and Biochemical Measurement	Points Scored for Increasing Abnormality 1	2	3
Encephalopathy (grade)	None	1&2	3&4
Ascites	Absent	Slight	Moderate
Bilirubin mg/dl	1-2	2-3	>3
Albumin g/dl	3.5	2.8-3.5	<2.8
Prothrombin time prolongation (sec)	1-4	4-6	>6

From: Pugh et al, Br J Surg 60:646-649, 1973

4. Metabolic Disorders

Orthotopic liver transplantation for inherited metabolic disorders results in the transferring of normal genetic information into patients with selected structural and biochemical defects. Hepatic transplantation completely corrects the abnormality when the disease is a primary genetic disorder of the liver such as Wilson's disease, hemochromatosis and alpha-1 antitrypsin deficiency and perhaps hemophilia (due to lack of antihemophilic activity, factor VIII:C, of the large factor VIII complex, synthesized in endothelium (7-9,23).



Possible mechanisms of enzyme replacement by transplantation.

Figure 4

From: Sutherland, Matas and Najarian, Transplantation Proc 12:643-652, 1980

In addition, orthotopic liver transplantation can correct substrate accumulation due to inherited disease. The transplanted organ may metabolize the substrate in situ, as in familial hypercholesterolemia, where the activity of LDL receptors on the transplanted liver cells results in substantial lowering of plasma cholesterol (24). Alternatively, an enzyme or other factor produced in the transplanted liver may be released and be active at extrahepatic sites as in Nieman-Pick disease where increased sphingomyelinase activity was detected in plasma, urine and cerebrospinal fluid following orthotopic liver transplantation (25).

Finally, liver transplantation may be indicated for metabolic disorders such as tyrosinemia, Byler's disease and the glycogen storage diseases that lead to cirrhosis and other disorders, including sea-blue histiocyte syndrome and tyrosinemia complicated by hepatocellular carcinoma (26).

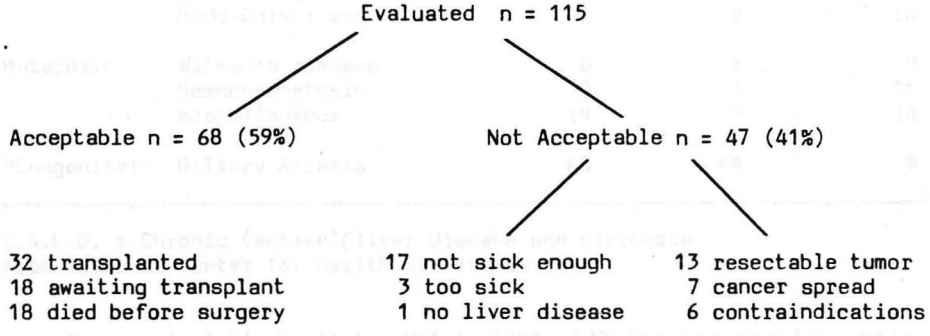
5. "Congenital" Disorders

Extrahepatic biliary atresia, a fatal disorder characteized by partial or total absence of permeable bile duct between the porta hepatis and the duodenum, has been treated by orthotopic liver transplantation. This disorder is associated with congenital anomalies but is considered an antenatal process possibly caused by infection (26).

The treatment of choice in this disorder is an hepatic portoenterostomy (Kasai procedure) before 60 days of age (26). Early intervention (<60 days) leads to establishment of good bile flow in up to 90% of patients but if delayed (>90 days) less than 20% achieve good bile flow (26). Hepatic transplantation should thus be considered for children in whom adequate drainage cannot be achieved and for children who develop progressive cholestasis, hepatocellular decompensation and malnutrition despite initial good results of portoenterostomy. In Starzl's series of patients, extrahepatic biliary atresia was the reason for liver transplantation in 24.3% (72/296).

OUTCOME OF ADULT PATIENTS EVALUATED FOR HEPATIC TRANSPLANTATION

Pittsburgh 1981-1982



From: Van Thiel et al, Hepatology 2:637-640, 1982

POTENTIAL RECIPIENTS OF HEPATIC TRANSPLANTATION IN USA

In order to identify the number of people who die with conditions for which hepatic transplantation may be indicated, mortality data can be obtained from the National Center for Health Statistics and from the Texas Department of Health. The appropriate disease codes are obtained from the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) to facilitate the retrieval of the required mortality data.

TABLE V

Potential Hepatic Transplant Recipients - USA 1983

Category	Disease	Age in Years (at Death) <1	1-14	15-54
Malignancy	Hepatocellular carcinoma	4	33	503
	Cholangiocarcinoma	0	2	197
Hepatitis	Massive necrosis (viral)	20	20	343
	(non-viral)	15	4	133
C.A.L.D.	Chronic hepatitis	2	2	241
	Cirrhosis (non-alcoholic)	8	12	3,621
	Alcoholic cirrhosis	0	1	3,041
	Biliary cirrhosis	2	0	75
	Sclerosing cholangitis	2	0	79
	Budd-Chiari syndrome	0	2	16
Metabolic	Wilson's disease	0	2	9
	Hemochromatosis	0	4	11
	Miscellaneous	19	9	14
"Congenital"	Biliary Atresia	60	44	9

C.A.L.D. = Chronic (active) liver disease and cirrhosis
From National Center for Health Statistics

As seen in Table V, in the USA in 1983, 132 infants and 135 children and adolescents died from primary liver disease. In adults less than 55 years of age (the arbitrary upper limit for transplantation), there were 8,292 deaths with non-alcoholic and alcoholic cirrhosis being the commonest causes of fatal liver disease. The findings in Texas in 1984 are similar to those in the USA as a whole (Table VI). These results suggest that approximately 500 patients (excluding alcoholic cirrhosis and infants) per year in Texas may be considered for hepatic transplantation.

TABLE VI

Potential Hepatic Transplant Recipients - Texas 1984

Category	Disease	Age in Years (at Death) <1	1-14	15-54
Malignancy	Hepatocellular carcinoma	0	1	39
	Cholangiocarcinoma	0	1	7
Hepatitis	Massive necrosis (viral)	0	1	34
	(non-viral)	1	1	14
C.A.L.D.	Chronic hepatitis	0	0	20
	Cirrhosis (non-alcoholic)	0	2	363
	Alcoholic cirrhosis	0	0	140
	Biliary cirrhosis	0	0	11
	Sclerosing cholangitis	0	0	6
	Budd-Chiari syndrome	0	0	0
Metabolic	Wilson's disease	0	0	0
	Hemochromatosis	0	0	1
	Miscellaneous	1	0	0
"Congenital"	Biliary Atresia	5	4	0

C.A.L.D. = chronic (active) liver disease and cirrhosis
From Texas Mortality Statistics

LIVER PROCUREMENT AND PRESERVATION

Potential liver donors are between the ages of 2 months and 45 years with brain death. In such donors, cardiovascular and respiratory functions are sustained artificially with mechanical ventilation and death is based on documented cessation of integrated brain function. In addition, donors should have no history of hepatobiliary or potential compromising systemic disease and no prolonged episodes of hypoxia or hypotension. Liver function tests should be normal and HBsAg negative.

Estimates of the number of potential liver donors vary. Van Thiel considers that up to 2% of the one million hospital deaths per year would be potential donors (27). More realistic may be estimates based on the number of kidney donors providing suitable grafts (approximately 2,200 donors per year). The shortage of post-mortem donors significantly contributes to the mortality rate of patients dying before liver transplantation can be carried out. For example, there were 18 deaths and 32 transplants in 68 adult patients scheduled for transplantation between February 1981 and May 1982 at

the University of Pittsburgh Health Center. There is a continuing shortage of donors suitable for pediatric candidates for hepatic transplantation. In these cases, compatible donor size is the overwhelming requirement.

Locally, organ procurement is centrally administered from the Southwest Organ Bank. The considerable experience of this group in renal transplantation has allowed a smooth transition to dealing with other organs. The Southwest Organ Bank cooperates with other organ banks nation-wide in providing donor organs for renal, heart, liver, pancreas and heart-lung transplantations. As shown in Table VII, the number of transplantation operations being carried out each year is increasing. In particular, there were 40% more heart transplants and 84% more liver transplants in 1984 than in 1983 and these numbers have continued to increase in 1985 (further 80% increase in liver transplants). In Texas, donor shortage appears to be less of a problem than elsewhere in the country.

TABLE VII

Organ Transplantation 1983-1984

Organ	Transplant Centers	Number of Transplants 1983	1984
Kidney	160	6,112	6,730
Heart	69	280	400
Liver	20	167	308
Pancreas	30	61	87
Heart-Lung	5	13	17

From: National figures for co-operating organ banks

The transplantation operation begins with the donor hepatectomy and preservation of the donor liver during transport to the transplant center. Combination donor hepatectomy and nephrectomy can be carried out without compromising early graft function (28). The technique of donor hepatectomy involves division of the common bile duct and initial cleaning of the extrahepatic biliary tract with electrolyte solution to prevent later autolysis. Dissection of the hepatic arterial supply (anomalous or accessory left and right hepatic arteries in 23% and 17%, respectively) and preservation to allow rearterialization is then undertaken (28). This is followed by dissection of the portal vein and inferior vena cava above, behind and below the liver. The liver is cooled by rapid infusion of approximately 2 liters of cold lactated Ringer's solution through the portal system with pressures of approximately 100 cm H_2O. The infusion into the portal vein is changed to modified Collin's solution (high K^+ intracellular-like electrolyte solution) for the final 0.5 - 1 liter, to improve preservation. Finally, the hepatic artery is also infused with modified Collins' solution via the aorta before completion of the dissection and preservation of the liver in slush.

Using these techniques, donor livers may be preserved for up to 12 hours, however, cold storage time of less than 8 hours is preferred. In contrast, donor kidneys may be preserved safely using the same techniques for up to 48 hours. Improved preservation of livers is an active area of research at a number of institutions. A variety of preservation solutions, including ones containing fluorinated hydrocarbons and thereby having oxygen-carrying capacity, are being investigated.

HEPATIC TRANSPLANTATION SURGERY

The most difficult aspect of hepatic transplantation is the removal of the recipient liver, hence the attempts at heterotopic auxiliary grafting described above. The technical difficulties are usually determined by the underlying disease. In malignancy, both portal hypertension and previous surgery are less likely to complicate the procedure. In contrast, in post-necrotic cirrhosis with associated portal hypertension and coagulopathy there is greater difficulty. The technique involves dearterializing the liver and dissecting the vascular and biliary connections such that adequate anastomoses can be undertaken when the donor liver is transplanted.

Anhepatic Phase of Transplantation Surgery

Since the liver is connected not only to the hepatic artery but also to the portal vein and inferior vena cava, removal necessitates interruption of venous return from the abdomen and lower extremities. In the past during the "anhepatic" phase, anesthesia was extremely complex because of pooling of blood in the extremities and abdomen with subsequent hypovolemia. Maintenance of cardiac output with additional infusion of fluids was later complicated by volume overload. Early attempts to return the venous blood from the abdomen and legs to the heart with a passive bypass resulted in clots lodging in the lungs (2). A pump-derived system with a reservoir that required heparinization resulted in significant bleeding due to difficulty reversing the heparin (29). Finally, the pump-driven non-heparin bypass system was constructed (30). It consists of modified heparin-bonded Gott aneurysm shunt tubing for drainage and return cannulae and a centrifugal blood pump to maintain flow (30). The average duration of the veno-venous bypass is 100 minutes. It is initiated before extensive retrohepatic resection and allows time for completion of the recipient hepatectomy and implantation of the donor graft. There has been no evidence of the ex-vivo thrombosis that complicated earlier systems. In children, veno-venous bypass is usually not required since they tolerate combined portal and venocaval occlusion better.

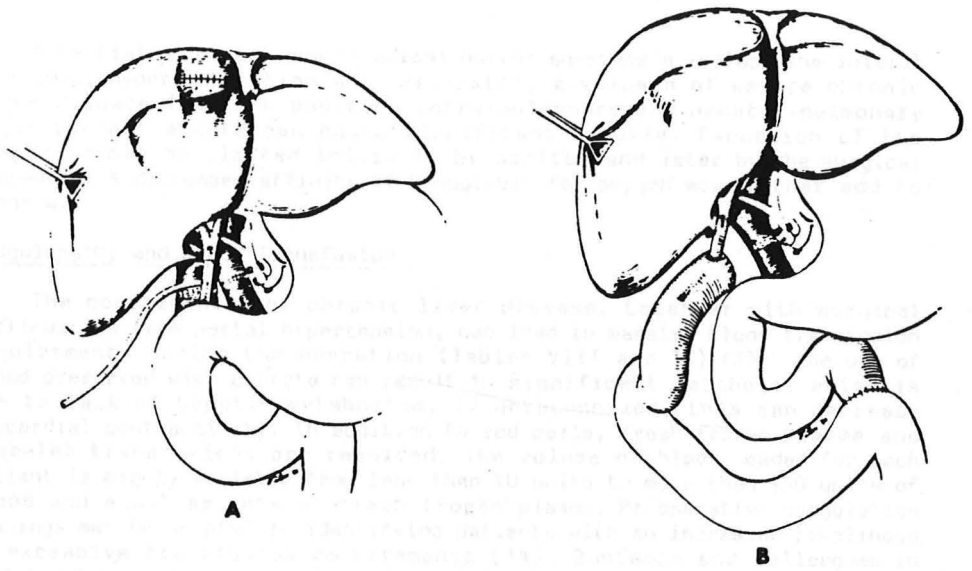


Fig. 5 - Completed orthotopic liver transplantation. (A) Biliary tract reconstruction with choledochocholedochostomy. (B) Biliary tract reconstruction with choledochojejunostomy, using a Roux limb.

From: Starzl et al, Hepatology 2:614-636, 1982.

The donor liver is transplanted into the site of the removed, diseased liver, anastomosing the vascular connections of the recipient to the donor liver. Following completion of the suprahepatic and infrahepatic vena caval anastomoses, the liver is perfused with electrolyte or plasma protein solution to flush out the high potassium preserving solution. Following completion of the vascular anastomoses, the biliary tract is anastomosed as a choledocho-choledochostomy (Starzl), or cholecysto-choledochostomy (Calne), each with a T-tube stent, if recipient common bile duct is present, or anastomosed to a Roux-en-Y jejunostomy.

ANESTHESIA FOR HEPATIC TRANSPLANTATION

There are many potential problems during anesthesia for hepatic transplantation. The choice of anesthetic agents is limited by the potential adverse interactions of drugs and inhalational agents requiring hepatic metabolism. Consequently the common technique is to employ nitrous oxide, narcotic and muscle relaxant. A Swan-Ganz catheter may be used to monitor pre-load in addition to routine monitoring procedures. Hypothermia during the long procedure (mean 13.5 hours in 32 adult patients) (31) is avoided by warming blood and use of a heating blanket under the patient.

Potential pulmonary complications during anesthesia include the initial hypoxemia, hyperventilation and respiratory alkalosis of severe chronic liver disease (32). In addition intra-pulmonary and hepatic-pulmonary right-to-left shunts can cause significant hypoxia. Excursion of the diaphragm may be limited initially by ascites and later by the surgical procedure. A decreased affinity of hemoglobin for oxygen may further add to hypoxia.

Coagulopathy and Blood Transfusion

The coagulopathy of chronic liver disease, together with surgical difficulties from portal hypertension, can lead to massive blood transfusion requirements during the operation (Tables VIII and IX) (33). The use of blood preserved with citrate can result in significant metabolic acidosis due to lack of hepatic metabolism. If unrecognized, this can decrease myocardial contractility. In addition to red cells, fresh frozen plasma and platelet transfusions are required. The volume of blood needed for each patient is highly variable from less than 10 units to more than 150 units of blood and equal amounts of fresh frozen plasma. Preoperative coagulation findings may be helpful in identifying patients with an increased likelihood of excessive transfusion requirements (34). Bontempo and colleagues in Pittsburgh measured prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, platelet count, antithrombin III, fibrinogen split products and euglobulin lysis time. Direct correlations were found between coagulation abnormalities, red blood cell usage and survival (34). Hospital transfusion services need to prepare in advance for liver transplantation. In the future, improvements in intraoperative autologous transfusion techniques may decrease the requirements for bank blood.

TABLE VIII

Intraoperative Blood Transfusion for Hepatic Transplantation

Recipient	n	Median	Range
		No. of units	
PBC	16	15	3-123
Malignancy	9	17	6-65
Sclerosing cholangitis	8	36	10-143
Hepatitis or cirrhosis	28	39	7-251
Adults (all)	68	29	3-251
Children	49	11	2-55

From: Butler et al, Transfusion 25:120-123, 1985

TABLE IX

Surgical and Perioperative Transfusion
in Adult Hepatic Transplantation

Blood Component	Mean	Range
	No. of units	
Red cell concentrate	71	6-254
Fresh frozen plasma	75	4-235
Platelet donor units	58	0-404

From: Butler et al, Transfusion 25:120-123, 1985

During the procedure, in addition to metabolic acidosis from citrate in transfused blood, there may be clinically significant hypocalcemia (etiology undetermined) and sudden marked hyperkalemia following initial perfusion of the implanted liver. Potassium levels as high as 7.8 mEq/l have been recorded in the pulmonary artery (35). Finally, at the end of the procedure or during the first 72 hours post-operatively, severe hypertension is common (36). This complication was observed before the introduction of cyclosporine but may have been worsened by the additional propensity of this agent to raise blood pressure.

SURGICAL AND PERIOPERATIVE COMPLICATIONS OF HEPATIC TRANSPLANTATION

During the early years of hepatic transplantation there was a very high intra-operative and peri-operative mortality. Some of these difficulties can be anticipated and avoided. Others require continued vigilance.

Air Embolism

Air embolism at the time of caval and portal anastomoses can be avoided by the use of positive end-expiratory pressure. Inability to complete portal venous anastomoses due to portal vein thrombosis can be avoided by non-invasive proliferative assessment with sonography, computerized tomography or magnetic resonance imaging. In some cases, portal vein interposition grafts may allow graft function.

Graft Ischemia

The state of the donor liver is critically important in the intraoperative and perioperative complications. Poorly preserved grafts or frankly ischemic grafts do not function well immediately, leading to severe continuing coagulopathy with associated anesthetic complications and massive blood transfusion requirements. Improvements in donor hepatectomy and preservation techniques have lessened the incidence of non-functioning grafts.

Vascular Thrombosis

Although the "normal" liver may tolerate either hepatic artery ligation or portal vein thrombosis with little or no effect on function, thrombosis or failure of either the hepatic arterial or portal venous anastomosis of a transplanted liver rapidly leads to graft ischemia and necrosis. Meticulous attention to surgical detail is essential for normal graft function.

Biliary Tract Anastomosis

Biliary tract complications were a major source of early operative morbidity and mortality before the introduction of the current anastomotic techniques. Starzl prefers the duct-to-duct anastomosis, reproducing normal anatomy where possible, and a choledocho-jejunostomy using a Roux-en-Y loop in the absence of sufficient recipient common bile duct. The incidence of biliary leaks and ascending cholangitis has diminished markedly with these procedures. Early postoperative complications due to obstruction with "biliary sludge" have been avoided since introduction of the technique to wash out the biliary tract of the donor liver before preservation.

Other Intra-abdominal Complications

Other gastrointestinal complications such as intraabdominal abscess formation and gastrointestinal hemorrhage have also been observed in the perioperative period (37). In general, 50% of patients require post-transplant surgery (31) for management of anastomotic leaks, bleeding and abscesses. These complications prolong hospitalization (mean hospitalization of 57 days in 32 adult patients) (31).

TABLE X

Early Mortality After Hepatic Transplantation
Patients dying <3 months after operation

Cause	% (n=274)*
Operative/technical	38.3
Hemorrhage	11.0
Hepatic failure	7.7
Infection	26.6
Rejection	8.8
Recurrent tumor	0.7
Unspecified	43.0

*Multiple causes often listed
From: Scharschmidt, Hepatology 4:95S-101S, 1984

Medical Complications

Major medical complications occurring as the result of the surgery also cause significant post-operative disability. These complications include acute renal failure requiring dialysis and infectious consequences of immunosuppression (9-13,29,31). Cholangitis, peritonitis, intra-abdominal abscess formation and septicemia have contributed to early mortality (9,12).

INFECTION AFTER HEPATIC TRANSPLANTATION

1. Related to graft and abdominal surgery:
   cholangitis, peritonitis and intra-abdominal abscess

2. Related to immunosuppression:
   fungal (candida, nocardia, aspergillus) and viral
   (CMV, varicella, adenovirus, herpes)

3. Sepsis (often gram-negative)

4. Pneumonitis

Psychiatric Complications

The psychiatric aspects of hepatic transplantation are of great importance during the perioperative period. House and colleagues conducted formal psychiatric evaluation of 34 patients. All patients evaluated before the transplantation surgery (seven children and 19 adults) exhibited obvious psychiatric disturbances (38). Organic brain syndromes, anxiety and depression were the most common problems. All patients also experienced psychiatric problems post-operatively (38). Long-term psychiatric complications have not been extensively examined. Recent reports on the quality of life following tansplantation do not emphasize such problems.

IMMUNOSUPPRESSION AND REJECTION

Rejection and immunosuppression and their consequences are the major problems following successful completion of the surgery required for orthotopic liver transplantation and avoidance of technical graft difficulties related to preservation, anastomoses and vascular thrombosis. With improvements in intraoperative techniques and graft preservation, the consequences of immunosuppression have become the major limiting factor in survival.

Transplantation Immunology

Almost all cells appear to bear genetically-determined cell surface antigens (histocompatibility linked antigens, HLA) that stimulate a rejection response when transplanted into a non-identical recipient. In man, there are two major classes of histocompatibility linked antigens. Class I antigens, which include HLA-A, -B and -C, are found on most cells (39). Class II antigens, which include HLA-DR, -DP and -DQ, are normally found on

monocytes and tissue macrophages, interstitial dendritic cells, B lymphocytes and endothelial cells (40). Recent studies have also demonstrated class II antigens on a variety of epithelial cells, lymphatics and capillaries (40).

In the liver, class I (HLA-A, -B and -C) antigens are expressed on blood vessel endothelium, bile duct epithelium, fibroblasts, sinusoidal lining cells and Kupffer cells and interstitial dendritic cells (39). In contrast to the clearly positive results in these cells, varied results were obtained when hepatocytes were examined. Of 5 samples investigated, hepatocytes were negative for class I antigens in 2, and variably positive in the remaining 3 (39). Similar variation was not observed in other tissues or other cell types in the liver tissue. When class II (HLA-DP, -DQ and -DR) antigens were examined, hepatocytes were always negative. Both sinusoidal lining cells and capillary endothelium expressed class II antigens (40). Similar transplantation antigens are expressed in animal tissues, thereby allowing studies of experimental transplantation immunology.

Animal Studies of Liver Transplantation Immunology

Although transplanted organs are rejected by most species in the absence of immunosuppression, in some species the transplanted liver appears to behave differently than most other tissues. This was suggested following the observation that transplants of livers, between apparently genetically dissimilar pigs, were not rejected. Furthermore, pigs receiving liver transplants were also partially tolerant of other organ grafts that would normally be rejected (3). The tolerance was donor-specific in that transplanted organs from third party donors were rejected with a normal time course. The mechanism of donor-specific tolerance related to liver transplantation in the pig has not been defined.

More recently, a rat model of liver transplantation immunology has been examined (6). These studies demonstrated the following:

1. Rejection of transplanted livers in the rat is dependent on the immune response of the recipient.

2. Rats not rejecting transplanted livers develop profound donor-specific tolerance.

3. Possible mechanisms of tolerance include:
   (a) Specific deletion of clones responsible for graft rejection and cytotoxic T cell responses, but not of clones responsible for graft-versus-host and mixed lymphocyte responses.
   (b) Presence of soluble donor class I antigens in recipient serum derived from donor liver.

These studies suggest that the liver may be immunologically "different" from other organs. The mass of donor tissue may play a role, if the governing factor is the surface area of donor endothelium presented by the transplanted tissue (41). The sinusoidal endothelial cells of the liver that line all the hepatocyte cords may be critically important in this regard and clearly the mass of endothelial cells in a transplanted liver is much greater than in other organs.

Donor-Recipient Matching

Matching of donor and recipient for transplantation antigens in order to improve graft survival is much less important in liver transplantation than in renal transplantation. Indeed, the most critical "match" is that of the size of the donor and recipient in order to avoid technical difficulties in surgery. However, matching for some antigens may decrease post-operative problems.

The following factors may be taken into consideration when matching donor and recipient:

1. Size of liver
2. ABO blood group
3. Anti-lymphocyte cytotoxicity
4. HLA match

ABO blood group

ABO incompatibility of renal transplants leads to immediate hyperacute rejection with loss of graft function (42). Consequently, ABO-incompatible liver transplants are avoided where possible, although successful transplantation has been reported (7,29). However, ABO-unmatched transplants (group O liver transplanted into non-group O recipient or group A or B liver into group AB recipient) are used frequently (43). The occurrence of anti-recipient ABO antibody after ABO-unmatched liver transplantation has been reported (43). In 3 of 8 patients with antibody, it resulted in hemolysis. The antibodies were not detected initially but appeared 8 to 16 days after transplantation and were last detected at 11 to 41 days after surgery. Antibodies were detected in less than 50% of ABO-unmatched transplants. The authors concluded that the antibodies were probably produced by donor lymphocytes transplanted in or with the livers. The presence of transient antibodies had no effect on long-term graft survival.

Anti-lymphocyte Cytotoxicity

Complement-dependent lymphocytotoxic antibodies are also responsible for rejection of renal transplants. They are detected by incubation of recipient serum with a pool of 50 to 100 target lymphocytes and measuring cytotoxicity-induced killing of target cells. Recipient antibodies cytotoxic for donor lymphocytes can be detected in a similar manner, termed a lymphocyte cross-match test. Although important in renal transplantation, the presence of recipient antibodies against donor lymphocytes does not appear to be clinically important in hepatic transplantation (44). Starzl and colleagues reported successful transplantation despite positive anti-donor cross matches detected with standard cytotoxicity tests (44). Graft survival was initially thought to be equivalent in the presence or absence of anti-donor lymphocyte antibodies. Later analysis, however, suggested that positive cross-matches resulted in a more difficult post-operative course and poorer results (29).

HLA Match

The shortage of suitable donor organs and the short preservation time available after donor hepatectomy preclude systematic tissue typing. Good matches at HLA-A, -B and -DR loci are therefore unlikely with random allocation. The importance of HLA-A, -B and -DR typing in renal transplantation has decreased since the introduction of cyclosporine (45). No significant difference can now be attributed to matching at these loci. Future research into the identity of the active transplantation antigens responsible for rejection may improve graft survival.

IMMUNOSUPPRESSION

In the absence of immunosuppression, transplanted livers in man are rejected. Consequently, long-term immunosuppression is required for survival of graft and patient following hepatic transplantation. Immunosuppression, with prednisone and azathioprine (or cyclophosphamide) in combination, achieved renal graft survival in early trials in 1963. This immunosuppressive regimen was the major one used in most transplantation centers until 1979-1980 and the introduction of cyclosporine. The addition of splenectomy, anti-lymphocyte globulin or thoracic duct drainage did not improve graft survival (9).

Using prednisone and azathioprine for immunosuppression, acute rejection accounted for approximately 20% of the early mortality. The major causes of early mortality were technical and mechanical, as described above. Chronic rejection and subsequent liver failure, however, was an important contributor to late mortality (9). Overwhelming infection, often the consequence of immunosuppression, also contributed (see above). Thus, prednisone and azathioprine were suboptimal in controlling hepatic transplant rejection and alternative immunosuppressive regimens were sought.

Cyclosporine

Cyclosporine, a cyclic endecapeptide (mol wt 1203), is a metabolite of the two strains of the fungus Tolyplocladium inflatum Gams found in soil samples from a treeless plateau in southern Norway (46). It is extremely hydrophobic, consisting of 6 N-methylated aliphatic amino acids, 4 other aliphatic amino acids and one new amino acid. Because of its complex structure, cyclosporine is difficult to synthesize for commercial applications. It is produced by fermentation and chromatographically refined to 98% purity.

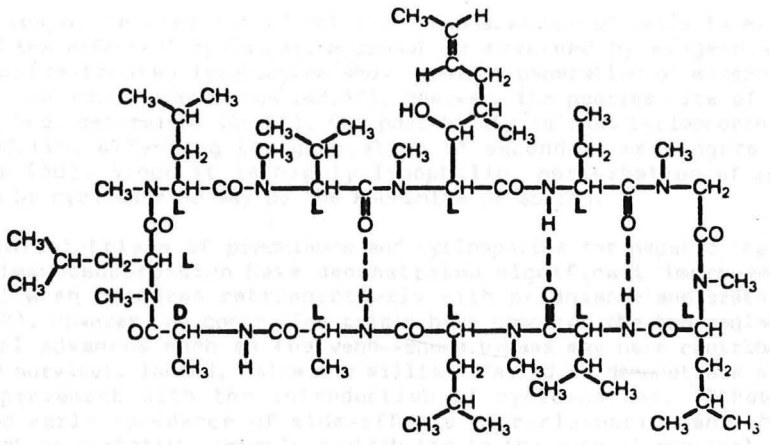


Fig. 6 - Chemical structure of cyclosporine

Cyclosporine is a potent inhibitor of T cell responses to transplantation antigens, thereby suppressing the immune response and prolonging the survival of transplanted foreign tissues (46-51). The mechanism of action is complex and includes:

1. Inhibition of interleukin-1 (IL-1) generation by macrophages

2. Inhibition of lymphokine generation by T helper cells including interleukin-2, interleukin-3, B cell growth factor, macrophage-activating factor, monocyte/macrophage procoagulant activity, migration inhibition factor, lymphocyte-derived macrophage chemotactic factors, gamma interferon and colony-stimulating factor.

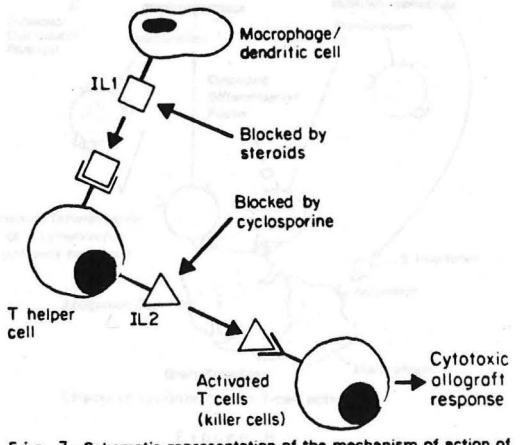
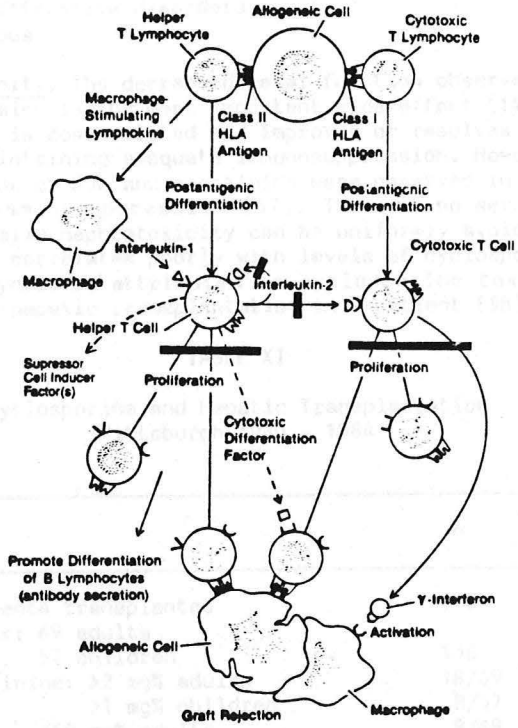


Fig. 7 - Schematic representation of the mechanism of action of cyclosporine. IL = interleukin.

From: Fine et al, Ann Intern Med 100:246-257, 1984

Cyclosporine does not affect the responsiveness of cells to exogenous IL-2 and the effect of cyclosporine cannot be reversed by exogenous IL-1. Cyclosporine-treated lymphocytes show impaired generation of messenger RNA for IL-2 and other lymphokines (48,49), however, the precise site of action has not been determined (46-51). One possibility is that cyclosporine binds to calmodulin, affecting the generation of secondary messengers in the membrane (50). Since it is highly lipophilic, perturbation of membrane function by cyclosporine may be the mechanism of action.

Clinical trials of prednisone and cyclosporine for hepatic transplantation immunosuppression have demonstrated significant improvement in survival when compared retrospectively with prednisone and azathioprine (13,29,52). However, no controlled trials have compared the two regimens and technical advances such as the veno-venous bypass may have contributed to improved survival. Indeed, Calne and Williams failed to demonstrate significant improvement with the introduction of cyclosporine, although the increased early incidence of side-effects of cyclosporine and the high perioperative mortality probably contributed to the overall survival.



Effects of cyclosporine on T-cell activation.

Figure 8

From: Cohen et al, Ann Intern Med 101:667-682, 1984

The prednisone regimen used by Starzl is an initial dose of 200 mg/day and a rapid taper over 5 days to 40 mg/day. The dosage of cyclosporine used by Starzl and colleagues in adults has been based on 5 mg/kg/day intravenously or 17.5 mg/kg/day orally in two divided doses. The pharmacokinetics of cyclosporine are complex. It is highly lipid-soluble and water-insoluble and thus oral administration results in marked individual variation in bioavailability. Drug levels, measured by radioimmunoassay or high-performance liquid chromatography, are therefore essential for patient management. Blood levels of cyclosporine reflect 50-70% associated with erythrocytes and 10-20% with leukocytes and in plasma (bound to lipoproteins) (53). The majority of the drug is metabolized by the liver and excreted in the bile, therefore cyclosporine levels are affected by hepatic function and dosage in hepatic transplantation may be unpredictable. Furthermore, cyclosporine side-effects include hepatotoxicity, thereby complicating assessment of the adequacy of immunosuppression.

The major side effects of cyclosporine include:
1. Nephrotoxicity
2. Hepatotoxicity
3. Hypertension
4. Lymphoproliferative disorders
5. Misellaneous

1. Nephrotoxicity. The decreased renal function observed with cyclosporine immunosuppression is the most important side-effect (14,54-58). Some of the nephrotoxicity is dose-related and improves or resolves with a decrease in dosage while maintaining adequate immunosuppression. However, as shown in Table IX, elevations of BUN and creatinine were observed in adult survivors after 1 year of immunosuppression (57). There is no serum or whole blood level below which mild nephrotoxicity can be uniformly avoided. Severity of the nephrotoxicity correlates poorly with levels of cyclosporine and dosage. Hemolytic-uremic syndrome, attributed to cyclosporine toxicity, has been reported following hepatic transplantation in 1 patient (58).

TABLE XI

Cyclosporine and Hepatic Transplantation
Pittsburgh 1980 - 1984

	n	%
Number of patients transplanted	178	
Survived 1 year: 69 adults		
57 children	136	76%
Elevated creatinine: >2 mg% adults	18/69	26%
>1 mg% children	8/57	14%
Elevated BUN: >50 mg% adults	9/69	13%
>30 mg% children	8/57	14%

From: Iwatsuki et al, Transplantation Proc 17:191-195, 1985

2. Hepatotoxicity. Preliminary animal studies and early clinical trials in renal transplantation demonstrated hepatotoxicity that responded to dose-reduction. Hepatotoxicity has not been a significant clinical problem except in hepatic transplantation where elevated liver function tests may be due to rejection, drug toxicity or many other causes.

3. Hypertension. Persistent hypertension within the first weeks after transplantation has been a common problem. The cause of the hypertension remains unknown.

4. Lymphoproliferative disorders. Early data suggested that lymphoma may occur more commonly with prednisone and cyclosporine than with prednisone and azathioprine (14). Recent analysis indicates that this side effect may be no greater than with other agents. In a survey of 3,000 patients, 15 lymphomas were documented, an incidence of 0.5%, in contradistinction to the 2% to 11% incidence in patients receiving conventional immunosuppressive therapy (46). Starzl and coworkers reported regression of lymphoproliferative lesions following reduction or discontinuance of cyclosporine immunosuppression, often without subsequent rejection of the grafts (59).

5. Miscellaneous. Hypertrichosis, gingival hyperplasia and neurologic manifestations including tremor and paresthesias have been reported. In high doses via a central vein, cyclosporine can induce adult respiratory distress syndrome (60).

In summary, the introduction of the combination of cyclosporine and prednisone for immunosuppression has coincided with markedly improved survival statistics for hepatic transplantation. Although technical improvements may account for some of this improvement, better control of acute and chronic rejection has also been a significant contribution.

REJECTION

Livers transplanted into HLA non-identical recipients are rejected by the normal immune response recognizing foreign transplantation antigens. Without immunosuppression, there is a quiescent phase of at least 2-3 days during which there is initial activation and proliferation of responding recipient T cells (29). After a few days, the responding mononuclear cells migrate to the liver and accumulate, mainly in the portal tracts but also around the central vein and the sinusoidal endothelial cells. Associated with the cellular infiltration there is disruption of blood flow and necrosis of hepatocytes, initially in the central zones and then progressing to mid-zonal areas. Cholestasis becomes marked and there may be fibrinoid necrosis of small hepatic arteries before hepatic necrosis is complete (29).

When rejection is modified by immunosuppression, the cellular infiltration and hepatocyte necrosis are diminished. However, residual centrilobular necrosis and subsequent collapse together with centrilobular cholestasis may persist. In addition, larger interlobular bile ducts may be damaged by continuing cellular infiltration and may eventually disappear (29,61-67).

Progressive hepatic fibrosis may accompany continuing rejection in some patients. The exact mechanism whereby fibrosis occurs has not been determined. Chronic rejection is also associated with progressive intimal thickening of the hepatic artery branches, similar to, but less striking than, the arterial changes in chronic rejection of transplanted kidneys. There is accumulation of immunoglobulins and complement in the altered vessel wall suggesting a humoral response (61).

Clinical Manifestations of Rejection

The clinical symptoms and signs of rejection are non-specific and include malaise, fever, abdominal discomfort and worsening liver function tests (29,63-65,67). The graft may be swollen, hard and tender. Radioisotopes used to assess parenchymal and reticuloendothelial function are poorly concentrated. Bilirubin, alkaline phosphatase and transaminase levels may rise. Markedly elevated transaminases are more likely in early rejection with disproportionate elevation of alkaline phosphatase being observed later in the course (63). Ratios of branched chain to aliphatic amino acids in plasma and measurements of beta$_2$-microglobulin and serum amyloid A protein may help in following hepatic dysfunction (68-70). Prolongation of the prothrombin time appears to most readily detect failure of synthetic function.

The major problem is the differential diagnosis of these non-specific manifestations. The major alternative etiologies include:

1. Ischemic injury to graft - vascular thrombosis
   - poor preservation
2. Biliary obstruction and cholangitis
3. Viral hepatitis - hepatitis B
   - CMV, adenovirus, herpes
4. Drug toxicity - cyclosporine
5. Intra-abdominal abscess and sepsis

The evaluation of these potential etiologies often includes diagnostic procedures such as cholangiography and needle biopsy of the grafted liver. Empiric treatment of rejection with bolus steroids is used temporarily until the diagnosis is established. Management is particularly difficult if initial graft function is not achieved.

Liver Biopsy

The importance of graft liver biopsy in diagnosing rejection has been recently stressed. Biopsies taken at the time of initial graft rejection demonstrate predominantly mononuclear cell infiltration of portal tracts with bile duct damage, less marked cellular infiltration of central veins and sinusoids and cholestasis (63-65,67). Mild changes of a similar nature are seen when routine biopsies are performed in the absence of clinical findings (64).

Follow-up biopsies may demonstrate focal necrosis, fibrosis, bile duct proliferation (pseudoduct formation) and bile duct destruction. Bile duct damage, observed in both acute and chronic rejection is non-specific (62). Similar histologic findings have been reported in acute and chronic hepatitis (viral and non-viral), obstructive liver disease, drug-induced hepatitis, primary biliary cirrhosis and graft-verus-host disease. The distinction between bile duct changes with rejection and those observed in primary biliary cirrhosis may be difficult (62). Consequently, the diagnosis of recurrence of primary biliary cirrhosis in transplanted livers by Neuberger and associates (71) has been questioned (62). In a retrospective study, Fennell and colleagues in Colorado concluded that non-suppurative destructive cholangitis, a major pathologic finding in PBC, occurred frequently in grafted livers (62). They found no relationship between the frequency and severity of bile duct damage and original hepatobiliary disease, age, sex, duration of graft survival or cause of death.

Fine needle aspiration biopsy, rather than core needle biopsy has been recently used in the diagnosis of renal graft rejection (72). Preliminary studies of fine needle aspiration biopsies of transplanted pig livers have been carried out (73). The cytological assessment of inflammatory cells associated with rejection was consistent with the results obtained with core needle biopsy. In the future, routine cytology from fine needle aspiration biopsy specimens may aid in the management of patients undergoing hepatic transplantation.

RECENT RESULTS OF HEPATIC TRANSPLANTATION

Coincident with the introduction of cyclosporine for transplant immunosuppression in 1980, there has been a significant improvement in survival following hepatic transplantation. As shown in Table XII, before 1980 one year survival was 33% (9). Of the 56 survivors, an additional 13 died in the second year following transplantation and 10 died in the third or fourth year. Twenty patients have survived more than 5 years and four more than ten years from this original group of 170 patients transplanted by Starzl (29).

TABLE XII

Recent Results of Hepatic Transplantation

Year Transplanted	n	1 year survival (%)
1963 - 1979	170	33
1980 - 1983	178	76
1984*	135	85

*Survival for >3 months
From: Starzl et al, Hepatology 2:614-636, 1982; Iwatsuki et al, Transplantation Proc. 17:191-195, 1985

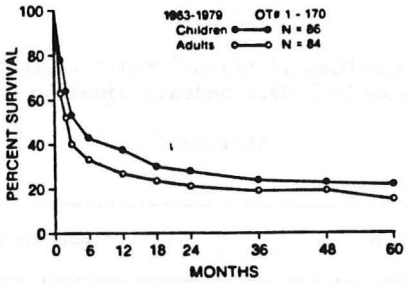


Fig.9-The life survival of adults vs. children in patients treated with conventional immunosuppression.

From: Starzl et al, Hepatology 2:614-636, 1982

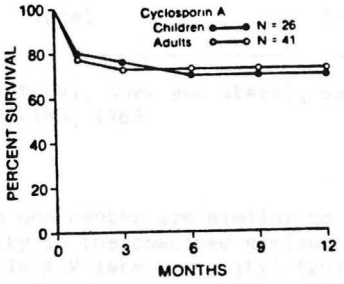


Fig.10-The 1-year actuarial survival of adults vs. children after liver transplantation under immunosuppression with cyclosporin A and steroids.

From: Starzl et al, Hepatology 2:614-636, 1982

Although the follow-up period is short, the results from Starzl's group since 1980 demonstrate significantly improved survival and the 5 year survival in this group is expected to be nearing 60%. As mentioned above, the contribution of technical advances, in particular the veno-venous bypass procedure, cannot be evaluated separately from the contribution of improved immunosuppression. The causes of death of 100 patients transplanted in one program since 1980 (74) are outlined below (Table XIII). Biliary tract complications continue to be an important cause of post-operative morbidity and mortality (75).

TABLE XIII

Mortality After Hepatic Transplantation
100 patients treated with cyclosporin

1980-1982

Cause of Death	n	(%)
Surgical and technical	15	(37%)
Graft preservation	5	(12%)
Rejection	10	(25%)
Infection	7	(17%)
Recurrence of original disease	3	(7%)
Pulmonary a-v shunt	1	(2%)
Total	41	

From: Iwatsuki, Shaw and Starzl, Semin Liver Dis 3:173-180, 1983

These results from one center are similar to the early (<3 months) and late (>3 months) mortality in the combined series from 4 programs (Table X early mortality and Table XIV late mortality) (20). Operative and technical difficulties are more important early, whereas hepatic failure (etiology unspecified) is more important late. Infection is a major contributing factor both early and late. The infectious complications include aspergillus and nocardia, varicella and bacterial infections (7,9,12). The major difficulty in comparing the results of different centers and of pooling data from 4 centers is the lack of evidence of equivalency. No uniform requirements have been established in order to standardize recipient selection (see above). In addition, the preoperative general condition of the patient influences survival. Patients at home or in hospital have better overall survival than patients requiring intensive care life support systems (52). The timing of the decision to pursue hepatic transplantation as an alternative form of therapy is therefore critical.

TABLE XIV

Late Mortality After Hepatic Transplantation
Patients dying >3 months after operation

Cause	% (n=101)*
Operative/technical	17.8
Hemorrhage	5.0
Hepatic failure	21.8
Infection	27.7
Rejection	8.9
Recurrent tumor	8.9
Recurrent disease (non-malignant)	6.9
Unspecified	44.5

*Multiple causes often listed
From: Scharschmidt, Hepatology 4:95S-101S, 1984

TABLE XV

Effect of Disease Stage on Early Survival
After Hepatic Transplantation

	Number	Survival (%)
Outpatient or inpatient	88	73
I.C.U.	26	42

From: Starzl et al, Hepatology 4:475-495, 1984

Recurrence of Original Disease

The major late cause of death in patients undergoing transplantation for malignancy is the recurrence of the original tumor (20). Pre-operative evaluation is able to exclude patients with metastatic disease, however, micro-metastases are presumably present in patients with recurrence. The role of immunosuppression in increasing the likelihood of persistence and growth of micrometastases has not been clearly defined. In transplantation for hepatocellular carcinoma, 30-40% of patients survive for at least one year and long-term survival has been achieved. The results of treating cholangiocarcinoma have been less favorable and no patient with duct cell carcinoma has ever been cured (29).

In pediatric transplant patients, recurrence of non-neoplastic disease has not been observed (20,29,76). However, recurrence of the original disease has been reported in adults (71,77-79). Hepatitis B virus infection has recurred in the transplanted liver with eventual patient demise, although long-term carrier state has also been described (29). Hyperimmune globulin (HBIG) is used postoperatively, with consequent transient HBsAg negativity, followed by return to positivity in all but one case (80).

The recurrence of both primary biliary cirrhosis and chronic active hepatitis has been reported (71,79). However, histologic and clinical differentiation of PBM from rejection and of recurrent chronic active hepatitis from newly-acquired post-transfusion hepatitis is difficult. Recurrence of Budd-Chiari syndrome has been reported by both Starzl and Calne and Williams (78,81). Recent studies demonstrating an underlying myeloproliferative disorder in the majority of patients with Budd-Chiari syndrome (82) emphasizes the need for continued anti-coagulation following liver transplantation. Re-transplantation for chronic rejection or disease recurrence has often been unsuccessful, however, more recent results suggest that up to 50% survival may be achieved (52).

Local Experience in Hepatic Transplantation

Two successful local programs are at present in operation at Children's Medical Center/UTHSCD Southwestern Medical School (Dr. W. Andrews) and at Baylor University Medical Center (Dr. G. Klintmalm). The results of both programs are thus far equivalent to those of Starzl's program at the University of Pittsburgh Health Center. At Children's Medical Center, Dr. Andrews has carried out liver transplantations in 24 children and has 36 children on a waiting list. The shortage of pediatric donors continues to limit the number of operations performed. As at Baylor, the results of the pediatric liver transplantation program compare favorably with those elsewhere. Pericardial tamponade, pulmonary hemorrhage and cytomegalovirus pneumonitis were major factors in the 3 deaths at Children's Medical Center.

TABLE XVI

Local Experience in Hepatic Transplantation

	Children's Medical Center/UTHSCD	Baylor University Medical Center
Surgeons	W. Andrews	G. Klintmalm B. Husberg
Program Start	10/84	12/84
No. of patients	24	21
No. of transplants	27	23
No. of survivors	21 (87%)	18 (86%)

At Baylor, 2 patients have received combined liver and kidney transplants and five of the 20 adult patients were over 50 years of age at the time of surgery. The length of hospitalization (mean 41 days for 14 adult patients discharged, median 31 days) and blood transfusion requirement (mean 10 units, range 2-36 units) also compares very favorably with long-established programs. Intraoperative pulmonary embolus and immediate pre-operative sepsis contributed to the deaths of the 3 non-survivors.

Thus, there are two active programs in Dallas with excellent early results. Since the early problems in other centers have been greater than those arising after establishment of the program, future results are expected to be equally good.

PRESENT AND FUTURE CONSIDERATIONS IN HEPATIC TRANSPLANTATION

After reviewing the available data on hepatic transplantation, the NIH Consensus Development Conference recommended "expansion of this technology to a limited number of centers where performance of liver transplantation can be carried out under optimal conditions". The skills and resources required for liver transplantation include the following:

1. Trained transplant surgeons
2. Donor procurement and transplantation program
3. Operating room facilities and personnel
4. Intensive care, in-hospital and outpatient facilities
5. Medical, nursing and psychiatric staff
6. Pathology and Radiology services (including blood bank, chemistry, hematology, microbiology, histopathology, nuclear medicine, and ultrasound).

Institutional support for a transplant program must therefore be widespread in order for success to be attained.

Financial Aspects

The cost of hepatic transplantation is considerable. Major factors involved were intensive care hospital days (mean 13.5 in 32 adult patients) and duration of hospitalization (mean 57 days in 32 adult patients) when analyzed by Van Thiel (31). Physicians fees in Pittsburgh amounted to a mean of $9,800 whereas the average hospital bill was $30,600 (31). Estimates of costs for the first year of hepatic transplantation vary from $68,000 to $238,000 (83). The low estimate is more likely to apply to children while the high estimate may reflect common costs for adults. The high estimate was compiled by the Massachusetts Task Force on Liver Transplantation with break-down as shown below.

TABLE XVII

Cost Estimates for Hepatic Transplantation

Cost Component	Cost per Patient surviving 1 year
Pre-operative	$20,500
Organ procurement	$ 5,700
Surgery	$12,900
Post-operative: ICU	$48,000
non-ICU	$54,900
Physician's fees	$15,700
Follow-up and re-hospitalization	$74,400
Cyclosporine	$ 6,700
Total	$238,800

From: Barnes et al, Final Report, Task Force on Liver Transplantation, Massachusetts, May 1983.

The Congressional Budget Office has also estimated the potential costs for coverage of liver transplantation, stating that overall costs "...could range from $40 million to $100 million a year" and that long-run costs could reach $400 million annually. Constraints on transplantation therefore include:

1. Reimbursement by public and private insurers
2. Number of donor organs available
3. Number of active centers

The latter factor is less important now than previously, with currently 29 centers in the USA participating in liver transplantation with future plans at an additional 6 or more. By harvesting livers from all kidney donors, the supply of organs is unlikely to be limiting. Consequently, financial considerations and cost-effectiveness analyses become important in governing the overall annual cost of hepatic transplantation. When analyzed, the quality of life in transplant survivors has been reported to be good (20), however, extensive evaluation has not been carried out. No randomized trials have compared liver transplantation with conventional supportive measures for the management of patients with advanced liver disease.

TABLE XVIII

Hepatic Transplantation
1984-1985

Number of Centers	Rate of Transplantation per Center	No. Patients Transplanted 1984	1985
11	<5 per year	16	22
11	5-15 per year	47	71
6*	15-30 per year	64	114
1	>30 per year	135	205

*Includes 2 centers in Dallas

Research Aspects

Experimental studies of hepatic transplantation in man have demonstrated the hepatic origin of haptoglobin, GC-globulin (vitamin D-binding), complement components C3, C6, C8 and factor B, transferrin, alpha-1 antitrypsin and plasminogen by donor-recipient genetic typing (84-86). Additional research has been mainly confined to aspects of the preservation of the donor liver, surgical techniques and the diagnosis of rejection. Recent studies in animals have demonstrated that hepatocytes from HLA-identical and non-identical donors were able to decrease mortality from drug-induced (d-galactosamine) and ischemic acute liver failure (87-92). The extension of these studies to man, with the potential to provide a liver support system during regeneration from acute hepatic failure, may be possible in the future.

Future plans include the establishment of a Liver Transplantation Data Bank at Pittsburgh. An initial meeting of representatives from transplant centers will be held in Chicago on November 1 and 2 before the annual meeting of the American Association for the Study of Liver Diseases. It is hoped that such a central approach will enable development of unified criteria for selection of patients and for reporting and evaluating all data relating to outcome.

CONCLUSIONS

Hepatic transplantation is an alternative therapeutic modality for progressive liver disease. Further experience and ongoing evaluation are necessary to define its precise role in the overall management of all patients dying from liver disease.

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