CHAPTER 2

Changing Perspectives on Liver Transplantation in 1988

ROBERT D. GORDON AND THOMAS E. STARZL

Department of Surgery
University of Pittsburgh
Pittsburgh, PA.

Liver transplantation services have continued to expand during the past year as indications for liver replacement have broadened, contraindications have diminished, and referrals to transplant centers have increased. The UNOS Liver Transplant Registry began collecting data officially on October 1, 1987 and by September 30, 1988 had received registration forms for 1,090 new patients from 42 centers in 23 states (Fig. 1). At this rate we estimate that approximately 1,400 liver transplantations will have been performed in 1988 in the United States.

Liver transplantation activity has also increased in Europe. The results for 1,238 patients receiving liver transplants at 32 European centers (Fig. 2) were described in the first report of the European Liver Transplant Registry in 1987 (1). In an update presented at the Congress of the Transplantation Society in Australia in 1988, Bismuth reported that the registry had grown to 2414 transplantations performed by 49 centers as of April, 1988 (2).

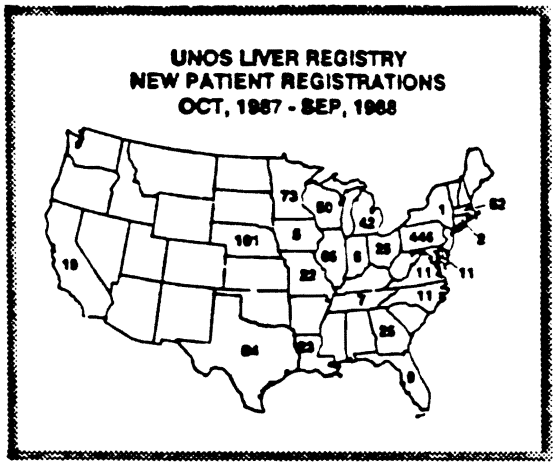

Fig 1. First year new patient registrations in the UNOS Liver Transplant Registry.

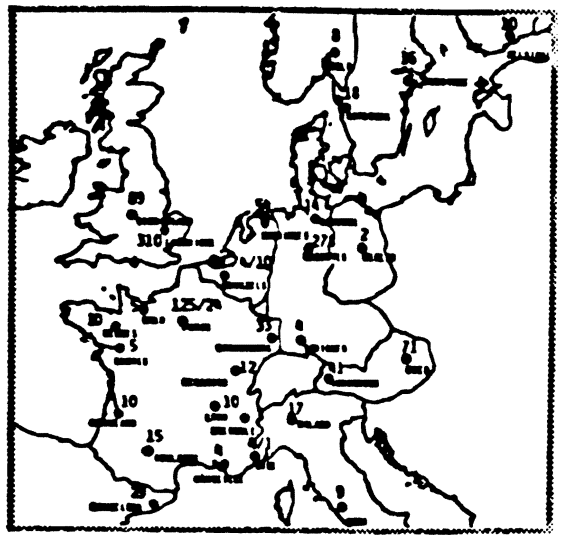

Fig 2. Liver Transplant Centers reporting in the European Liver Transplant Registry. From Bismuth H, et al.[1]

Clinical Transplants 1988, P. Terasaki, Ed. UCLA Tissue Typing Laboratory, Los Angeles, California.

Table 1. Patient survival after liver transplantation in selected series.

	Duke[a]	Australia[b]	UCLA[c]	Europe[d]	BCLT[e] (Boston)	Pittsburgh
Patients	24	11	83	1218	41	1258
Transplants	25		100	1315	47	1619
30 day survival	70%					88%
1 year survival	50%	73%	73%	44%	54%	73%

[a]McCann R, et al. N C Med J 49:324-7, 1988.
[b]Lynch S, et al. Transpl Proc 20:34-7, 1988
[c]Busuttil RW, et al. Ann Surg 206:387-402, 1987
[d]Bismuth H, et al. Lancet 2:674-6, 1987.
[e]Jenkins RL. Arch Surg 121:424-30, 1986.

Expected one year patient survival after liver transplantation in reported series ranges from 44 to 85% as shown by the examples in Table 1. Comparison of series is difficult because of substantial differences in case mix, time period, and methods of immunosuppression. The lower survival rates in some reports usually reflect start up experience or include cases from prior to 1984 when cyclosporine was not yet generally available in the United States and the risk factors associated with liver transplantation were not as clearly delineated. One year survival for cases after 1984 in the European registry is over 60% compared to the overall 1 year patient survival of only 44% (Fig. 3). In the Cambridge-Kings College Hospital experience, the reported one year survival for patients receiving transplants in 1986-87 is 69% (3).

Case mix is probably the most important factor determining center specific results and is difficult to analyze. However, as larger series are reported such as those from Pittsburgh, Cambridge, and Hannover, certain trends are becoming clear.

Survival is significantly affected by the indication for transplantation. Among adult patients transplanted in Pittsburgh since 1981, four groups of patients can be identified (Fig. 4): 1) cancer patients. 2) hepatitis B-virus (HBV) surface antigen positive (HBsAg+) patients, 3)

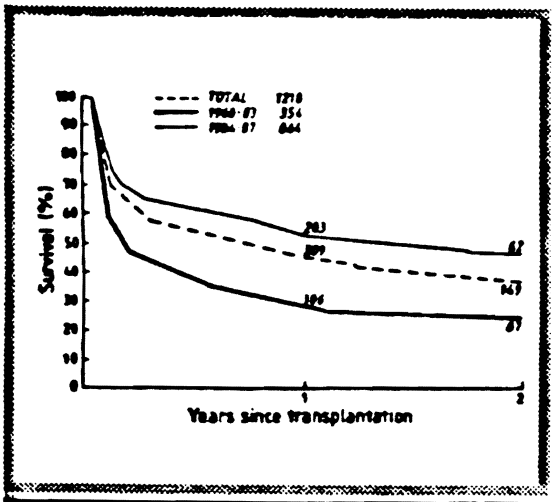

Fig 3. Patient survival before and after 1984 in the European liver registry. From Bismuth H, et al.[1]

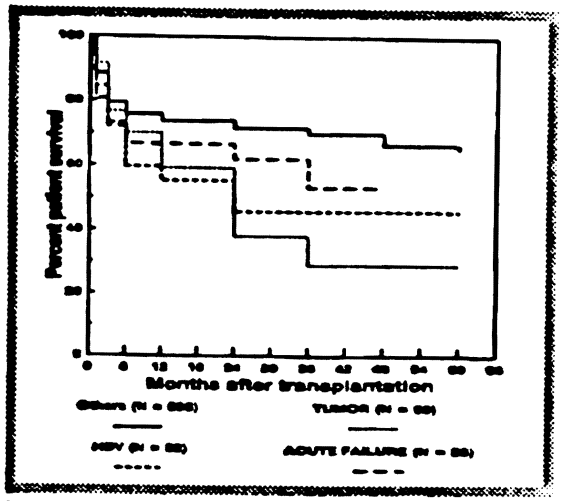

Fig 4. Adult patient survival in the Pittsburgh series for malignant tumors, chronic hepatitis B (HBV), acute liver failure, and other chronic benign diseases.

Table 2. Comparison of patient survival rates for benign and malignant diseases of the liver in the Pittsburgh and Cambridge/King's College series.

	30 day survival		One year survival	
	Malignant	Benign	Malignant	Benign
Pittsburgh	92%	88%	59%	72%
Cambridge/ King's College[a]	80%	70%	30%	50%

[a]Friend PJ, et al. Transplant Proc, in press.

acute hepatic failure patients, and 4) those receiving transplants for other chronic liver diseases (primary biliary cirrhosis, sclerosing cholangitis, metabolic errors, alcoholic and other non-HBV causes of cirrhosis, etc.). There is already an extensive literature on transplantation concerning the fourth group of patients but a brief commentary on liver transplantation in the management of variceal hemorrhage and for alcoholic cirrhosis is warranted.

LIVER TRANSPLANTATION IN ADULTS

Transplantation for Cancer

Thirty day survival after liver transplantation for malignant liver tumors has been very high but long term survival has been disappointing because of the high incidence of tumor recurrence, usually within 18 to 36 months in most reported series, and because of a tendency of the cancers to recur in the transplanted liver (4-8). Thirty-day and one year patient survivals after transplantation for malignant and benign disease for the Pittsburgh and Cambridge/Kings Hospital series are shown in Table 2.

Factors influencing survival include histologic cell type, concurrent cirrhosis, and involvement of regional lymph nodes. Pichlmayr has recently reported some success with liver transplantation for cancer (9). In a series of 95 patients receiving transplants for malignancy, 22 survived more than one year and 10 more than 2 years, 5 more than 3 years, and 4 more than 5 years. Of particular note, he reported 54% one year survival in patients with carcinomas of the central bile duct and improved one year survival to 91% in patients with cancer free regional lymph nodes. Best results for hepatocellular cancer were obtained in patients without concurrent cirrhosis.

We still have much to learn about the behavior of cancer in patients receiving transplants and immunosuppressive drugs. It has generally been assumed that the immunosuppressive drugs required after liver transplantation would promote tumor growth by further weakening of immunological defense mechanisms. If this were the case, one might expect that the more efficacious immunosuppression afforded by cyclosporine would have a further adverse effect on both tumor free interval and patient survival after liver transplantation. However, the Cambridge/King's Hospital group recently compared patients getting liver transplants for hepatocellular carcinoma under azathioprine-prednisone with those getting cyclosporine-low dose prednisone (10). The proportion of patients with cirrhosis and with fibrolamellar hepatoma and the median tumor sizes were similar in both groups. The mean oncologic free interval and the length of asymptomatic recurrence were significantly longer in the cyclosporine treated patients. It was therefore suggested that tumor growth rates are lower under cyclosporine-prednisone therapy than under azathioprine-steroid therapy.

The frequency of microscopic regional lymph node involvement which cannot be detected preoperatively suggests that an extended surgical approach might be of benefit in the treatment of patients with hepatic tumors unsuitable for subtotal hepatic resection. Encouraged by recent experience with multiple abdominal visceral transplantation in small children with short gut syndrome (11,12), Starzl has performed a series of cluster organ grafts in a series of 11 patients with sar-

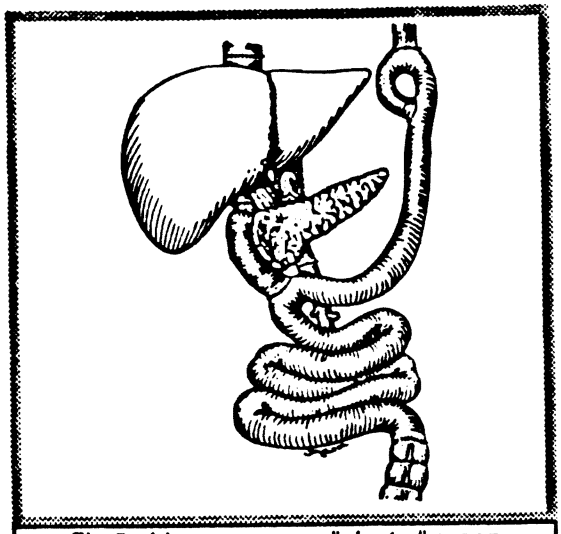

Fig 5. Liver-pancreas "cluster" organ transplant.

comas or carcinoid tumors of the pancreas or duodenum and liver metastasis, bile duct carcinomas with liver metastasis, or hepatocellular carcinomas with invasion of duodenum and colon (13). The native liver, pancreas, duodenum, spleen, stomach, proximal jejunum and ascending and transverse colon were resected en bloc and replaced by a composite cluster consisting of liver, pancreas, and duodenum removed en bloc from the donor (Fig. 5). Nine of the 11 patients have survived and are tumor free one to six months after surgery. Thus, the technical feasibility of the cluster graft has been established. The impact on tumor free interval and long term survival remains to be seen.

Transplantation for Chronic B-virus Hepatitis (CAH-HBV)

About 10% of patients infected with HBV develop a chronic carrier state and approximately half of these go on to chronic active hepatitis and cirrhosis. Integration of the viral genome may be causally related to the later development of hepatocellular carcinoma. Even HBV carriers who do not develop cirrhosis are at increased risk of hepatocellular cancer (14).

HBV is a double stranded DNA virus. The hepatitis delta virus (HDV) is an incomplete RNA virus which can only enter mammalian cells in the presence of HBsAg and cannot cause infection without prior or concurrent infection by HBV. The cellular injury produced by HBV is believed to be immunologically mediated by T-cells which produce immune lysis of hepatocytes displaying viral antigens on the cell surface in association with HLA antigens. HDV, however, is a virulent infection with direct cytopathic effects and can produce cell injury independent of immunological mechanisms (14).

After liver transplantation, most patients with CAH-HBV retain the carrier state and there is a high incidence of reinfection (5,6,15-19). Thus, recurrent hepatitis is a common cause of graft loss more than six months after transplantation. Nevertheless, a significant number of patients may persist with a low grade hepatitis for years after transplantation but with an excellent quality of life.

A variety of approaches have been tried to prevent or modify HBV reinfection after liver transplantation, including hyperimmune globulin (HBIG) or interferon therapy. The Milan group has reported its experience with 14 HBsAg positive patients treated with both passive and active immunization beginning during the anhepatic phase of surgery and found clearing of HBsAg in some patients (17). Five patients cleared HBsAg from their sera with three patients survivng out to 9, 19, and 20 months followup. One patient died of tumor recurrence and another of septic complications. Three of the long term survivors have surface antibody (HBsAb).

Rizzetto et al have reported a series of 7 patients positive for HDV-RNA prior to transplantation (18). Two patients have survived for more than a year without detectable HDV or HBV. Three of the five patients with reinfection developed clinical hepatitis.

The Hannover group has also treated 14 patients with combined passive and active immunization (19). In 13 of the patients, a transient decrease in the titer of HBsAg was observed and 10 had detectable hepatitis B surface antibodies (HBsAb). Six patients survived more than 3 months and all had detectable HBsAg within 6 to 9 weeks after transplantation. Three long term survivors are rehabilitated despite a chronic carrier state and mild hepatitis related enzyme abnormalities.

The Hannover results are similar to our own experience in the Pittsburgh series where the chronic carrier state continues in nearly all patients after transplantation and an unpredictable but significant percentage of patients are able to persist indefinitely despite reinfection of the graft. Given the variability of outcome, it seems imprudent to deny liver transplantation to HBsAg positive patients with end stage cirrhosis, since no other therapy is available that offers them a better chance of survival.

It is important to study liver tissue carefully in all patients transplanted for HBV. Although it is unusual for patients who develop HBsAb to have detectable viral antigen, patients with HIV infection have been reported to revert from an immune state to an active carrier state. Immunosuppression could produce the same result with HBV. Secondly, viral antigen may be discovered in liver tissue even though absent from serum. Finally, in two patients in the Milan series, HDV was subsequently found in the allograft despite absence of detectable HBV in plasma or the liver. This unusual finding might be unique to the transplant situation or might represent suppression of HBV by virulent HDV infection.

A probable flaw in the use of commercial HBIG preparations has been that the dose required to neutralize virus may be so large as to be impractical to administer. A human monoclonal anti-HBsAg antibody has been developed by the Sandoz Corporation that has 50,000 times the potency of commercial HBIG (20). The agent has been used in two patients by Starzl. One cleared HBsAg but died of recurrent hepatoma after relatively short followup. Another patient cleared antigen for 5 months before it was again detected in low titer and HBcAg was found on liver biopsy. It is not yet known what effects treatment with this agent will have on the clinical course of reinfection by HBV after transplantation. Clinical trials will continue in 1989.

Transplantation for Fulminant Hepatic Failure

Acute fulminant hepatic failure is defined as severe liver dysfunction progressing to advanced hepatic encephalopathy within 8 weeks of onset of symptoms in the absence of previous liver disease. Subacute fulminant hepatic failure is defined as irreversible liver failure within 8 to 28 weeks from onset of symptoms. Liver transplantation for cancer and for HBV related cirrhosis are both characterized by a high late mortality from recurrent disease. In contrast, transplantation for acute or subacute fulminant hepatic failure is associated with high early mortality related to the difficult circumstances of urgent surgery in high risk, acutely ill patients, but excellent long term survival (Fig. 4). The difficulty in regard to patients with acute hepatic failure concerns how to determine who will recover without transplantation and who will not.

The more common causes of acute fulminant hepatic failure include viral infection (A, B or nonA, nonB types), drug overdosage or hypersensitivity or exposure to other chemical toxins, and metabolic disorders, especially acute Wilson's disease. Liver function

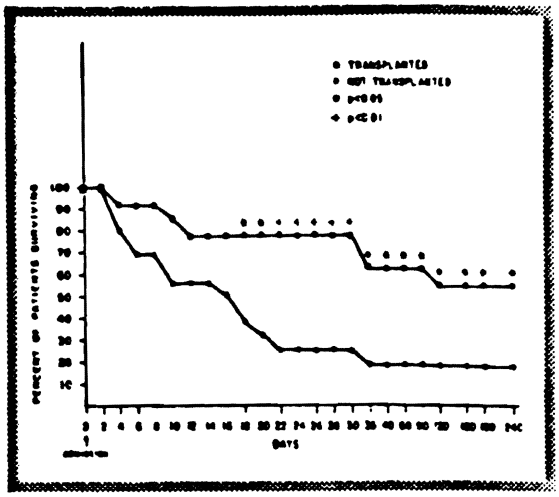

Fig 6. Survival for acute fulminant liver failure for transplanted versus not transplanted patients (Pittsburgh series). From Peleman RR, et al. [21]

studies including asparate aminotransferase (AST), alanine aminotransferase (ALT) and prothrombin time are quite variable in acute hepatic failure and are often not a reliable quide to prognosis. It is common with acetaminophen and mushroom poisoning to find extremely high enzyme levels or prolongation of prothrombin time but recovery without transplantation often occurs.

Of 29 patients admitted to the heptatology service at Presbyterian-University Hospital between February, 1981 and July, 1985 for fulminant hepatic failure, only 3 recovered without transplantation (one patient with acute Wilson's disease - the only such recovery yet reported, one with halothane hepatitis, and one with acetaminophen toxicity) (21). In contrast, 13 patients died awaiting transplantation. Patients getting a transplant spent less time in the intensive care unit, less time on ventilatory support, and fewer days in coma despite a longer hospital course than those not getting a transplant. Survival for the patients getting a transplant was 54% compared to 19% for those who did not (Fig. 6). Similar survival rates of 55 to 70% have been reported in other series (22-24). Withholding of transplantation in circumstances of uncertainty is probably more dangerous than aggressive efforts to perform transplantation in most patients with fulminant liver failure.

Some guides to choice of therapy do exist. Although recent study of charcoal hemoperfusion in acute patic failure failed to demonstrate a significant benefit this method, the study revealed important prognostic ormation (25). Included were 85 cases of acute etaminophen toxicity, 6 cases of acute hepatitis A AV), 18 cases of acute HBV (one with HDV also), 20 ses of non-A, non-B hepatitis (NANB), and 8 cases of lothane or other drug toxicity.

Recovery with medical therapy was highest for tients with acute hepatitis A (66.7%) and etaminophen overdose (52.9%), intermediate for patitis B (38.9%), and poorest for acute non-A, non-B patitis (20.0%) and other drug or chemical toxins 2.5%) (Fig. 7). Cerebral edema, renal failure and metabolic acidosis provided useful guides to prognosis. ecovery in patients with acetaminophen toxicity with rebral edema but without renal failure or metabolic idosis was 71.4% but fell to 52.5% in patients with nal failure and 6.7% in patients with metabolic idosis. Patients with acute hepatitis A or B with rebral edema and renal failure had only a 30% rate of covery (Fig. 8).

In general, most patients with acute acetaminophen xicity or acute hepatitis A will recover. Patients with

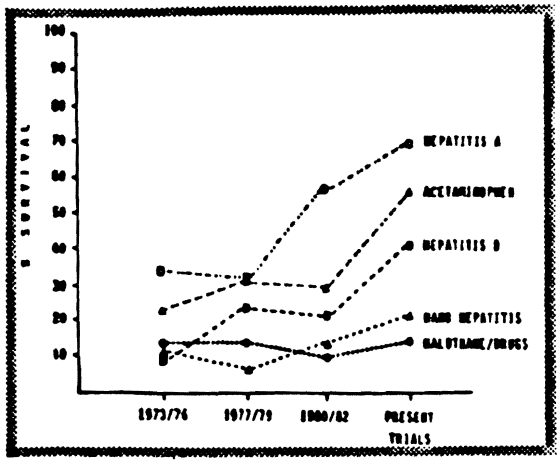

Fig 7. Serial survival rates for the major etiologies of fulminant hepatic failure. From O'Grady JG, et al.[25]

acute non-A, non-B related fulminant hepatic failure have a poor prognosis without transplantation. Hepatitis B induced fulminant liver failure can be difficult

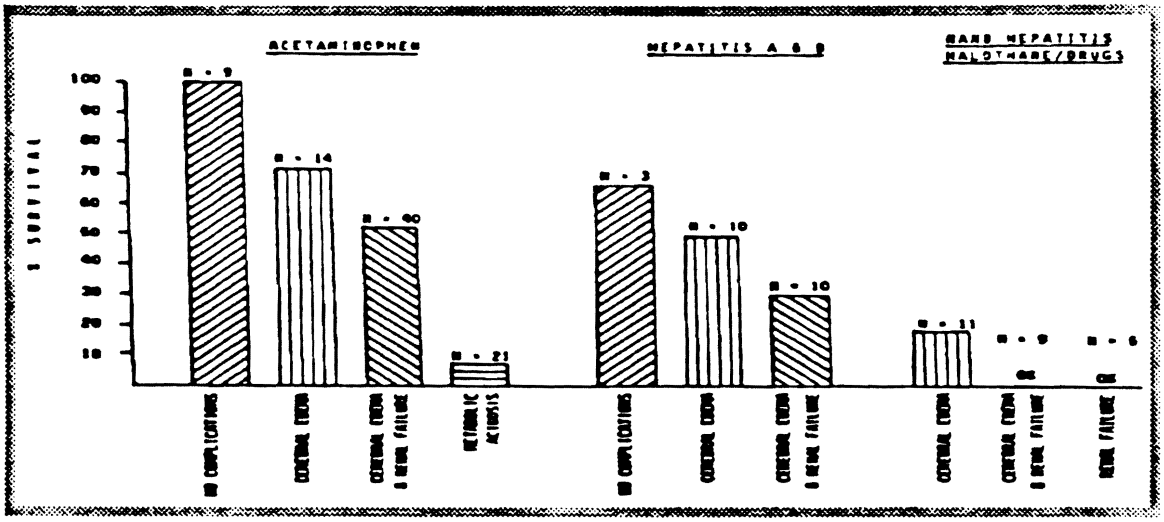

Fig 8. Correlation between survival and complications present in the main etiologic subgroups of fulminant hepatic failure. Form O'Grady JG, et al.[25]

Table 3. Actuarial patient survival rates after liver transplantation for fulminant hepatic failure in the Pittsburgh - Baylor (Dallas) series.

	Number	Actuarial patient survival	
		30 day	One year
Drug or toxin	7	57.1%	25.7%
Acute hepatitis B (HBV)	10	90.0%	80.0%
Acute non-A, non-B hepatitis	29	93.1%	79.3%
Acute hepatitis A (HAV)	4	75.0%	50.0%
Unknown	13	53.9%	38.5%

Baylor data courtesy of Dr. Goren Klintmalm.

to judge. In the past year, we have taken several acute HBV patients to the operating room for open liver biopsy with a donor organ available. Biopsy has accurately predicted recovery and transplantation was aborted. In other cases, severe liver damage provided confirmation of the need to go ahead with transplantation.

Deepening coma, progressive renal failure, rapid shrinkage of the liver on serial imaging studies and uncorrectable coagulopathy are indications to press ahead with surgery. Rapidly progressing coma is associated with a poor prognosis. Although prothrombin time is an unreliable indicator, specific coagulation factors can be predictive. Factor V and factor VII levels below 20% of normal carry a high mortality (24,26).

Although plasmapheresis is of limited value in improving long term survival, it may be valuable as a temporary assist for patients in fulminant failure waiting for transplantation. Temporary improvement in jaundice, lessening the severity of coma, and control of coagulopathy can be obtained (27).

Sixty three patients received liver transplants for acute liver failure at the University of Pittsburgh or Baylor University Medical Center (Dallas) between January, 1981 and June, 1988 including 7 patients with drug associated failure, 10 patients with acute HBV, 29 with acute NANB, 4 with acute HAV, and 13 with acute failure of unknown cause. Survival is summarized in Table 3. The poor results for patients with drug related liver failure reflect referral of patients in late stages of hepatic failure with grade 4 coma and patients with severe systemic complications. Nineteen (65.5%) of the 29 patients receiving transplants for acute NANB hepatitis, which carries a poor prognosis without transplantation, have survived.

Reinfection after transplantation for acute HBV has been common but clinical severity has often been mild with many patients surviving with a low grade chronic hepatitis. One patient converted to an HBsAb+/HBsAg- immune state.

Given the poor prognosis for survival with medical management for many types of acute hepatic failure, prompt consultation with a liver transplant center is now an essential component in the management of fulminant hepatic failure.

Liver Transplantation and Portal Hypertension

In the past, the management of upper gastrointestinal variceal hemorrhage has depended on balloon tamponade, selective or peripheral infusion of pitressin, non-selective portocaval or mesocaval shunting, selective splenorenal shunting, or esophageal transection and devascularization. Although each of these methods has been effective in control of hemorrhage, each has had significant drawbacks. Balloon tamponade and pitressin infusion have a high incidence of early rebleeding. Non-selective shunts frequently result in encephalopathy and have had a high mortality. Selective shunting has been effective in preventing rebleeding, but cannot correct severe liver failure. Esophageal transection and devascularization procedures are more invasive and mutilating and probably less effective than selective shunting, and also do nothing to correct severe liver failure.

In recent years, endoscopic sclerotherapy has been established as an effective, relatively non-invasive method for the control of acute variceal hemorrhage. There is good evidence that the effectiveness of sclerotherapy in preventing rebleeding and improving patient survival relates to the severity of the underlying liver disease (28-30). Rebleeding occurs most often, and after a shorter interval, and mortality is highest after

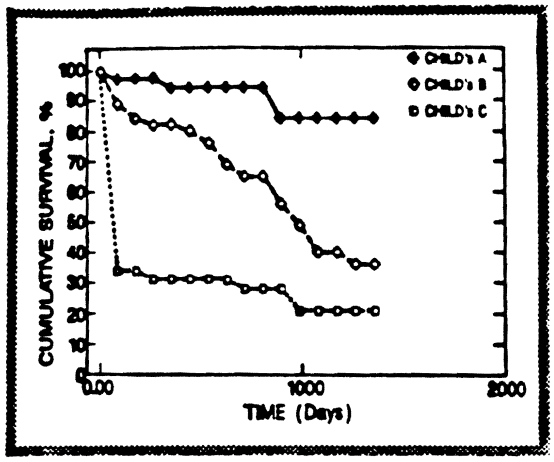

Fig 9. Actuarial survival for all patients undergoing sclerotherapy for variceal hemorrhage according to Child's class. From Garrett KO, et al.[29]

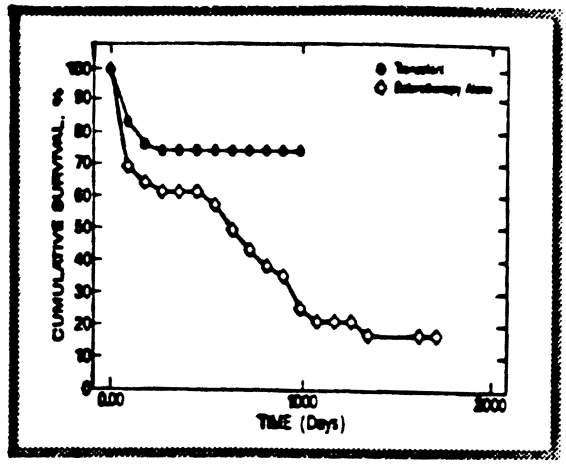

Fig 10. Actuarial survival for sclerotherapy alone versus sclerotherapy followed by liver transplanatation. From Garrett KO, et al.[31]

sclerotherapy in patients with the poorest hepatic reserve as estimated by Child's classification (Fig. 9). Patients requiring urgent sclerotherapy in class B and elective or urgent patients in class C have the worst results and are most likely to die of progressive hepatic failure within 100 days after sclerotherapy.

Sclerotherapy alone or sclerotherapy and mesocaval or selective splenorenal shunts are best reserved for patients with good hepatic reserve unlikely to die in the short term of progressive liver failure. Portocaval shunts and esophageal transection and devascularization procedures should be avoided since they offer no advantages over these other approaches and make transplantation, if needed later, much more difficult. Sclerotherapy for acute control of bleeding followed by liver transplantation to prevent death from progressive liver failure today is the preferred treatment for high risk Child's class B or class C patients.

Garrett et al (31) have recently retrospectively compared the fate of 46 patients treated in Pittsburgh by sclerotherapy followed by liver transplantation with the fate of a control group of 36 non-alcoholic Child's class B and C patients treated with sclerotherapy alone. Overall survival of the transplanted group at 3 years was 73% compared to 17% for the non-transplanted group (Fig. 10).

Iwatsuki et al (32) have recently reviewed the Pittsburgh experience with liver transplantation for patients with a previous history of bleeding esophageal varices. Of the first 1000 patients receiving transplants under cyclosporine-steroid therapy, 302 had a prior history of variceal bleeding, including 22 patients treated by non-selective shunting, 15 treated with a selective shunt, 5 treated with a non-shunting operation, and 219 treated by sclerotherapy. One year patient survival was 79% for patients with a previous history of bleeding compared to 69% for those without. A prior history of bleeding does not, therefore, increase the risk of liver transplantation. There was, however, an increased early mortality in patients with a history of invasive surgery for control of bleeding. Only 8% of patients treated without surgery died in the first month after transplantation compared to 17% of those who had surgery.

In summary, liver transplantation is the ultimate treatment of choice for patients who present with variceal bleeding and who are at high risk of progressive liver failure over the next several months. Experience suggests that this includes most patients who require urgent sclerotherapy in Child's class B and elective and urgent patients in class C. For other patients, sclerotherapy alone or selective shunt procedures which avoid the hepatic hilum are appropriate alternatives.

Liver Transplantation for Alcoholic Cirrhosis

Alcoholic cirrhosis is probably the most common cause of liver disease in our society (33) but has been considered a poor indication for liver transplantation because of the often advanced state of disease in alcoholic patients, their tendency to present with a serious acute complication such as massive bleeding, massive ascites, or encephalopathy, and the high or at least uncertain risk of recidivism. The NIH Consensus Development Conference statement on Liver Transplantation in 1983 recommended that liver transplantation "may be considered for the patients who develop evidence of progressive liver failure despite medical treatment and abstinence from alcohol" (34). Schenker (35) recommended that only patients with six months abstinence should be considered for liver tranpslantation. In fact, such a requirement would be a death sentence for many such patients who are too ill to wait so long for a transplant.

It has been argued that transplantation of alcoholics might result in wastage of a limited supply of organs on patients whose illness is self inflicted, whose behavior is more likely to be noncompliant or unpredictable, and for whom the medical risk of transplantaion is especially high. However, as Atterbury (33) has cogently noted, in the debate over liver transplantation objective medical criteria for patient treatment have been tainted with medical care based on economic resources, chance, and social worth.

To make matters worse, experience since 1984 suggests that even medical considerations have been based more on presumption than fact (36,37). In 1988, a brief overview of the Denver-Pittsburgh experience with the liver transplantation for alcoholic cirrhosis was published (36) and demonstrated that survival and quality of life for 41 patients getting transplants in the cyclosporine era has not been significantly different than for most patients getting transplants for non-alcoholic disease. An updated survival analysis is presented in Fig. 11 showing survival for 73 adults getting transplants for alcoholic cirrhosis between January, 1984 and June, 1988 compared with 229 adults with other causes of cirrhosis (cryptogenic cirrhosis, autoimmune hepatitis, non-A, non-B hepatitis, but excluding

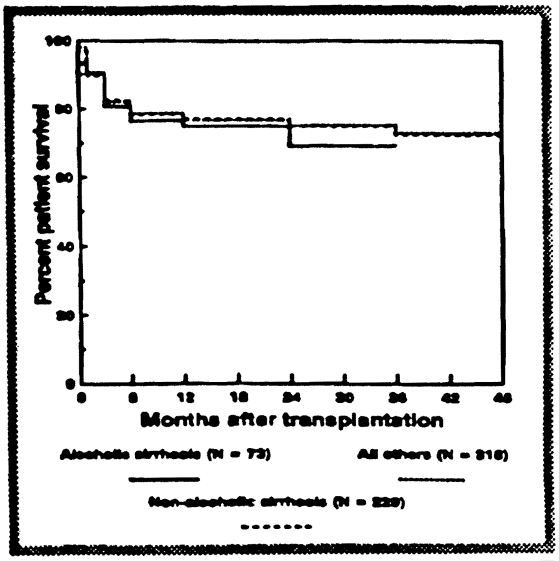

Fig 11. Actuarial patient survival for adults after liver transplantation for Laennec's cirrhosis compared to non-alcoholic cirrhosis and all other non-malignant chronic liver diseases (Pittsburgh series).

HBsAg positive patients) and with 318 adults with other benign causes of chronic liver disease (primary biliary cirrhosis, metabolic errors, sclerosing cholangitis, etc.) getting transplants in the same period. There is no significant difference in operative or thirty day survival or in long term survival out to three years of follow up. Although recidivism is slightly higher than previously reported, it still has involved only a small fraction of patients. With proper attention to psychiatric and social support, many patients with end stage alcoholic liver disease can be successfully managed with liver transplantation.

There appears to be no valid basis for excluding alcoholics from liver transplantation except on the basis of objective conditions such as intractable, irreversible cardiomyopathy or central nervous system degeneration that would prevent satisfactory recovery or conscious and deliberate refusal of the patient to cooperate in the process despite adequate medical and psychiatric input.

ISSUE IN PEDIATRIC LIVER TRANSPLANTATION

Progress continues to be made in pediatric transplantation and several series have now reported overall one year patient survivals in the 65-80% range (38-45). Controversy continues over the place of portoenterostomy in the management of biliary atresia given the current success of liver transplantation, and its current limitations because of the continued shortage of organs for children and factors contributing to a higher mortality after liver transplantation for small infants.

Biliary atresia and portoenterostomy

A single attempt at portoenterostomy within 3 months of birth is still an appropriate consideration for infants with extrahepatic biliary atresia, but portoenterostomy is stated to be successful in only 25% of patients on whom it is attempted (46). Thus, in the majority of children, adequate bile flow cannot be established or progressive biliary cirrhosis and/or recurrent cholangitis with inflammatory destruction of intrahepatic bile ducts occurs. Repeated operations to obtain drainage or to vent the reconstruction make transplantation much more difficult and probably should not be attempted in most patients. Reoperation is best limited to patients in whom good bile flow, lost after an initially successful first operation, can be easily restored by removal of stones or correction of a technical defect.

Reduced liver transplants

It is estimated that 25% of the children who might benefit each year from a liver transplant die waiting for a suitable donor (47). The largest group of such children are infants with biliary atresia, in whom the mortality while waiting may be even higher. One pediatric program recently reported that 59% of its referrals were under 1 year of age, but only 18% of those who received transplants were in this age group because of the organ shortage (41). In order to meet the critical need for organs for these children, there has been an increasing trend to use reduced sized liver grafts for these patients, a technique first used in 1975 by Starzl, who transplanted an adult left lateral segment into an infant with biliary atresia. Successful application of this technique has now been reported from centers in Brussels (48,49), Chicago (50,51), Hannover (52,53), and Paris (54,55), with recent mortality statistics equal to or better than results for whole organ transplants, and a reduction in waiting list mortality.

The segmental anatomy of the liver provides considerable flexibility for the surgeon in tailoring the graft to fit the recipient, as illustrated in Fig. 12. Other variations are possible, such as leaving the recipient's vena

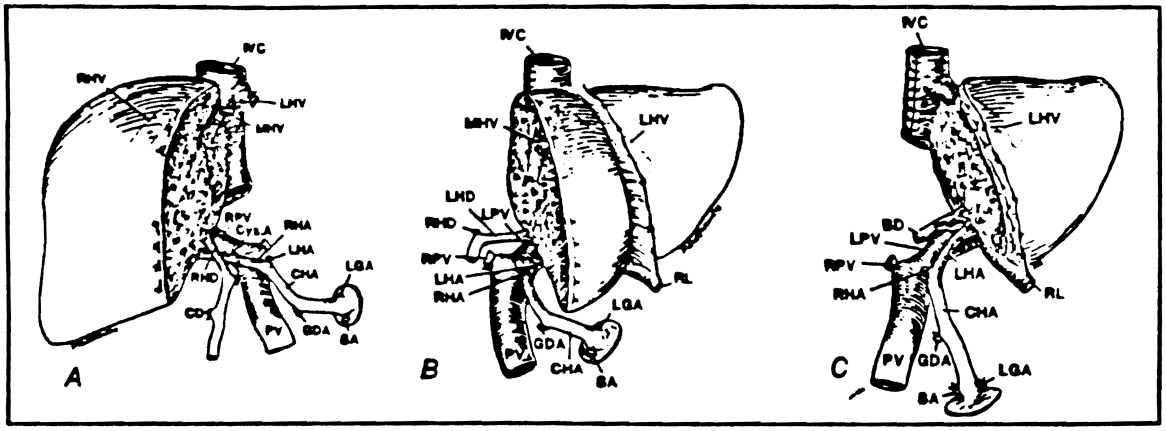

Fig 12. Reduced liver grafts for orthotopic transplantation. A. Right lobe graft. B. Left lobe graft. C. Left lateral segment graft. From Broelsch CE, et al.[51]

cava in place and piggybacking the liver onto it (56). This avoids some of the difficulty that may be encountered in interposing the vena cava from a much larger donor into a small recipient.

The use of adult livers for small children versus the need for grafts for adults has generated some controversy (57). In addition to the question of increased technical risk, the use of reduced livers puts the potential recipients for these grafts in competition with other candidates for whole organ grafting. However, there is less demand for organs for larger children, and the safety of the technique has improved with experience. The use of reduced-sized grafts adds some complexity to the problems of recipient selection, and further emphasizes the need for objective criteria (58).

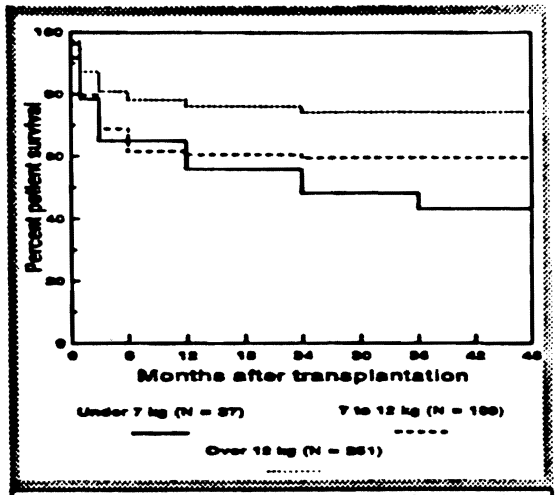

Fig 13. Pediatric survival based on body weight.

Vascular thrombosis

Fig. 13 compares the survival after liver transplantation for children, based on body weight at the time of transplantation in the Pittsburgh cyclosporine series. The figure demonstrates the high mortality for very small (under 7 kg) infants and intermediate mortality for larger infants (7 to 12 kg), compared to children over 12 kg. Hepatic artery thrombosis and, to a lesser extent, portal vein thrombosis, account for much of this increased mortality in smaller pediatric recipients (59,60).

Technical failures, including errors in suture technique, damage to donor or recipient vessels, and failure to assess arterial flow correctly, account for some failures. Failure to properly assess arterial or portal vein flow can be minimized by intraoperative use of flow meters (61-63). Vessels less than 3 mm in diameter, anastomotic revision, and use of aortic conduits or iliac artery grafts are also associated with a higher risk of thrombosis (64). However, other physiological factors also play an important role.

Severe rejection with swelling of the liver and arterial constriction may result in impaired flow in the liver or portal vein and result in thrombosis. Furthermore, rejection can be associated with venous and arterial endotheliitis, resulting in thrombus formation in small- and medium-sized vessels of the transplanted liver. Bismuth (65) has reported that in 7 of 9 patients retransplanted for acute or chronic rejection, thrombi were found in the portal vein in 3, in the hepatic artery in 3, and in both in 1. A severe endarteritis was present in patients with arterial thrombosis, and a phlebitis in patients with portal vein thrombosis.

Cold storage, reperfusion, and cyclosporine may have deleterious effects on the microvasculature of the liver graft and promote thombosis. Extensive injury to the sinusoidal lining of the liver has been shown to be a critical feature in a rat liver preservation model, and cyclosporine has been implicated in prostanoid metabolism and endothelial cell injury (66-68).

It has been known for many years that a hypercoagulable state may contribute to the increased risk of hepatic artery thrombosis after liver transplantation (69). Postoperative anticoagulation therapy with heparin and dextran may reduce the incidence of hepatic artery thrombosis (64). Recently, it has been reported that there is a relative deficiency of protein C and antithrombin, as well as impaired fibrinolysis, in the first 10 days after transplantation in children (70).

Portal vein thrombosis is less common than hepatic arterial thrombosis, but many of the same factors contribute to both. Technical considerations include excessive length or improper alignment, donor-recipient size discrepancy, disease of the portal vein wall, undetected thrombi in the mesenteric and splenic veins which later propagate into the portal vein, or steal of flow by large collaterals (71-73).

Portal vein thrombosis may result in catastrophic failure with acute massive ascites or massive variceal bleeding, or it may be tolerated. There have been reports of successful thrombectomy and repair of an obstructed portal vein (74) and use of a splenorenal shunt in patients whose livers remained viable after portal occlusion (75). Spontaneous recanalization of a thrombosed portal vein has also been reported (76).

The approach to be taken to portal vein thrombosis requires a thoughtful assessment of the patient's situation. If a correctable technical fault is present, and the liver has not been irreversibly damaged, direct repair should be considered. If the problem is physiological with a viable liver but persistent complications from portal hypertension, a shunt procedure may be appropriate. If liver function is severely compromised by lack of portal flow or by concomitant rejection, retransplantation is the treatment of choice.

MANAGEMENT OF THE ABSENT PORTAL VEIN IN THE TRANSPLANT CANDIDATE

Absence of a patent portal vein has until recently been a contraindication to liver transplantation. This is a common problem in children with biliary atresia in whom the portal vein frequently becomes atretic. It has been suggested that non-invasive monitoring with sonography of portal flow and portal flow and portal vein size can be a guide to the timing of transplantation in patients with biliary atresia (77). In patients with long standing end stage cirrhosis and portal hypertension, portal flow is severely impaired and thrombosis may occur. Similarly, patients who have had shunting procedures with subsequent reduction of portal flow are also at risk.

In long standing portal hypertension, the wall of the portal vein may become diseased and be unsuitable for suturing, even if a lumen remains. If the confluence of the mesenteric and splenic veins is not involved, a piece of iliac vein from the liver donor can be sewn on, to replace the proximal recipient vein. In some cases, however, the confluence itself may be occluded. Starzl has successfully anastomosed the donor portal vein to a large coronary vein in a patient who is well more than three years after transplantation. Hiatt et al (78) have reported anastomosis of the donor portal vein to a large choledochal vein. In many patients with this problem, however, it may be possible and preferable to use a jump graft of donor iliac vein from the superior mesenteric vein to the donor portal vein (Fig. 14) (79).

Doppler ultrasonography is a useful screening test for portal vein patency, but large, high flow collaterals in the hepatic hilum may be misinterpreted as a patent portal vein. Magnetic resonance imaging (MRI) is a more reliable non-invasive test available for assessment of portal vein patency and can, in many cases, suffice in place of angiography for assessment of portal and mesenteric vein patency.

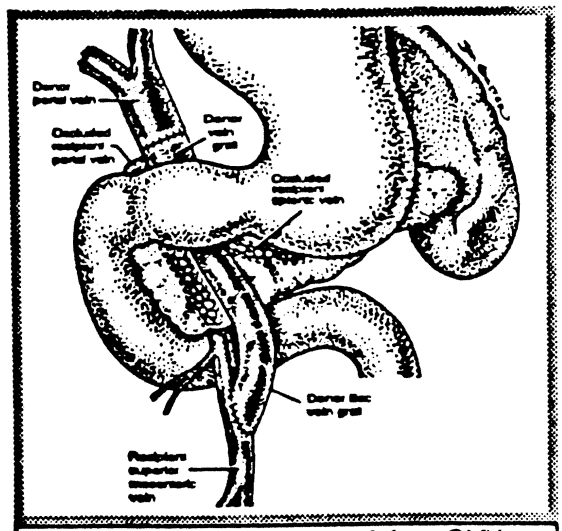

Fig 14. Donor iliac vein graft from SMV to portal vein.

IMMUNOSUPPRESSION AND IMMUNOBIOLOGY

Immunosuppression

The mainstay of immunosuppressive therapy in clinical liver transplantation remains cyclosporine and low doses of prednisone. Short term high dose steroids or OKT3 monoclonal antibody therapy remain the preferred treatments for acute cellular rejection. However, nephrotoxicity and hypertension remain significant problems with use of cyclosporine and therefore, many centers have turned to triple or quadruple drug regimens in an effort to manage these side effects until another, less toxic agent, becomes available.

Hypertension requiring multiple drug therapy is a frequent complication after liver transplantation under cyclosporine. In the King's College series, the incidence of hypertension rose from 15.3% at 3 months to 63.6% at 4 years after transplantation in liver recipients maintained on cyclosporine.(80) Calcium channel blockers, beta blockers and diuretics, and angiotensin converting enzyme (ACE) inhibitors have all been used to control hypertension, and therapy must be tailored to the individual patient. Cyclosporine dosage does not always correlate with the degree or ease of control of chronic hypertension after liver transplantation (81).

The chronic nephrotoxic effects of cyclosporine were evident early in the Pittsburgh and Cambridge liver transplant series, and a strategy adopted was to maintain high cyclosporine levels early after transplantation, but to lower them later in order to reduce long term effects on the kidneys and to relieve hypertension (82). Parenteral cyclosporine is associated with more severe degrees of renal dysfunction (83) and therefore, another strategy that has been used in recent years is to avoid, delay, or minimize the use of intravenous cyclosporine in the early period after transplantation by substituting other therapy, especially polyclonal or monoclonal antibody therapy, in the first week after transplantation (84-86). A third strategy is to convert from high-dose cyclosporine-prednisone to low-dose cyclosporine-prednisone with azathioprine to minimize the chronic nephrotoxicity of cyclosporine (87-89).

Meyers (90) has recently reported significant persistent pathologic findings in kidneys of Stanford heart transplant recipients treated for 12 or more months with cyclosporine. Progressive, probably irreversible reduction in glomerular filtration rate (GFR), increased renal vascular resistance, proteinuria, and ischemic glomerular collapse and sclerosis were found. Eight percent of this group developed end stage renal failure. Reduction of cyclosporine dosage offered only marginal benefit in preventing the microvascular injury from chronic administration of cyclosporine.

Should these findings in the Stanford heart patients raise concern for liver transplant patients on cyclosporine? Gonwa et al (91) have studied the early and long term effects of cyclosporine therapy on serum creatinine (Fig. 15) and GFR (Fig. 16). This study demonstrated a severe depression of GFR early after transplantation which persisted but did not progress at one and two years after transplantation. Nevertheless, the persistence of such a significant depression in GFR is noteworthy.

The King's College group has reported reversibility of early cyclosporine nephrotoxicity if the drug is withdrawn, but a high incidence of chronic nephrotoxicity in patients maintained on cyclosporine for over 2 years (80). Experience in Pittsburgh has been similar (92), but end stage renal disease requiring renal transplantaton so far has been unusual, except in a small subset of patients requiring one or more retransplantations, usually for graft rejection.

Children after liver transplantation have a much higher and more variable mean cyclosporine clearance per kilogram of body weight than adults (93). In addition, the Roux-en-Y choledochojejunostomy for biliary reconstruction frequently used in pediatric patients, is associated with decreased bioavailability of cyclosporine (94,95). Thus, pediatric liver transplant recipients usually require higher doses of intravenous and oral cyclosporine doses, and a longer period of initial therapy with intravenous cyclosporine.

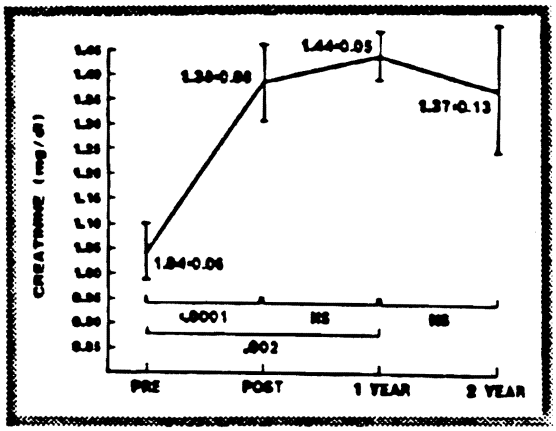

Fig 15. Mean serum creatinine before and after liver transplantation with cyclosporine. From Gonwa TA, et al.[91]

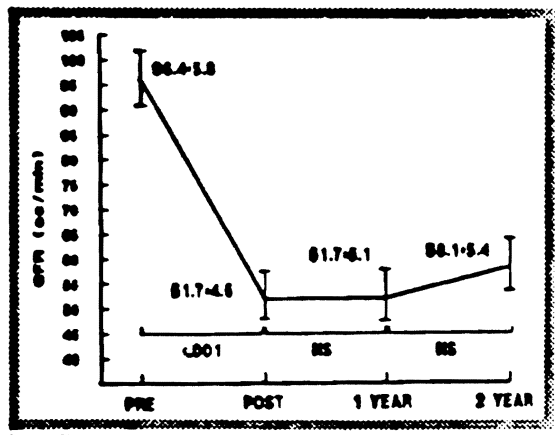

Fig 16. Mean glomerular filtration rate (GFR) before and after liver transplantation with cyclosporine. From Gonwa TA, et al.[91]

The most promising new drug on the horizon is FK506, a macrolide antibiotic produced by Streptomyces tsukubaensis (96,97). It has been demonstrated to have a synergistic activity with cyclosporine in animal allograft models (98). In vitro, cyclosporine resistant alloreactive lymphocyte clones appear to be sensitive to FK506 (99). In the most recent studies, the drug has produced excellent survival of kidney allografts in outbred baboons with minimal toxicity (100). Phase 1 clinical trials in kidney and liver transplantation recently began in Pittsburgh.

Is there hyperacute rejection of the liver?

It is now well established that there is an increased risk associated with liver transplantation between ABO mismatched and/or incompatible donors (101-103). A graft versus host, anti-ABO blood group antibody mediated hemolytic reaction may be seen after liver transplantation across an ABO compatible mismatch (104), and in some cases, can be severe enough to be life threatening (105,106). Aggressive therapy with mannitol and diuretics, plasmapheresis, transfusion with donor ABO blood group red cells and, in some cases, retransplantation can be required. Some of the increased risk demonstrated for transplantation across an ABO compatible mismatch may be a consequence of this graft versus host reaction.

Transplantation between an ABO incompatible donor and recipient may have more serious consequences. Recent studies of liver tranplantations across an ABO incompatibility found a marked increased incidence of acute graft failure compared to a matched control group of age, sex, clinical priority, and antibody cross-match negative ABO compatible transplants (107,108). Failed grafts demonstrated widespread hemorrhagic necrosis with diffuse intrahepatic coagulation. Tissue bound, donor specific isoagglutinins were found on elution studies and marked antibody and complement deposition were seen in arteries on immunofluorescent staining. These findings are highly suggestive of an antibody mediated early graft destruction which cannot necessarily be predicted preoperatively, but which is a significant risk when transplantation is carried out across an ABO incompatibility. Bismuth has recently also reported accelerated rejection with hemorrhagic necrosis in 4 of 11 ABO incompatible liver transplantations for fulminant hepatic failure (109).

Liver transplantation across a positive lymphocytoxic antibody crossmatch has not been associated with decreased graft survival or predictable hyperacute graft loss (110), although patients with a high panel reactive antibody titer tend to have higher intraoperative blood loss and more problems with platelet transfusions than patients with low titers (111). Furthermore, a liver transplant graft performed before a kidney transplant from the same donor in a recipient with a positive donor specific crossmatch will usually protect the kidney from hyperacute rejection (112).

It is postulated that the liver either absorbs and neutralizes circulating anti-donor antibody and/or releases soluble donor antigens which have a protective effect. High levels of circulating donor HLA antigens which persist for years can be demonstrated in recipient sera within 24 hours of the transplantation of the liver (113). However, there have been exceptional cases in which both organs have failed with hemorrhagic necrosis of the liver and typical hyperacute rejection of the kidney (114).

In both a rat model (115) and a primate model (116), it has been possible to presensitize liver recipients with prior skin grafts from a liver donor and produce findings similar to those seen in the human cases in which hyperacute rejection has been suspected. It thus appears that hyperacute rejection of the liver is a real phenomenon, but the conditions under which it occurs in the clinical setting and the factors that determine outcome remain poorly defined. Only ABO incompatibility has been established as a significant risk factor.

Can primary graft failure be predicted?

A reliable test of liver viability that can be applied preoperatively has yet to be developed. Efforts to predict the quality of early graft function from conventional clinical parameters such as liver function tests, systemic cardiopulmonary parameters and acid-base balance, cause of donor death, length of cardiac arrest, or pressor requirement have been unsuccessful (117-119). Assessment of bile production after revascularization remains the simplest and most reliable clinical parameter of liver graft viability after transplantation, and in a rat model bile flow has been shown to correlate with liver cellular ATP levels and graft survival (120). Moreover, cellular ATP levels in biopsies of donor livers have been reported to predict graft performance in a recent clinical study (121). Depression of factor V below 20% of normal and factor VII below 10% of normal are accurate predictors of graft failure after transplantation, especially when aspartate aminotransferase (AST) is also high (over 5000 I.U.),

but these indicators still have approximately 30% false positive rates (122).

One of the more promising approaches to development of a reliable assay of graft viability has been to study the clearance of lidocaine by the liver. A TDX fluorescent polarization assay of monoethylglycinexylidide (MEGX) concentration in serum 15 minutes after injection of a lidocaine bolus has been shown to be a sensitive indicator of hepatic function and predicted primary function in 32 of 37 cases and primary failure in 4 of 6 cases (123). MEGX formation appears to correlate with the oxidative metabolizing capacity of the liver graft (124). In another study, seven donors whose livers were discarded on the basis of conventional clinical criteria were found to have MEGX serum concentrations comparable to accepted donors, suggesting that this assay may be valuable in preventing inappropriate discards of viable organs (125).

Liver preservation--the UW solution

The recent introduction by Belzer and his associates (126-128) of a new cold-storage solution, the "UW solution," represents the first major innovation in liver preservation since the first descriptions of slush preservation more than 10 years ago (129-130). Lactobionate, raffinose, and glutathione are believed to be the essential components of the UW solution (131-132). Lactobionate,a large and relatively impermeable anion, and raffinose, a large molecular mass saccharide, provide osmotic support and prevent cellular swelling. Glutathione is needed for reduction of cytotoxic molecules, such as hydrogen peroxide, lipid peroxides, disulfides, ascorbate, and free radicals. UW solution does not contain glucose, which is more easily metabolized to lactic acid by the cold preserved liver than by the kidney (131).

The Pittsburgh liver group recently reported comparison of 185 cadaveric liver allografts procured using UW solution compared to 180 cadaveric grafts procured in the immediately prior period using Euro-Collins solution (133). Preservation times ranged from 3 to 9 1/2 hours in the Euro-Collins group, but 44% of the UW preserved livers were stored for more than 9 1/2 hours, with a maximum extending out to 24 hours. Despite the much longer preservation times, patient survival was equivalent and graft survival superior, with lower rates of primary non-function and retransplantation in the UW preserved group.

The extended and higher quality of liver preservation now possible with the UW solution will have great impact on the practice of liver transplantation. In addition to the convenience and economy afforded by being able to work in a more manageable time frame, the superior preservation provided by this remarkable solution should permit further liberalization of the criteria for donor acceptability.

AUXILIARY LIVER TRANSPLANTATION

Almost all of the progress in liver transplantation in this past decade has been orthotopic replacement of the native liver, but recently there has been a renewed interest in auxiliary liver transplantation (134). This technique is attractive in that failure of the graft might not lead to sudden death of the patient or require immediate retransplantation, the operative risk might be reduced by avoidance of a difficult total hepatectomy, and matching of donor and recipient for size might be less of a problem if partial liver grafts are used.

Terpstra et al (135) have recently reported a successful series of six patients treated with auxiliary partial liver transplantation, who were considered too high a risk for an orthotopic procedure. In their operation (Fig. 17), after the removal of the gallbladder and segments II and III of the graft, a short cuff of suprahepatic graft vena cava is anastomosed to the side of the host

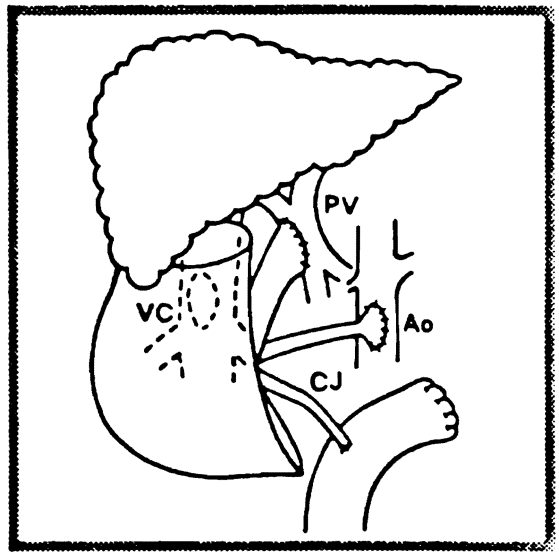

Fig 17. Auxiliary liver transplantation. From Terpstra OT, et al.[135]

portal vein. The hepatic artery is placed end to side on the infrarenal aorta. Biliary reconstruction is by Roux-en-Y choledochojejunostomy. All patients were surviving at 5 to 14 months after surgery. Mean operating time was 7.9 hours (range, 7 to 9) and mean blood loss was 12.7 units (range, 10 to 22).

The patients reported in this series would today not be considered prohibitive risks for orthotopic transplantation in Pittsburgh, and the reported range of operative time and blood loss is comparable to results being achieved today in Pittsburgh and elsewhere. Nevertheless, the results are encouraging, and further work will better define the proper indications for this procedure.

SUMMARY

After liver transplantation for cancer, there is a high incidence of disease recurrence within 18 to 36 months for most tumors, although there are a small number of long-term survivors. An extended resection of the upper abdominal viscera with replacement by a liver-pancreas cluster is being tried in Pittsburgh for lesions which have not been successfully managed with liver transplantation alone.

Despite a high incidence of graft reinfection after liver transplantation for hepatitis B virus (HBV) related disease, a significant proportion of patients achieve long-term survival. Hyperimmune globulin and interferon have been of little benefit in preventing reinfection. Clinical trials with a human monoclonal antibody to HBsAg are in progress.

Transplantation for alcoholic liver disease has been considered controversial. However, survival after liver transplantation for Laennec's cirrhosis is comparable to survival after liver transplantation for other chronic, benign, and non-HBV related liver diseases.

Sclerotherapy followed by liver transplantation is the treatment of choice for patients with acute hemorrhage from esophageal varices and end-stage liver disease. Sclerotherapy alone or followed by selective shunting is an appropriate alternative in patients with good hepatic reserve.

Only 25% of infants with biliary atresia benefit from portoenterostomy. To meet the demand for small infants waiting for transplantation, several transplant programs have successfully expanded their efforts to use partial (reduced) liver grafts.

Cyclosporine and low-dose prednisone remain the basis for immunosuppression after liver transplantation. However, nephrotoxicity and hypertension are frequent and troublesome side effects of cyclosporine. Triple and quadruple drug regimens have been increasingly popular in an effort to minimize cyclosporine toxicity. Phase 1 clinical trials with a new drug, FK506, recently began in Pittsburgh.

Hyperacute rejection of the liver has been demonstrated in animal models and has been strongly suspected in recent clinical descriptions of acute hemorrhagic necrosis after liver transplantation. So far, only transplantation across an ABO incompatibility has been identified as a risk factor for hyperacute rejection.

The new preservation solution developed by Belzer and associates at the University of Wisconsin has significantly extended the preservation time for liver grafts, and improved the quality of liver preservation.

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