962

2 Parts

MEDICAL PROGRESS

LIVER TRANSPLANTATION

(First of Two Parts)

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ADVANCES in the management of both chronic and acute hepatic disease have been made possible and even mandated by the development of liver transplantation. The clinical use of transplantation has proceeded at a rapid pace since a Consensus Development Conference of the National Institutes of Health concluded in June 1983 that liver transplantation had become a service and not simply an experimental procedure.[1]

The liver can be transplanted as an extra (auxiliary) organ at an ectopic site, or in the orthotopic location after the removal of the host liver (Fig. 1). This article will focus primarily on the orthotopic procedure. However, there has been renewed interest in the auxiliary operation, which will be discussed separately.

CANDIDACY FOR TRANSPLANTATION

The conceptual appeal of liver transplantation is so great that the procedure may come to mind as a last resort for virtually every patient with lethal hepatic disease. The selection of appropriate recipients from such a large pool requires strict individual assessment. A 1982 estimate of the annual need for liver transplantation was 15 per million population,[2] but the current need is undoubtedly higher because there are now fewer restrictions on candidacy. Between 4000 and 50,000 liver transplantations a year may be needed in the United States.

The supply of organs will increasingly influence the criteria for candidacy and limit the use of the procedure. Discussions about rationing transplantation services for this reason are nonetheless premature, because the balance between need and supply has not been determined. In the United States, the yearly rate of liver transplantation has reached approximately 1600; it averaged 147 a month between July and December 1988 (Vaughn W, United Network of Organ Sharing: personal communication). The annual rate in Europe approaches this figure.

Policies on organ donation will have to be reexamined if substantial growth is to occur. Many potential liver donors are probably rejected unjustifiably. The arbitrary upper age limit observed by most programs[3] cannot be justified, because senescence largely spares the liver.[4] Atherosclerosis of the hepatic arteries is not usually found beyond the origin of the celiac axis.[4] Our own limited experience with livers from donors over 50 years old has been encouraging.

Potential donors of all ages are often excluded because of poor arterial-blood gas levels, their need for inotropic or vasopressor drugs, minor abnormalities of liver function, or diseases such as diabetes mellitus.[3] The results with livers from such donors in both the United States[5] and Europe[6] have been as good as those with healthier donors. The use of better techniques of preservation,[7-9] which allow the safe storage of liver grafts for a day instead of the previous six or eight hours, should reduce organ wastage, since with this extra time, countrywide and worldwide networks of organ sharing can be created.

If there is an adequate organ supply and a way to finance transplantation, the medical issues of candidacy are relatively clear. In a patient with nonmalignant end-stage liver disease that will not recur in the hepatic graft, there is little debate about the rationale for transplantation. Transplantation is more debatable if the recurrence of a non-neoplastic disease is predictable. The most controversial indication for liver transplantation is for the treatment of hepatic cancers. However, none of these applications should be arbitrarily excluded from future trials.

Non-neoplastic Liver Diseases

By 1982 liver transplantation had been used to treat more than 20 benign diseases.[2] Since then, the list has become so long[10-15] that it is increasingly reported in broad categories, such as cholestatic or parenchymal disease[16] (Table 1). It is therefore easy to lose sight of the fact that more than 60 distinct diseases have been

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Table 1. Native Liver Disease in 400 Pediatric and 858 Adult Recipients of Liver Transplants at the University of Pittsburgh, 1981–1988.

DISEASE	NO. OF CASES
Parenchymal	522
Postnecrotic cirrhosis	348
Alcoholic cirrhosis	76
Acute liver failure	54
Budd–Chiari syndrome	18
Congenital hepatic fibrosis	9
Cystic fibrosis	6
Neonatal hepatitis	8
Hepatic trauma	3
Cholestatic	544
Biliary atresia	217
Primary biliary cirrhosis	186
Sclerosing cholangitis	100
Secondary biliary cirrhosis	25
Familial cholestasis	16
Inborn errors of metabolism	114
Tumors	78
Benign	10
Primary malignant	60
Metastatic	8
Total	1258

treated with liver transplantation, including 16 in the broad category of inborn errors of metabolism and 14 in the category of cholestatic disease.

In adults, the most common diagnoses have been chronic active hepatitis, cryptogenic cirrhosis, primary biliary cirrhosis, alcoholic cirrhosis, and inborn errors of metabolism. Half or more of the pediatric recipients have had biliary atresia, with inborn metabolic errors a distant second.[10-13]

A number of diseases in which transplantation might have been precluded or strongly discouraged 5 or 10 years ago are no longer absolute contraindications for the procedure, and some are not even questionable. A prime example is alcoholic cirrhosis. With multidisciplinary care for substance abuse in properly selected cases, the results of transplantation for Laennac's cirrhosis are as good as those for other diseases.[17] Somewhat more controversial is transplantation in patients with cirrhosis due to hepatitis B virus, because the recurrence of viral infection cannot be reliably prevented. However, many such patients have benefited from transplantation, and it is therefore difficult to make the carrier state an absolute contraindication.

An even more difficult issue is whether patients with antibodies to the human immunodeficiency virus (HIV) should be excluded from candidacy. Shortly after screening tests for this disease became widely available in the spring of 1985, HIV infections were reported in kidney, heart, and liver recipients. At our institution, HIV antibodies were found in the stored serum of 18 of 1043 kidney, heart, or liver recipients (1.7 percent) treated between 1981 and 1986.[18] The incidence of HIV in the liver recipients was 2.6 percent, and in one third the antibodies predated transplantation. Seroconversion after transplantation — through infection from blood-component therapy or (uncommonly) from the donor's liver — made up the other two thirds.[18] The rate of seroconversion at our institution and others has remained unchanged, despite the use of screening assays for HIV antibodies beginning in March 1985.[18,19]

The patients infected with HIV have been available for study since their transplantation. We have followed 10 children who were six months to 16 years old at the time of transplantation for 1½ to 6 years, with only one late death from a complication related to the acquired immunodeficiency syndrome (AIDS). Among 16 adults, the AIDS-related mortality has been 37 percent. Many patients can thus have prolonged benefit from liver transplantation in spite of positive tests for HIV. How this fact has been used in decision making varies with the transplantation center. The most commonly accepted policy in the United States is to screen all recipients for HIV, but not to exclude transplantation solely because of a positive test. The screening of potential donors is obligatory at all centers. Tests that identify both HIV antigens and antibodies may make the screening of recipients as well as donors more foolproof than it is now.

In addition to disease states that at one time would have ruled out liver transplantation, inflexible age proscriptions have been dropped. An upper age limit was eliminated when it was demonstrated that recipients over 50 have a 5-year survival after transplantation, similar to that of younger adults.[20] At the other extreme, liver transplantation in very small infants and even newborns has become common, although the results are better with older children.[21]

Extensive thromboses of the portal, mesenteric, or splenic veins, which previously made transplantation difficult or impossible, have been eliminated in many cases through the use of vein grafts. The vein grafts are connected to the superior mesenteric vein and brought through the transverse mesocolon anterior to the pancreas into the liver hilum for anastomosis to the portal vein of the new liver.[22,23] The routine use of imaging techniques to measure the size of the liver and determine the state of the host vessels helps to identify these cases in advance, and appropriate plans can be made.

Scarring from multiple upper-abdominal operations, once considered a contraindication by many transplantation teams, is no longer an overriding deterrent in major centers. Earlier splenectomy or portal–systemic shunts cause the greatest concern. Since any of these operations can alter the portal vein, it is no surprise that the majority of complications of portal-vein reconstruction during transplantation have been in patients with earlier shunt operations.[24] Mesocaval and distal splenorenal shunts have been least harmful, since they do not involve dissection of the portal hilum. The shunt must be closed at the time of transplantation for optimal vascularization of the graft.

Should shunting operations ever be recommended to treat variceal hemorrhage, given that these proce-

dures can jeopardize the success of the ultimate step, liver transplantation? Probably only rarely, since endoscopic sclerosis of the varices is an effective alternative. In some patients with grade A (good-risk) cirrhosis according to Child's system, a distal splenorenal anastomosis may be the best way to relieve portal hypertension. However, it is important to emphasize that a liver transplantation itself decompresses portal hypertension throughout the capillary bed of the healthy new liver. Among patients with variceal bleeding who were too sick to be considered for any operation other than transplantation, the five-year survival after their livers were replaced was far superior to that reported in series of patients at generally better risk who underwent shunting operations.[25] The obvious limitations of the shunt in treating variceal bleeding have greatly reduced the frequency of portal diversions in Western countries.

Inborn Errors of Metabolism

Since the products of hepatic synthesis permanently retain the metabolic specificity of the donor, patients with inborn errors of metabolism involving the liver can be treated by transplantation of a normal liver (Table 2).[26-41] The longest follow-up in such a patient is more than 18 years. The inborn errors of metabolism that result partly or completely from known deficiencies of specific liver enzymes or from abnormal products of hepatic synthesis (Table 2) have been treated with the most predictable results. With other, less well understood disorders, the transplantation itself helps clarify the pathogenesis, either by correcting the inborn error or, equally illuminating, by failing to do so. By contrast, in one case a coagulation defect present in the donor was conferred on the recipient.[42]

In the majority of recipients with errors of metabolism, the inborn error itself had damaged the liver, and a conventional indication of liver failure or the development of malignant hepatic tumors prompted its replacement. The correction of the metabolic error was therefore incidental. However, anatomically normal livers have also been replaced solely to correct inborn errors (Table 2).

Many inborn errors that cannot be corrected by liver transplantation can be treated with allogeneic bone marrow engraftment.[43] Determining which kind of transplantation will be effective is crucial, and the guidelines for decision making have become increasingly clear.[27,43]

Cancer

Most of the first patients treated with liver transplantation had primary or metastatic hepatic cancers that could be removed only by total hepatectomy.[44] Although the rate of recurrence proved to be overwhelming,[45-47] the use of liver transplantation to treat cancer is still being investigated by many transplantation teams, often in combination with adjuvant chemotherapy or other experimental treatment protocols. The percentage of patients with a tumor in large transplantation programs ranges from 4 to 34 percent[10-15,47,48]; at our institution it has been about 5 percent (Table 1).

Certain kinds of neoplasms have a better prognosis than others. Since the recurrence of the original tumor is the most common cause of death after liver transplantation under even the best of circumstances, a crucial condition of candidacy involves ruling out the possibility that the tumor has spread beyond the liver. The uncertain prognosis with transplantation should be made clear to patients and their families.

Patients with liver tumors and normal hepatic function who are referred for transplantation can often be treated instead with major hepatic resections with the use of techniques that were developed or refined to meet such patients' need for more extensive operations. Resection if feasible or transplantation if necessary should be done promptly. A quick decision and action are even more imperative when a liver cancer is found in a patient whose liver is failing because of an underlying chronic non-neoplastic disease.

Timing of Transplantation

Liver transplantation once seemed so drastic that it was used only as a last resort for benign hepatic disease. Today, allowing a patient's condition to deteriorate to the point at which life-support systems are required before thinking of the transplantation option is unacceptable. However, the speed of deterioration is highly variable.

Fulminant Hepatic Failure

A diagnosis of fulminant hepatic failure can be made when sudden massive necrosis occurs in a formerly healthy liver,[49,50] but not when a previously unrecognized chronic disease is exacerbated or acute Wilson's disease is present. Before 1982,[2] transplantation's results were not good enough to justify this step, because recovery without the procedure occurred in 5 to 20 percent of cases.[49,50] Since then, emergency transplantation for fulminant hepatic failure has been widely accepted.[51-54] The predominant causes have been non-A, non-B hepatitis, hepatitis B, and toxic hepatitis caused by a variety of agents.

A decision to replace the liver must often be made within a few hours. Systematically assessing the features of the liver disease can help to distinguish the patients with a good chance of recovery from those who will die without transplantation.[55,56] The cause of the disease may be an important prognostic determinant.[56] Features that predict imminent death include relentless progression, grade 3 or 4 encephalopathy, severe coagulopathy, rapid shrinkage of the liver as documented by imaging, metabolic acidosis, cardiovascular instability, and sepsis. When a patient has grade 4 encephalopathy and is dependent on mechanical ventilation, it is usually too late.

If transplantation is performed before these grave developments, some livers whose lesions are reversible may be replaced unnecessarily. A liver biopsy performed after the coagulopathy has been corrected may

Table 2. Inborn Errors of Metabolism Treated with Liver Transplantation.

Disease	Cause/Description	Correction of Metabolic Defect	Longest Survival	Associated Liver Disease	Study
Alpha$_1$-antitrypsin deficiency	Structural abnormality of the protease inhibitor synthesized in liver	Yes	13 yr*	Cirrhosis	Hood et al.,[26] Starzl[27]
Wilson's disease	Abnormal biliary copper excretion, decreased copper binding to ceruloplasmin, and copper accumulation in tissues; autosomal recessive gene mapped to chromosome 13	Yes	16½ yr*	Cirrhosis	Starzl,[27] Groth et al.[28]
Tryrosinemia	Fumarylacetoacetate deficiency	Nearly complete	7½ yr*	Cirrhosis, hepatoma	Starzl et al.[29]
Type I glycogen storage disease	Glucose-6-phosphatase deficiency	Yes	7 yr*	Hepatomegaly, fibrosis, liver tumors	Malatack et al.[30]
Type IV glycogen storage disease	Amylo-1,4-transglucosidase (branching enzyme) defect	Incomplete†	4½ yr*	Cirrhosis	Starzl[27]
Cystic fibrosis	Unknown; pancellular disease, liver often affected	Not known	4½ yr*	Cirrhosis	Mieles et al.[31]
Niemann–Pick disease	Sphingomyelinase deficiency, sphingomyelin storage	Not known	2 yr (died)	None	Daloze et al.[32]
Seablue histiocyte syndrome	Unknown; neurovisceral lipochrome storage	No	7 yr*	Cirrhosis	Gartner et al.[33]
Erythropoietic protoporphyria	Hepatic ferrochelatase deficiency; possible overproduction of protoporphyrin by erythropoietic tissues	Incomplete	1½ yr	Cirrhosis	Samuel et al.,[34] Polson et al.[35]
Crigler–Najjar syndrome	Glucuronosyltransferase deficiency	Yes	4 yr	None	Wolff et al.[36]
Type I hyperoxaluria	Peroxisomal alanine–glyoxylate aminotransferase deficiency	Yes	8 mo	None	Watts et al.,[37] McDonald et al.[37a]
Urea-cycle enzyme deficiency	Ornithine carbamoyltransferase deficiency	Yes	8 mo*	None	Starzl: unpublished data
C-protein deficiency	Defective C-protein synthesis	Yes	2¼ yr*	None	Casella et al.[38]
Familial hypercholesterolemia	Low-density lipoprotein–receptor deficiency, overproduction of low-density lipoprotein	Incomplete	6 yr*	None	Bilheimer et al.[39]
Hemophilia A	Factor VIII deficiency	Yes	4 yr*	Cirrhosis, a complication of blood-component therapy	Lewis et al.[40]
Hemophilia B	Factor IX deficiency	Yes	6 mo	Cirrhosis, a complication of blood-component therapy	Merion et al.[41]

*Patients in University of Colorado–University of Pittsburgh series. Follow-up is reported to January 1989.

†Amylopectin deposits were found in a heart-biopsy specimen four years after transplantation.

provide decisive information. If the clotting disorder cannot be sufficiently corrected to permit a closed-needle biopsy, the abdomen can be explored when a new liver is available for transplantation; the operation can be stopped if the histopathological examination of the open-biopsy specimen is favorable. In spite of the pitfalls associated with liver replacement for fulminant hepatic failure, current survival rates of 55 to 75 percent after transplantation[51-54] compare favorably with the most optimistic projections of 20 percent for medical management alone. The perioperative mortality associated with transplantation has frequently been due to brain-stem herniation during or just after the procedure, sometimes despite the continuous monitoring of intracranial pressure. To improve results, early referral to transplantation centers, extremely aggressive evaluation, and an early decision for surgical exploration and biopsy with the option of immediate transplantation are necessary.

End-Stage Chronic Disease

A decision to proceed with transplantation requires the participation of the primary physician, who may have seen a gradually evolving social and vocational invalidism that is not evident on first examination. The disability may involve encephalopathic dementia and the loss of intellectual capacity, frequent hospitalizations for other complications of liver failure, the inability to function in a domestic environment, and arrested growth and development in infants and children. These issues of the quality of life loom large for most patients long before the truly terminal events of chronic hepatic failure occur. Formulas to determine candidacy for transplantation on the basis of liver-function tests have not been helpful because the test results vary from disease to disease and even within the same disease. Patients with cholestatic disorders (such as biliary atresia and primary biliary cirrhosis) usually become jaundiced but have well-preserved hepatic synthetic functions for a long time, whereas patients with hepatocellular disease may not become jaundiced despite profound disturbances in the synthesis of albumin and prothrombin.

The risks of procrastinating too long before deciding to undertake transplantation have not been defined. In a study in which 12 percent of the candidates died while waiting, most of that number had arrived at the transplantation center on mechanical ventila-

tion and with gastrointestinal bleeding, a coagulation disorder, the hepatorenal syndrome, aspiration pneumonitis, subacute bacterial peritonitis, or other end-stage complications.[57] At another center,[58] the mortality among patients who were considered too healthy for the active waiting list was higher than that among patients who were immediately accepted as candidates. When the severity of the disease is underestimated and a catastrophic complication occurs, resuscitation is sometimes successful. However, the outlook after subsequent transplantation is demonstrably poorer.[59]

The influence of the stage of the liver disease on outcome after transplantation has been studied in adult patients with primary biliary cirrhosis.[60,61] In the most complete of these investigations, the severity of the disease was defined with the use of a formula that included age, serum bilirubin level, serum albumin level, prothrombin time, and severity of edema; life expectancy was predicted without transplantation.[62] The transplant recipients' actual survival was markedly better than predicted.[60] However, patients with less severe liver disease had a low perioperative mortality and a two-year survival of 80 percent, whereas those whose conditions had deteriorated more seriously before transplantation had a high perioperative mortality and a two-year survival of only 55 percent.[60] Clearly, transplantation should be considered before the stage of catastrophic complications is reached.

An increasing number of patients with normal liver function have had orthotopic transplantation for polycystic disease,[63] cystic hygroma,[64] and adenomatosis. The size of their lesions, the consequent disability, and the life-threatening complications of mass lesions were the indications for urgent operation. The largest of the excised livers weighed 16.5 kg.[64]

The Replacement Procedure

The evolution of liver transplantation as a practical form of treatment has been summarized elsewhere.[2,45,65] In orthotopic liver transplantation, the diseased organ is removed and replaced with a cadaveric liver in the most anatomically normal way possible (Fig. 1). Many methods of dealing with anomalies or other features of the donor's or recipient's blood vessels have been described.[22,23,45,66-68]

Extracorporeal venovenous-bypass techniques have been used in adults since 1983 to decompress the splanchnic and systemic venous systems, which are obstructed while the native liver is being removed and the homograft inserted.[69] The bypass is often too cumbersome to use in very small infants, and some surgeons omit it in adult patients.[65,70]

The biliary tract can be reconstructed by connecting either the donor's and recipient's common ducts end to end over a T-tube stent (inset, Fig. 1)[2] or the common duct of the homograft to a limb of the jejunum in a Roux anastomosis (Fig. 1).[2,71] There is a 10 to 15 percent incidence of late bile-duct obstruction, which requires correction with interventional radiology, secondary duct reconstruction, or occasionally retransplantation.[71-73] In a technique that incorporates the donor's gallbladder in a conduit between the donor's common duct and the recipient's anastomotic site,[74] a high incidence of late sludge and stone formation occurs.[75]

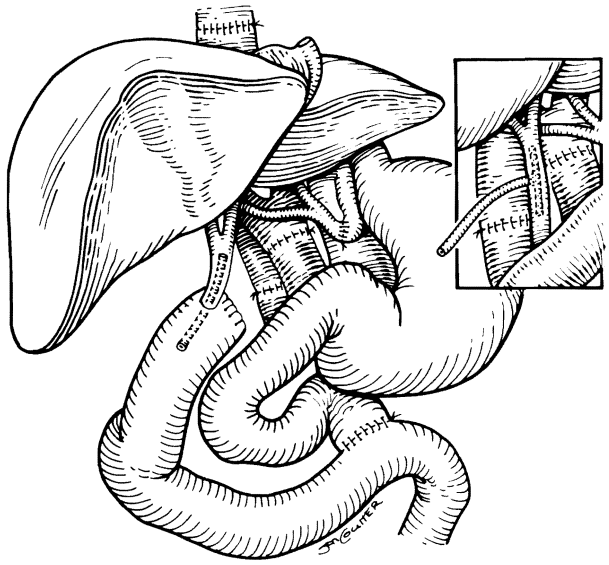

Figure 1. Orthotopic Liver Transplantation.
Biliary reconstruction can be accomplished through choledochojejunostomy or duct-to-duct anastomosis (inset).

Methods of reducing the size of transplants, which permit the transplantation of part of a liver, have been perfected in recent years in Paris,[76] Hanover, West Germany,[77] and Chicago,[78] allowing greater flexibility in matching available donors to the needs of recipients. Pediatric recipients have benefited most.

Perioperative Graft Failure

If a graft fails to function, the only recourse is retransplantation before cerebral edema and brain-stem herniation occur.[79] Lesser degrees of graft injury can allow short-term survival, but retransplantation or death remains the end point. The rate of retransplantation in the first three postoperative months is 10 to 20 percent.[9,79] There are four general reasons for graft failure, which are not mutually exclusive: a technically imperfect operation, unrecognized liver disease in the donor, an ischemic injury in the graft, and accelerated rejection. The least likely is undetected disease in the donor, although in a few indisputable cases donors' livers have had diffuse fatty infiltration.[80,81]

Obvious technical complications account for less than 10 percent of the primary graft failures in adults but 30 percent of those in infants and children.[79] The risk in infants is inversely related to the patient's size,[21] and complications are mainly attributable to vascular thrombosis.[21,82] A multivariate factor analysis of pediatric recipients[83] found that the risk of arterial thrombosis increased if the vessels were smaller than 3 mm in diameter, if the anastomoses had to be revised, or if aortic or iliac grafts were needed as con-

duits to the hepatic artery. Unsuspected reductions in portal venous or hepatic arterial flow can be detected with routine electromagnetic flow monitoring.[84]

Portal-vein thrombosis is rare and usually occurs only when the recipient's splanchnic venous bed has been altered by a portal-systemic shunt, a splenectomy, or another operation.[24] Venous thrombi can be carried to the recipient through the portal vein of the liver graft, particularly if the donor has had a splenic injury.

Iatrogenic problems, such as the overzealous correction of clotting defects[83,85] and polycythemia caused by overtransfusion,[86] can contribute to the thrombosis of a hepatic artery or portal vein. Deficiencies in protein C and antithrombin and defective fibrinolysis have been described in children.[87] Injury to the hepatic microvasculature caused by ischemia and refrigeration,[88] cyclosporine-induced changes in the prostanoid metabolism and other homeostatic processes of vascular endothelial cells,[89] and reductions in hepatic blood flow due to rejection[90,91] may be other nontechnical factors.

When thrombosis occurs in the hepatic artery, it may be asymptomatic in 20 to 30 percent of cases,[82,92] and the diagnosis can only be made with the routine use of Doppler ultrasonography.[93] However, the complications that can result are serious, and they include failure of the primary graft to function, septic hepatic infarction of part of the liver, bacteremia, abscess, the rupture of the dearterialized ducts with bile peritonitis or bile leakage, and the formation of biloma within the graft parenchyma.[45,65,68,82,92,94] Later, multiple intrahepatic biliary strictures that resemble sclerosing cholangitis may form.[72,94,95] Although secondary rearterialization has been attempted, retransplantation is usually the only recourse.

Early portal-vein thrombosis usually requires retransplantation,[24] but a few patients have been saved by immediate or delayed secondary reconstruction of the portal vein.[2] Two patients in whose reconstructed portal veins thrombosis occurred had distal splenorenal shunts to treat portal hypertension.[96,97]

The most common cause of postoperative graft dysfunction is ischemic injury incurred during the death of the donor, the procurement operation, or the period of refrigeration. In controlled experiments in animals, the degree of damage to the liver graft was related to the length of time it was refrigerated.[98] This association is far less clear in a clinical setting,[9] particularly when an improved preservation solution developed at the University of Wisconsin is used. This solution, which is infused through the portal vein or hepatic artery, allows the safe cold storage of canine and human livers for at least 24 hours and possibly longer.[7-9] It has a number of cryoprotective ingredients, and its effectiveness has been explained as a result of their cumulative action.

Intracellular pH, energy charge, mitochondrial function, and the level of free-radical scavengers in preserved liver tissue do not accurately predict graft quality in laboratory animals. The ATP content of the preserved graft falls sharply, even during the initial chilling infusion. In laboratory animals, it is the rapidity with which levels of ATP can be restored after revascularization rather than its level under storage that is a useful prognostic sign. Consequently, the measurement of ATP levels during preservation has not been considered helpful as a prospective indicator, except in a single clinical report.[99]

Once the liver has been revascularized, the production of bile is the most important predictor of success.[2,65] In humans, there is an almost perfect correlation between the production of bile, the rapidity with which ATP levels in the liver are restored after revascularization, and survival.[100] Next to the production of bile, the restoration of clotting function[85] and the absence of lactic acidosis[101,102] are the best predictors of success. The coagulopathy that occurs during the transplantation procedure is characterized by fibrinolysis, the deficiency of specific clotting factors and platelets, and the consumption of the clotting components.[44,85] Standard liver-function tests during the days that follow almost always verify the accuracy of the simple assessments of bile production and clotting made during the operation. Measurements of blood amino acid clearance and other products of intermediary metabolism have been used to distinguish between patients whose new livers are and are not expected to recover.[101,102]

If other explanations for primary failure to function or dysfunction have been eliminated, host immune factors may be responsible. No unequivocal examples of the kind of hyperacute rejection that can immediately destroy human kidneys and hearts have been reported,[103] and this supports the widely held opinion[104] that the liver is resistant to such antibody-mediated injury. Because of this resistance, liver transplantation is often performed in spite of major-blood-group incompatibilities[105] that because of the antigraft specificities of the isoagglutinins would preclude renal or cardiac transplantation.[103] However, the risk of rejection is increased.[105-108] Isoagglutinin fixation has been demonstrated in the microvasculature of major blood group–incompatible liver grafts in a collection of cases in which hemorrhagic infarction occurred five times more frequently than in patients with compatible grafts.[107] The loss of the liver graft proceeded more slowly than a hyperacute rejection of kidneys, but the result was the same.

The role of cytotoxic antilymphocyte antibodies in the failure of liver grafts has been less well delineated. These antibodies, which have antigraft specificity in kidney recipients, are highly predictive of hyperacute rejection[109]: the microvasculature of the renal graft is occluded by rapidly sequestered blood elements and clotting factors.[103,110] If the process is not promptly completed, a consumptive coagulopathy, fibrinolysis, or both can develop.[111]

Hyperacute rejection of the liver was suspected in one of the first clinical attempts at orthotopic liver transplantation.[112] A child's graft developed hemorrhagic necrosis a few hours after the operation in a

manner similar to that described many years later in rats[113] and in Rhesus monkeys[114] sensitized with skin homografts before orthotopic liver transplantation. However, other experiments in animals have demonstrated the liver's special protection from humoral rejection.[115]

The liver's resistance to cytotoxic antibodies is so strong that a positive cytotoxic crossmatch does not preclude transplantation.[103,104] At the same time, it is becoming evident that accelerated (possibly humoral) rejection of liver grafts can occur.[116-118] The process develops more slowly than in the kidney and presumably other organs, may be reversible, and is not strongly associated with the antigraft antibodies that are measured in standard blood typing.[116] A progressive and severe coagulopathy that develops shortly after hepatic revascularization should arouse suspicion of an accelerated rejection, even without a positive cytotoxic crossmatch.[116] The prompt destruction of second transplants in patients whose first liver grafts were lost for unclear reasons has been reported by several centers.[116]

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MEDICAL PROGRESS

LIVER TRANSPLANTATION

(Second of Two Parts)

THOMAS E. STARZL, M.D., PH.D., ANTHONY J. DEMETRIS, M.D., AND DAVID VAN THIEL, M.D.

REJECTION AND HISTOCOMPATIBILITY

Although the possibility of rejection is always present, nonimmunologic causes of early hepatic dysfunction must be ruled out systematically. The differential diagnosis can include suboptimal revascularization; defects in biliary reconstruction that cause obstruction or bile fistula; opportunistic infection with cytomegalovirus,[119,120] herpes simplex viruses,[120] Epstein–Barr virus, or adenovirus[121]; infection by various bacterial or fungal pathogens[122]; toxicity caused by hyperalimentation or sepsis[123]; and hepatotoxicity of the drugs used to prevent rejection.[45,124] Later graft dysfunction can be caused by a recurrence of the disease that destroyed the native liver, infection of the transplant by a hepatitis virus, defects in the reconstruction of the bile duct, or chronic rejection. Needle biopsies of the liver can provide some of the most important evidence for or against rejection.[80,123,125-129]

It has been suggested that the liver is less susceptible to rejection than other organs, because permanent or prolonged acceptance of a graft has been achieved relatively easily in dogs after a three- or four-month course of immunosuppression[45,130] and because pigs frequently have long survival with no treatment at all.[131] However, in humans the advantage, if it exists at all, is only nominal; histopathologic evidence of rejection can be found after two thirds or more of clinical transplantations.[125,132-134]

The principal features of acute cell-mediated rejection in dogs and other species[126] are mononuclear-cell infiltration (which is heavily concentrated in the portal triads), edema, and parenchymal necrosis. The bile ducts, veins, and arteries appear to be most commonly damaged.

Acute cellular rejection causes various degrees of cholestatic jaundice, failure of hepatic synthetic processes, and elevations in the levels of enzymes that denote liver necrosis or injury.[45] Lymphocytosis[135] and eosinophilia[136] can also occur, but they are not consis-

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tently present or specific. Measuring levels of interleukin-2 receptors may be useful.[137]

Another kind of rejection has been called chronic rejection because it usually evolves insidiously and cannot be reversed with intensified therapy. Frequently, hepatic synthetic functions are well preserved while obstructive jaundice develops.[45,138] Cellular infiltration may be minimal. The identifying pathologic characteristics are the presence of occlusive arterial lesions similar to those found in other kinds of organ grafts, the destruction of the small intrahepatic bile ducts, and fibrosis, which occasionally evolves into cirrhosis.[45,123,126,127] Paradoxically, these "chronic" features can develop within a few weeks after transplantation.[138] Some observers have noted an increased incidence of chronic rejection, especially the disappearance of small bile ducts, in patients who had lymphocytotoxic antibodies before their operations[139,140] or bouts of cytomegalovirus hepatitis.[141]

Drastic changes in the expression of Class I and Class II major histocompatibility antigens by liver parenchymal and vascular endothelial cells have been reported in human hepatic allografts during rejection as well as in grafts damaged by ischemia, duct obstruction, hepatitis, and other adverse conditions.[142-147] Functional analyses of the T lymphocytes invading a graft during rejection have suggested that early acute cellular rejection is associated with a Class I–specific infiltrate, whereas later episodes and chronic rejection are associated with Class II alloreactive cells.[148] Although these observations may be relevant to an understanding of pathogenic mechanisms, none of the patterns appear to be entirely specific or clinically useful. Dendritic cells that are normally present in the portal tracts of the liver as "passenger leukocytes" are potent stimulators of the mixed-lymphocyte reaction and may have a key role in localizing the inflammation in rejection.[142,149,150] Later, the obliterative lesions that develop in the intraparenchymal hepatic arteries can contribute to the loss of small bile ducts and to strictures in large ducts, since the ducts depend on the supply of arterial blood.[149,150]

It is not clear whether the extent of matching of the Class I and Class II antigens has a major effect on these pathologic and clinical events. An inverse relation has been described between the extent of matching and the outcome.[140,141,151] Although hypotheses have been advanced to explain these unexpected findings, further observation is needed before any conclusions can be reached.

Another unexplained phenomenon is a transplanted liver's protective effect on other tissues and organs transplanted at the same time or later from a single donor. It has recently been shown that Class I antigens of donor specificity appear in the plasma of liver recipients less than 24 hours after transplantation and that these soluble, circulating antigens persist in large quantities for the life of the liver graft.[152] The recipient's original histocompatibility antigens did not disappear from the plasma, proving that the liver is not their only source. The continued presence of soluble donor antigens may help explain the liver graft's ability to reduce humoral antibody titers and to shield a kidney from the same donor from the hyperacute rejection that a positive cytotoxic-antibody crossmatch would ordinarily foreshadow.[153] Kupffer cells may also have a role in protecting the liver from humoral rejection. The nontoxic absorption of immunoglobulins by sinusoidal nonparenchymal cells (probably Kupffer cells) of liver grafts has been documented in sensitized rats.[154]

The liver's protective effect against cell-mediated rejection of the skin, heart, and kidney was first noted in pigs[155] and studied extensively in rats.[156] The lack of an effective cellular immune reaction against donor organs after liver grafting in animals may be due to the presence of enhancing or protective antibodies, the clonal deletion or sequestration of cells capable of causing rejection, and increased suppressor-cell activity.[156]

Not all immunologic reactions after liver transplantation involve rejection. Graft-versus-host disease has been reported in patients given livers whose major blood groups were compatible but not identical to their own (for example, a liver from a type-O donor given to a type-A recipient).[157] A donor's lymphoid tissue, carried with the liver,[126,158] apparently produced antihost red-cell isoagglutinins, which caused hemolysis. In addition, graft-versus-host disease including a skin rash has been reported in a recipient whose own tissue contained monocytes from the donor.[159] Increased immunosuppression relieves these syndromes.

Preventing Rejection

Liver transplantation was a passive follower of kidney transplantation in the development of immunosuppressive techniques.[2] Today, cyclosporine is the most commonly used maintenance drug,[160] and steroids are almost invariably added to it.[161] Azathioprine may be used as a third agent to reduce the dose of cyclosporine,[133,162] and in some cases it has replaced cyclosporine altogether after a few months or later. Antilymphocyte-globulin preparations,[133] including the monoclonal antibody OKT3,[163,164] have been given prophylactically and for the specific indication of rejection. OKT3 reacts against all mature T lymphocytes. Many of the polyclonal antilymphocyte globulins[133] affect B lymphocytes as well.

The liver's ability to regenerate and to regulate its size is important after transplantation, when recovery from ischemic injury or rejection is usually necessary. In addition, the transplanted liver promptly adjusts its volume, shrinking or growing to reach a size appropriate to the recipient.[165,166] Some drugs, such as doxorubicin, that patients undergoing liver replacement for hepatic tumors may take are known to inhibit regen-

eration.[167,168] In contrast, cyclosporine actually enhances regeneration after partial hepatectomy.[169-171] This hepatotrophic effect resembles that of insulin in nontransplantation models.[172]

The development of cyclosporine has been the single most important factor in making liver transplantation practical. The history of the field is usually described in terms of the eras before and after cyclosporine (Fig. 2). However, even when cyclosporine is used in multidrug regimens, rejection remains a common cause of early and, especially, late graft losses.[2,79] Cyclosporine's principal side effect, nephrotoxicity,[160,161,173] limits the permissible dose. In human recipients of livers and hearts, evidence of renal dysfunction has included azotemia, hyperkalemia, and hypertension. Because the morphologic changes in the kidneys of these patients may not be reversible,[174-176] the eventual cost of short- or long-term cyclosporine therapy has yet to be determined.

Nephrotoxicity can be limited if renal function is used as the principal guide in determining the dose of cyclosporine, as it was[161,177] before blood levels of the drug could be measured. Even today, there is much to be said for this approach. Because the therapeutic ranges of cyclosporine trough levels vary with different methods of measurement,[178] each transplantation center usually develops its own standards based on observed toxicity and the frequency of rejection. The desirable blood or plasma trough level varies with a number of factors, among them the patient, the use of other drugs, the time after transplantation,[179] the changing quality of graft function,[180] the presence of bile-duct obstruction or T-tube drainage,[181] and the existence of bile fistulas.[182,183]

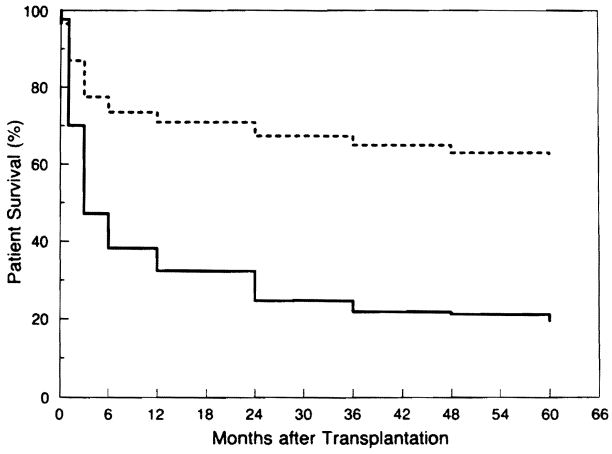

Figure 2. Survival of 170 Liver-Transplant Recipients Treated before Cyclosporine Became Available (1963–1979), as Compared with the Survival of 1258 Recipients Treated between 1980 and Mid-1988.

The patients were treated by a single team at the University of Colorado through 1980 and at the University of Pittsburgh thereafter. The solid line denotes patients receiving azathioprine (n = 170), and the broken line those receiving cyclosporine (n = 1258). Survival is calculated with use of the life-table method.

Without new drugs, further improvements in the management of rejection will probably be minor. A promising agent called FK 506, which was described in 1987[184,185] and tested extensively in rats, dogs, monkeys, and baboons,[184-187] is undergoing its first clinical trials in liver and kidney recipients with encouraging results (unpublished data).

The balance between immunosuppression and susceptibility to infectious diseases is more delicate in liver recipients than in heart and kidney recipients, because the hepatic graft is directly exposed to the microorganisms of the intestinal tract.[45,122,133,188-190] Animal studies have shown that a liver graft damaged by ischemia or rejection becomes a sieve through which bacteria pass.[191] Tissue barriers must be maintained intact while the patient is undergoing potent immunosuppressive treatment in order to prevent this "leakage" of bacteria.[45] Patients have been treated before transplantation with oral antibiotics that suppress pathogenic gram-negative organisms and fungi but allow anaerobes to survive in a process of selective intestinal decontamination.[192] The morbidity, but not the mortality, from postoperative infection has been reduced. In addition to its unproved value, selective decontamination has practical limits: a cadaveric liver may not be available when the results of antibiotic treatment reach their peak.

Much remains to be learned about the subtle relations between host defenses and invasive bacteria in liver transplantation. The recipient's macrophage system, of which the liver is an important component,[193] is profoundly altered by transplantation. Within a short time after the operation, all of the Kupffer cells in the graft are replaced with host macrophages,[126,143,194] whereas the hepatocytes and vascular endothelial cells remain specific to the donor.[126] The dysfunction or absence of Kupffer cells may cause or contribute to the wave of endotoxemia that occurs in dogs during the anhepatic phase of the operation and afterward.[195] The increased level of endotoxin may also be responsible for serious perioperative complications in humans.[196]

Viral infections occur at some point after transplantation in the majority of liver recipients.[119,122,197] Cytomegalovirus is the most common cause of postoperative hepatitis.[119,197] Protection against serious cytomegalovirus infection has been reported with hyperimmune globulin.[198] Patients generally recover if immunosuppressive treatment is reduced and especially if they are treated with ganciclovir.[199] However, strains of cytomegalovirus that are resistant to ganciclovir have recently been reported.[200] Hepatitis caused by adenovirus[121] or herpesviruses[123] is uncommon, but because hepatic necrosis can result, immunosuppressive treatment should be stopped temporarily when such infections are diagnosed.

After the transplantation of any organ, primary infection with the Epstein–Barr virus or its reactivation can produce conditions ranging from an infectious mononucleosis syndrome (as seen in the general popu-

lation) to life-threatening lymphoproliferative disease. Lymphoproliferative tumors (B-cell lymphomas) have been found most frequently in liver recipients[201,202] — especially infants and children, in whom the risk during the first two years after transplantation may be as high as 10 percent.[202] The liver graft itself is often involved. If immunosuppressive treatment is reduced[201,202] and acyclovir therapy added,[203] many (but not all) of the lymphomas will regress without rejection of the graft.[201,202]

Recurrence of Native Disease

Hepatic Cancer

Small incidental cancers usually do not recur, but larger cancers of all cell types generally metastasize.[10,45-48,204] Death has been caused by their recurrence as early as 3 months after transplantation, but the highest mortality occurs between 6 and 36 months (Fig. 3). In addition to tumor size, cell type and the presence of hilar-lymph-node metastases or underlying liver disease influence results.[2,15,46-48,204] Hepatocellular carcinomas — except the fibrolamellar variant[2,46,47,204,205] — almost always recur.[46] Duct-cell carcinomas, even the small Klatskin's tumors that are located high in the hepatic hilum, almost always recur,[46,47,204] although they did not in a recent German study.[48] In more than half the reported patients with epithelioid hemangioendotheliomas, survival for at least two years has been achieved.[47,206]

In the dismal record of transplantation in patients with primary hepatic tumors, there has been little or no emphasis on adjuvant therapy. Immunomodulation and chemotherapy are now being attempted for the first time. Even a few patients with metastatic liver disease have benefited from liver transplantation (Fig. 3),[10,11,204,207,208] particularly if their primary tumors were neuroendocrine.[10,204,208] In one case, a patient with multifocal liver metastases from a carcinoma of the breast had prolonged palliation with chemotherapy, autotransplantation of the bone marrow, and liver transplantation,[207] although recurrences ultimately developed (Margreiter R: personal communication, August 1986).

Hepatitis B

Removing the diseased liver reduces the titer of hepatitis B, as measured by the level of surface antigen in the blood,[209,210] but with rare exceptions[212-215] the graft becomes infected despite passive immunoprophylaxis.[15,210-213] Viral immunity has been demonstrated in patients with fulminant hepatitis,[210,211] but in most of those with chronic aggressive hepatitis, the recurrence of the disease in the graft jeopardizes recovery[209,210,213] and substantially reduces long-term survival (Fig. 4). Coinfection with the delta virus is a confounding factor that recurs with the hepatitis B infection.

Efforts to treat hepatitis B carriers perioperatively with hyperimmune globulin or interferon alfa have failed.[210,211,213,215] However, a human monoclonal antibody directed against hepatitis B has been produced (Sandoz, East Hanover, N.J.) by fusing peripheral-blood lymphocytes from an immune man with cells of a mouse × human myeloma–cell line.[216] The resulting human monoclonal hyperimmune globulin is 50,000 times more potent than commercially available hyper-

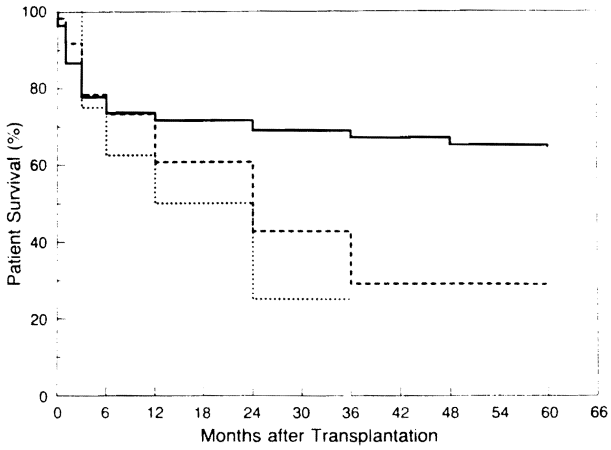

Figure 3. Survival after Liver Transplantation of 60 Patients Treated for Primary Hepatic or Bile-Duct Cancers and 8 Patients Treated for Metastatic Liver Cancer as Compared with That of 1190 Patients Treated for Benign Liver Disease.

Patients are from the University of Pittsburgh series, from the period (1980–1988) during which cyclosporine was available. The solid line denotes patients with benign liver disease, the broken line those with primary tumors, and the dotted line those with metastatic tumors. Survival is calculated with use of the life-table method.

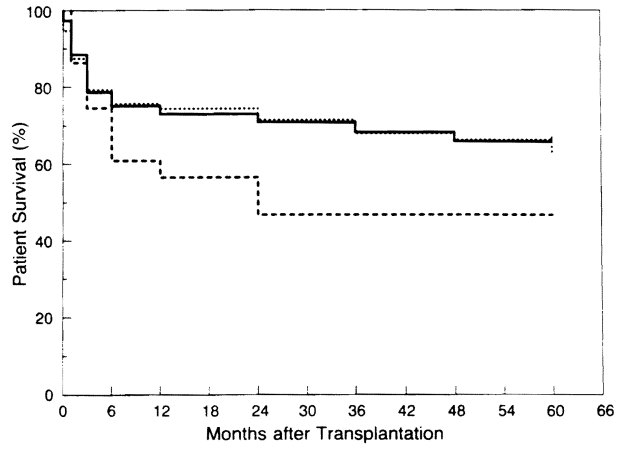

Figure 4. Influence on Survival of the Hepatitis B–Carrier State.

Survival is compared in 51 adult patients with chronic active hepatitis (broken line) who underwent transplantation between 1983 and 1988 (before 1983 positivity for hepatitis B surface antigen was considered a contraindication), in 332 contemporaneous patients without cancer (dotted line) who had post-necrotic cirrhosis from other causes (cryptogenic, hepatitis B immune, non-A, non-B hepatitis, autoimmune, alcoholic, or drug related), and in 412 contemporaneously treated adults (solid line) with other benign causes of end-stage liver disease (mostly cholestatic). Survival is calculated with use of the life-table method. Patients are from the University of Pittsburgh series.

immune globulin prepared from the blood of immune donors. This monoclonal antibody has been given to a few patients after liver transplantation,[217] with inconclusive results. Further trials have been slowed by a shortage of the antibody.

Non-A, Non-B Hepatitis

The recurrence of non-A, non-B hepatitis has been documented tentatively[123,218] but not often. Since this low incidence of recurrence may reflect merely the difficulty of establishing the diagnosis, the recent description of a specific non-A, non-B marker called "hepatitis C" may clarify the issue.[219] Bone marrow aplasia, which can also complicate milder attacks of non-A, non-B hepatitis that do not require liver transplantation, has been observed in children a few days or weeks after their livers have been replaced.[220,221] Four of the nine who had bone marrow aplasia survived, usually with a slow recovery of the hematopoietic system.[221]

Other Recurrent Diseases

The recurrence of the Budd–Chiari syndrome[211,222] can be prevented with anticoagulants.[222-224] An initial report of the recurrence of primary biliary cirrhosis[225] has not been confirmed in a larger series,[226] although the antimitochondrial antibodies found in this disorder either do not disappear after transplantation or reappear after a transient disappearance.[226,227] A syndrome resembling sclerosing cholangitis has been reported in a liver homograft,[228] but the same diagnosis has been made after transplantation in patients who did not have biliary tract disease.[123] There has been one report of recurrent autoimmune hepatitis.[229]

Transplantation of More Than One Organ

There have been many reports of the transplantation of the liver and a kidney; the liver and pancreas, liver and heart, and liver, heart, and lung are less frequent combinations. In these cases, the organs were transplanted separately, so two standard procedures were performed in the same patient.

The liver has also been transplanted as part of visceral organ clusters, which included the pancreas and the entire gastrointestinal tract in two children with the short-gut syndrome and hepatic failure.[230,231] Maximal survival was six months.[230] In 10 adults the liver, along with the pancreas, duodenum, and proximal jejunum, were transplanted to replace upper-abdominal organs removed because of tumors.[232] Eight of these recipients are alive after 4 to 10 months without evidence of recurrence.

Quality of Life

In the early days of liver transplantation, the quality of life was both defined and predicted by the liver-function profile after a year of convalescence and the quantity of steroids needed to maintain that level of function.[233] Cyclosporine has minimized the need for steroids. Several studies have shown the remarkably restored physical and emotional well-being that can be expected in infants and children,[233,234] including resumed growth and even catch-up growth.[235] In adult liver recipients studied before and two years after surgery, social interaction, home management, alertness, the use of recreational and leisure time, and overall psychosocial functioning improved broadly.[236] The severity of the stress experienced by patients and their spouses after transplantation correlated closely with the ease of recovery. Over 90 percent of the patients who undergo a single transplantation say that they have no problems or only minor health problems two years later. More than 85 percent return to work and say that they are able to perform their jobs well. In contrast, the smaller number of survivors who have undergone more than one transplantation have a much poorer outcome; because of one or more disabilities, only 43 percent are able to work.

Patients treated in the period during which cyclosporine has been available have only been followed since 1980. However, a bellwether group of survivors remains from an original series of 170 patients treated between 1963 and 1979.[237] Twenty-eight of these recipients are alive after 10 to 19 years. They represent exactly half the survivors after one year. Only two patients who were alive after five years have since died. One of the late deaths was caused by chronic rejection after 12½ years. The other was from a lymphoma 13½ years after transplantation. Rehabilitation has been complete in the long-term survivors.[237]

Auxiliary Transplantation

In auxiliary transplantation, an extra liver is placed in the right paravertebral gutter, rearterialized from convenient adjacent vessels, and provided with a portal-venous inflow from the recipient's portal or superior mesenteric vein. Splanchnic-venous inflow is critical to optimal graft function,[238] because this blood contains so-called hepatotrophic factors, of which insulin is the most important.[239,240] In almost all clinical trials, which by 1978 numbered more than 50, a splanchnic-venous inflow to the auxiliary graft was provided.[241]

An auxiliary transplantation that truly prolonged life was first achieved in 1972.[241] The recipient, who had biliary atresia, is still alive more than 16 years later (Fortner JG: personal communication, April 1989). In 1980, the 29-month survival of an adult recipient was reported from Paris.[242] The patient, who had hepatitis B, died of a hepatocellular carcinoma in his native liver eight years after transplantation (Bismuth H: personal communication, January 1989).

As orthotopic liver transplantation became increasingly successful, interest in auxiliary transplantation waned. However, the transplantation of whole livers or liver fragments to the right paravertebral gutter of six adult recipients in essentially the same operation as that used in the past has recently been reported.[243] At the time of the report, all six recipients were alive and had been followed for 5 to

23 months.[243] The reports of cautious further trials will undoubtedly be forthcoming.

Financial Support and Public Appeals

The ability to pay for liver transplantation has a profound influence on candidacy. Ironically, the feasibility and then the practicality of transplantation were established before a way to finance it was considered. In 1983, a planning commission for the Commonwealth of Massachusetts estimated that the average cost of liver transplantation would be $238,800 in the first year,[244] although the actual costs were only a third of this amount in a large, existing program.[245] It is clear that the bill can be astronomical if a patient is severely disabled by the time of transplantation, if the first liver graft does not function well, and if serious complications develop and perhaps require a second transplant.[245]

Because of their fear of runaway expenses, many health insurance carriers and government agencies have avoided financial responsibility by classifying liver transplantation as experimental,[246] despite the Consensus Development Conference's conclusion to the contrary.[1] An answer to cost-conscious funding agencies has been that liver transplantation can eliminate the repeated and expensive hospitalization of patients who are slowly dying of chronic hepatic disease.[247-249]

Liver transplantation in the United States has been paid for by a heterogeneous system of private health insurance programs, government agencies, and public and private fund-raising activities. One highly visible consequence has been the recurrent spectacle of families and patients pleading on television and in the press for economic help or an organ donor. Meanwhile, statistics accrue showing that blacks and presumably other minorities are grossly underrepresented among liver-transplant recipients.[250] Developing a system that allows all citizens equal and reasonable access but avoids the extraordinary expense of past programs, such as the federally financed End Stage Renal Disease Program, may require new and creative administrative approaches.

Before anything can be achieved, more information about the true cost of liver transplantation is desperately needed. It is puzzling that no formal study has been published since 1983. It would be reasonable to expect a reduction in expenses as large numbers of patients are treated in the major transplantation centers, but evidence for this is entirely anecdotal. The next step in the evolution of liver transplantation may depend on a scholarly assessment of its fiscal impact on hospitals and the society that supports them.

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