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Medical Progress:

Liver Transplantation

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Abstract

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

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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 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 procedures 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 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 ventilation 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]

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 conduits 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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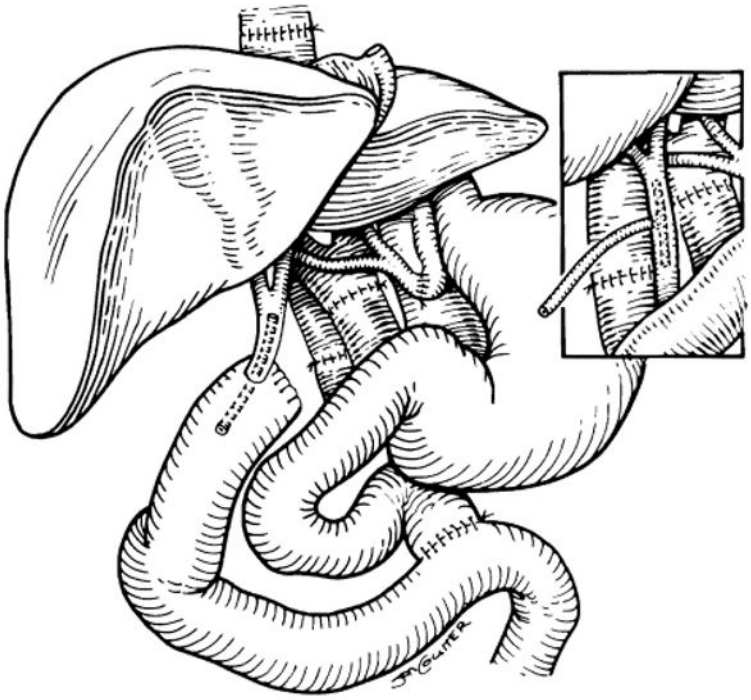

Figure 1. Orthotopic Liver Transplantation

Biliary reconstruction can be accomplished through choledochojejunostomy or duct-to-duct anastomosis (inset).

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

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	Incompletet†	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	l½yr	Cirrhosis	Samuel et al.,[34] Poison 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	4yr*	Cirrhosis, a complica-cation of blood-component therapy	Lewis et al.[40]
Hemophilia B	Factor IX deficiency	Yes	6 mo	Cirrhosis, a complica-cation 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.