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LIVER TRANSPLANTATION

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INTRODUCTION

Liver transplantation has undergone tremendous advances over the past 27 years and has become the accepted treatment for end-stage liver disease and fulminant hepatic failure. Its current success can be attributed to international collaborative efforts to achieve:

1) development of animal models for laboratory investigation of liver disease and liver transplantation
2) understanding of the pathophysiology and natural history of liver disease
3) identification of pathologic criteria of liver disease
4) establishment of multi-organ procurement and preservation techniques
5) standardization of surgical techniques
6) developments in anesthetic management
7) establishment of safe and efficacious immunosuppressive regimens
8) advances in critical care medicine
9) recognition of post-operative complications

The first report of experimental orthotopic liver transplantation was by Dr. Jack Cannon of the University of California, Los Angeles, in 1956.[1] Subsequent experimental efforts in the laboratory resulted in sufficient progress for initiation of human orthotopic liver transplantion in 1963. Seven such

transplants were performed without success until 1967 when the first longterm survival was achieved in Denver, Colorado.[2,3]

In the early years, liver transplantation developed in two directions: auxiliary and orthotopic liver transplantation. Although a number of auxiliary liver transplantations were attempted, almost all failed. However, auxiliary liver transplantation contributed to our knowledge of hepatic physiology, including the importance of splanchnic venous flow in the maintenance of the grafted liver.[4,5] Although Dr. Joseph Fortner reported the first longterm survivor of auxiliary liver transplantation performed at the New York Memorial Hospital in 1972,[6] this represented an exceptional case. Thus, auxiliary liver transplantation was abandoned in favor of orthotopic liver transplantation. More recently there has been a renewed interest in auxiliary transplantation for selected indications.

Prior to 1980, the results of liver transplantation were poor. Although the reasons for this were multifactorial, an important factor was the lack of safe and effective immunosuppressive regimens. The mainstay of anti-rejection therapy included azathioprine, steroids and anti-lymphocyte globulin (Table I). The rates of rejection and infection were high with various regimens employing these agents. Clearly, a better form of immunosuppression was required before liver transplantation could enter its next stage of development.

In 1979, Sir Roy Calne demonstrated the efficacy of a new immunosuppressive agent, cyclosporine A, in 34 patients receiving 36 cadaveric organ allografts[7]. However, the true potential of cyclosporine was only recognized when cyclosporine was combined with prednisone by Starzl and colleagues. Regimens employing cyclosporine allowed a better balance between prevention of rejection and minimizing the liability of infection in the immunosuppressed patient. Better control of rejection and a more manageable post operative course facilitated the rapid progress in the field of liver transplantation. The number of liver transplantations performed each year since 1981 increased tremendously, as did the number of new transplantation centers throughout the United States and the world (Table II).

Immunosuppression entered a new level of sophistication with the introduction of monoclonal antibodies specific for T-lymphocytes for the treatment of severe rejection. One such agent, OKT3, has successfully reversed unremitting rejection in many patients concurrently treated with steroids and cyclosporine, thereby averting retransplantation and even death.

Technical advances have also contributed to the increasing success of liver transplantation. One of the most important advances was the introduction, in 1983, of heparin-free veno-venous bypass.[8] The use of veno-venous bypass during the anhepatic phase has facilitated the maintenance of a stable hemodynamic state

during completion of the recipient hepatectomy and implantation of the new allograft. It has allowed the most critical part of the transplantation procedure to be performed in a calm and safe atmosphere thereby allowing the training of new transplantation surgeons, so important in the world wide dissemination of this procedure. Other technical advances have included standardization of the biliary tract reconstruction, segmental liver transplantation, new applications of auxiliary liver transplantation, liver transplantation in continuity with other abdominal organs and advances of the procedure in the very small pediatric patient. In addition, employment of vascular allografts has allowed transplantation to be performed in patients with portal vein thrombosis as well as inadequate hepatic arterial flow.

Liver transplantation is a multidisciplinary effort which has required advances in all fields of medicine. The technical growth has been paralleled by advances in anesthesiology, critical care, hepatology, radiology, blood banking, as well as most other medical specialties.

The standardization of the techniques of organ retrieval and the ability to procure multiple organs from a single donor have also been essential for the growth of liver transplantation. Furthermore, recent introduction of the new preservation solution, the University of Wisconsin Solution, has extended liver allograft preservation to 24 hours.[9] This has allowed more organs to be

retrieved from greater distances and has contributed to an increased donor pool.

Liver transplantation has contributed to the understanding of normal hepatic physiology as well as to the pathophysiology of liver disease. Through the correction of specific inborn errors of metabolism, the genetics and molecular biology of many of these diseases have been defined. Through the study of the effects of the disease process on the new allograft, hepatology has been advanced. However, the most important contribution of liver transplantation is its ability to cure many hepatic diseases for which there had been no alternative treatment. Patients with liver failure have been restored to health and returned to a normal, active, and good quality of life.

INDICATIONS

As the field of liver transplantation progressed from an experimental procedure to standard therapy, its indications markedly expanded. Early on, liver transplantation was predominantly offered to patients with unresectable hepatic malignancies, patients in fulminant hepatic failure, or patients who were so critically ill and debilitated from their hepatic failure that liver transplantation was the only alternative to

imminent death. In such patients, the outcome and survival rates were poor.

As the field progressed to its present state, the indications for liver transplantation expanded to include a large variety of liver diseases (Table III). The survival and quality of life resulting from liver transplantation for most of these indications is excellent, however, some indications are still evolving.

Adult

The three most common indications in adults include postnecrotic cirrhosis, primary biliary cirrhosis, and sclerosing cholangitis. The decision regarding the timing of transplantation for patients with these indications can often be difficult. Ideally, the patient should undergo transplantation at such time when morbidity and mortality would be minimized yet it is apparent that the patient's long term survival is jeopardized by the liver disease. Although much is known about the natural history of these diseases, there is no substitute for early referral and close monitoring for subtle signs of deterioration.

Hepatic malignancy has become a much less common indicaton for transplantation, the major reason being the poor long term survival. In most cases, there is an early recurrence of the malignancy with rapid progression to death. This has led to a closer look at the various types of malignancies for which

transplantation has been performed. For certain pathologic types there is a better prognosis than for others. Those malignancies with a better outcome include the fibrolamellar variant of hepatocellular carcinoma, epithelioid hemangioendothelioma and the coincidental tumor found at the time of transplantation for chronic liver failure. There have also been occasional long term survivors found with other types of malignancies including hepatocellular carcinoma.[10]

The reduced survival after transplantation for most hepatic malignancies compared to non-malignant diseases has led to variations in policy among different centers. Very careful evaluation is required preoperatively to determine the exact extent of the disease. In some centers this includes an exploratory laparotomy and lymph node sampling prior to consideration of transplantation. Various ancillary treatment modalities are being explored and it would appear that the future of transplantation for malignancies must include combinations of perioperative and adjuvant chemotherapy.

Cholangiocarcinoma has been found to rapidly recur following orthotopic liver transplantation.[10] New and much more aggressive methods of surgical treatment for this disease are being explored. Recently, a new approach employing an upper abdominal exenteration, the so called cluster procedure, with replacement of a liver or liver and pancreatic graft has been employed.[11] The results for

this procedure are preliminary and long term follow-up will be required to determine the efficacy of this approach.

Another important indication for which institutional policies have varied is for the patient with cirrhosis secondary to infection with hepatitis-B virus. The one and five year survival rates for patients who are surface antigen positive have been uniformly inferior to that of other liver diseases.[12] Recurrence is the rule. However, the natural history following transplantation spans a spectrum from fulminant hepatitis to recurrent bouts of hepatitis with spontaneous resolution to recurrent cirrhosis requiring retransplantation. There are, however, a large number of long term survivors and, accordingly, attention is being focused on the perioperative management of these patients. Various protocols have been employed to prevent recurrence including the use of interferon, hyperimmune hepatitis B immunoglobulin and monoclonal antibodies against hepatitis B surface antigen. Prevention of allograft infection and management of patients with recurrence will remain important topics of future research.

Another controversial indication is alcoholic cirrhosis. The determination of candidacy relies heavily on the psychosocial evaluation. Cardiovascular evaluation to assess cardiomyopathy is also an important focus of the evaluation procedure. Although the accompanying physical and psychiatric stigmata of patients with

alcoholic cirrhosis were once believed to result in poor outcome, it has been shown that success is common with proper patient selection. Indeed, recent results for transplantation of alcholic cirrhosis have been as good as for other adult disease indications.[13]

Transplantation is the therapy of choice for acute and subacute fulminant hepatic failure due to a variety of etiologies. This is the most dramatic of all indications for transplantation. The decision to undertake transplantation must be made rapidly as these patients can progress rapidly to grade 4 coma, at which point transplantation may have a poor outcome.[14] The decision is facilitated when there is evidence of rapid progression of encephalopathy and/or coagulopathy, as well as hemodynamic instability. Once it becomes clear that spontaneous recovery is unlikely, transplantation should be undertaken rapidly to prevent a poor neurologic outcome or death.

Through modification of genetic disease processes, transplantation has provided benefits to patients and increased understanding of hepatic physiology. Transplantation has been performed for the purpose of treating liver failure, as well as for the correction of a single metabolic error in selected diseases. Metabolic diseases which have been cured by liver transplantation include Wilson's disease, Tyrosinemia, Alpha-1-Antitrypsin deficiency, galactosemia, Crigler-Najjar type I,

hyperlipoproteinemia types II and IV, protoporphyria, sea-blue histiocyte syndrome, and several glycogen storage diseases. Equally striking is the correction of a number of coagulation defects following liver transplantation.

Pediatric

The medical indications for adult and pediatric liver transplantation are comparable. Any child with end-stage liver disease should be considered as a potential candidate for liver transplantation. Transplantation is indicated for life-threatening bleeding, recurrent episodes of encephalopathy, coagulopathy, malnutrition, severe jaundice, profound growth retardation or metabolic bone disease. When it is clear that survival greater than one year is unlikely, considerations for evaluation and candidacy for transplantation should be initiated. This is particularly important for small children for whom donor organ availability may be limited. Accurate assessment of the individual child's probability of survival may be difficult or impossible. If liver function is stable, specific therapy (i.e., sclerosis of esophageal varices, diuretics, fluid restriction, salt restriction, etc.) may be more appropriate. However, if liver function is progressively deteriorating, then transplantation therapy is indicated. The possibility of future transplantation must be considered whenever interventions are discussed. Any intervention which may jeopardize suitability for transplantation should be carefully contemplated. For example, a failed portacaval shunt

with thrombosis of the portal system may make liver transplantation technically impossible.

Numerous hepatic diseases in children have been successfully treated with liver transplantation. In all series, extrahepatic biliary atresia remains the most frequent pediatric diagnosis requiring transplantation.[15-19] Controversy surrounds the utility and the role of the Kasai portoenterostomy in the treatment of this disorder. In a significant percentage of individuals (25-30%), if surgery is performed within the first two months of life, biliary drainage and successful outcome may be achieved. However, multiple attempts at revisions to establish bile flow, peritonitis, and intraabdominal hemorrhage all contribute to technically more difficult surgery and a reduced likelihood of success if transplantation becomes necessary. Therefore, an attempt to establish bile flow before two months of age in children with extrahepatic biliary atresia should be made by surgeons experienced in the Kasai procedure. If bile drainage is not established, evaluation for liver transplantation should quickly ensue. Even if bile drainage is incomplete, the Kasai procedure may facilitate improved survival by allowing the child to grow thus increasing the availability of suitable donor organs.

Disorders in the formation and development of the biliary ductal system comprise the majority of the pediatric patients who undergo orthotopic liver transplantation. While extrahepatic

biliary atresia represents the most common indication, Alagille's syndrome (arteriohepatic dysplasia), Bylers disease, and nonsyndromatic intrahepatic biliary hypoplasia entities are included in this category.[20]

The next largest category requiring liver transplantation in pediatric patients consists of genetic disorders of metabolism.[21-23] The more common inborn errors of metabolism requiring liver transplantation include alpha-1-antitrypsin deficiency, Wilson's disease, tyrosinemia, glycogen storage disease, and galactosemia. Rarer metabolic disorders for which hepatic transplantation has been utilized include Crigler-Najjar syndrome type I, hyperlipoproteinemia types II and IV, protoporphyria, and the sea blue histiocyte syndrome.[24,25]

Alpha-1-antitrypsin deficiency is inherited as an autosomal recessive disorder with a frequency of 1 in 2,000 individuals. While not all homozygous individuals develop liver disease, of those who develop liver disease, the majority will demonstrate cholestasis during infancy. Most of these infants will subsequently become anicteric, but the stigmata of significant liver disease will eventually ensue, usually during adolescence or early adulthood.

Liver transplantation corrects the enzyme deficiency with the recipient acquiring the protease inhibitor type of the donor.

Serum alpha-1-antitrypsin levels quickly return to the normal range after transplantation.[21] Long-term follow-up of children transplanted for alpha-1-antitrypsin deficiency has failed to disclose any evidence for pulmonary or other organ disease.

Evaluation for liver transplantation should proceed in any individual with the diagnosis of alpha-1-antitrypsin deficiency who manifests any signs of significant liver disease or demonstrates decompensation. While infusion of alpha-1-antitrypsin to adults with pulmonary complications of the disorder has been useful, this approach is not beneficial for hepatic complications of the disorder. Since patients with mild liver disease at presentation may decompensate rapidly, careful observation and prompt referral for transplantation should be considered if jaundice or mild coagulopathy develop.

Wilson's disease remains one of the few hepatic disorders in which early diagnosis can lead to effective medical therapy employing d-penicillamine or trientine therapy in conjunction with dietary copper restriction. Transplantation should be reserved for those patients with Wilson's disease who present with fulminant hepatic failure or failure of medical therapy. Transplantation cures the disordered copper metabolism. Transplantation should be undertaken prior to the development of significant neurologic deterioration, although reversal of severe neurologic deficits has

been observed following transplantation in Wilson's disease patients.

Hereditary tyrosinemia is an autosomal recessive disorder with a frequency of one in 100,000 births. The disease may present either acutely in the first weeks of life with fulminant hepatic failure, or after six months of life with cirrhosis, renal tubular defects, rickets and failure to thrive. Onset disease after 6 month of age has been associated with the development of hepatoma. Serum tyrosine and methionine levels are markedly elevated and succinylacetone is present in the urine. Transplantation results in normalization of serum tyrosine levels and prevention of hepatoma development; however, the effect on the status of metabolic derangements in other organs is not well characterized.

Glycogen storage diseases have been successfully treated by orthotopic liver transplantation.[25] Long-term follow-up has demonstrated normalization of glucose homeostasis.

While in adults posthepatic cirrhosis is the most common indication for liver transplantation, in the pediatric group this is a much less common indication. Infants in this group may include those with the diagnosis of neonatal hepatitis, hepatitis B and non-A, non-B hepatitis. Any child in this group who demonstrates life-threatening complications of the liver disease,

retarded growth or development, or poor quality of life should be evaluated for liver transplantation.[16-18]

Acute fulminant hepatic failure signifies another group of pediatric patients who may undergo hepatic transplantation.[26] This may be the result of a toxin-induced hepatic failure, a viral hepatitis, or a metabolic disorder (Wilson's disease, tyrosinemia). Frequently, the etiologic agent remains unidentified. Development of hepatic encephalopathy in conjunction with coagulopathy is an immediate indication for referral to a transplant center. Previous reports of poor results in patients with fulminant hepatic failure may be the consequence of waiting too long and attempting transplantation in individuals in deep coma.

Hepatic transplantation has also been utilized in the therapy of unresectable hepatic malignancies in children.[27] The primary tumor type has been hepatoblastoma. As in adults, survival rates have not been encouraging and the future approach will include the use of peri-, intra- and post-operative chemotherapy.

Numerous other disorders in children associated with liver failure have been treated utilizing hepatic transplantation. For example, hemochromatosis, cystic fibrosis, sclerosing cholangitis, drug-induced cirrhosis, autoimmune hepatitis, and Budd-Chairi syndrome may all occur in pediatric patients and necessitate a transplant evaluation and procedure.[16-19] The indications and

contraindications for these patients are similar to those already discussed. Of course, each patient requires an individual assessment as circumstances will vary for each.

EVALUATION

The evaluation process is directed towards the determination of the need and urgency for the performance of an orthotopic liver transplant as well as the feasibility of performing this procedure. The need and urgency are determined by obtaining a careful history, performing a physical examination and obtaining various laboratory data as well as reviewing any biopsies which may have been obtained in the past. The feasibility determination requires evaluation of the entire medical status of the patient including the cardiovascular, pulmonary and renal systems. Furthermore, the use of various radiologic techniques permits definition of the vascular anatomy and size of the liver that are required for liver transplantation.

As with approaching any medical disease, a careful history must first be obtained. Specific areas to be defined include: possible etiologies of the liver disease, prior complications secondary to liver disease, previous surgical procedures and the current disability of the patient. Liver disease resulting from

prior alcohol or IV drug abuse will require further evaluation. A psychiatric and sociologic evaluation should be performed to ascertain the patient's determination to abstain from further substance abuse, as well as the patient's ability to comply with the postoperative medication regimen and medical follow-up.

The specific areas of concern regarding complications of the liver disease include episodes of encephalopathy, ascites, edema, gastrointestinal bleeding, infections (particularly spontaneous bacterial peritonitis), and inability to perform one's daily routine. Prior complications in conjunction with ongoing hepatic disease, demonstrated by decreased synthetic function, are clearly indications for liver transplantation. The urgency must be determined based on the severity of the complications as well as the presence of current disabilities.

Necessary laboratory data include a complete blood count, with special attention to signs of hypersplenism, and chemistries to define the electrolyte status and liver function. Elevated bilirubin levels indicates impaired hepatic excretory function while an elevated protime and decreased serum albumin demonstrate impaired hepatic synthetic function. Hepatitis serologic tests are obtained to identify those patients who are hepatitis-B surface antigen positive as these patients will require concurrent medical treatment in addition to liver transplantation. A CEA and an alpha-fetoprotein are obtained and, should either one be elevated,

a search for occult malignancy or hepatocellular carcinoma must be undertaken. The CEA is especially important in those patients with sclerosing cholangitis as a 10% incidence of a concomitant cholangiocarcinoma has been reported.[28] A 24 hour urine collection for creatinine clearance is obtained to define the presence and degree of renal dysfunction, which may require adjustments in the dosage of postoperative immunosuppressive medications.

Various bacterial, viral and fungal cultures and titers are obtained to establish a baseline for each patient as well as to identify those infectious disease processes which may require treatment prior to transplantation. A tuberculin skin test is performed with an appropriate control panel. In addition, an HIV antibody test is obtained.

Additional laboratory examinations, aimed at the determination of the etiology of the liver disease, are tailored for each individual patient. These include antimitochondrial antibody, anti-nuclear antibody, anti-smooth muscle antibody, ceruloplasmin, urine copper, alpha-1-antitrypsin level and phenotype, and drug screen.

Cardiopulmonary evaluation is individualized for each patient. An arterial blood gas and chest x-ray are routinely obtained. Should there be an indication, such as hypoxemia, history of extensive smoking and/or prior pulmonary disease, pulmonary

function tests are also performed. An EKG is routinely obtained and once again should there be an indication, a cardiac stress test, 2-D echocardiogram and/or coronary angiogram may be required.

The radiologic evaluation is primarily directed towards the elucidation of the technical feasibility of transplantation as well as the collection of data which will be required for suitable donor-recipient matching. Doppler ultrasonography is performed to determine the patency of the hepatic veins, hepatic artery and particularly the portal vein as well as the presence of biliary tract disease. Should portal vein patency be in question, an angiogram must be performed to define the portal system anatomy. Although previously thought to be a contraindication to orthotopic liver transplantation, portal vein thrombosis is now no longer an absolute contraindication. The presence of an adequate superior mesenteric vein, however, is required for the performance of the procedure.

A CT scan of the head and abdomen are performed. The presence of intracranial lesions must be determined prior to undertaking the transplantation procedure as the presence of any vascular anomaly may lead to catastrophic events intraoperatively. Furthermore, the presence of encephalopathy requires the exclusion of other causes of altered mental status. The CT scan of the abdomen will demonstrate any intra- or extrahepatic malignancies and provide the

liver volume which is so important in the donor-recipient matching.[29]

We are finding an increasing value in the use of magnetic resonance imaging in the evaluation process. This procedure provides us with similar data as the CT scan of the abdomen and demonstrates the presence of flow in the portal vein. With further studies confirming the reliability of this modality, MRI may become the primary radiologic test in the evaluation of these patients.

Patients with sclerosing cholangitis are scheduled for percutaneous transhepatic cholangiography and brush biopsies. As previously stated, there is a 10% coincidence of cholangiocarcinoma. Due to the dismal results of orthotopic liver transplantation for patients with a biliary tract malignancy, it is important to evaluate its presence prior to transplantation. In the presence of cholangiocarcinoma new alternative treatment methods, such as the cluster procedure, may prove to be of value.

Endoscopic evaluation of the upper gastrointestinal track is performed to determine the presence of and potentially treat esophageal varices. Colonoscopy is performed in patients over 40 years.

Once the evaluation process is completed, the final determination for the need and urgency for transplantation is made

by a multidisciplinary institutional selection committee. Transplantation is indicated in the presence of end-stage liver disease manifested by: encephalopathy, ascites, impaired renal function, gastrointestinal bleeding, inability to perform one's daily routine, and decreased hepatic synthetic function. In the presence of these factors, a determination of feasibility is rendered. Currently, the contraindications for orthotopic liver transplantation are:

1) presence of active infection exclusive of the hepatobiliary system
2) acquired immune deficiency syndrome
3) technical impossibility
4) multiorgan system failure which is irreversible by orthotopic liver transplantation
5) irreversible brain damage
6) inability to comply with the postoperative medication and medical follow up regime.

The evaluation and selection process for orthotopic liver transplantation has undergone major extensions to include aged patients, small infants, critically ill patients, and patients with portal vein thrombosis.

There are currently no age limits set for patients to be considered for transplantation. The oldest patient to have received an orthotopic liver transplant is a 76 year old women with primary biliary cirrhosis. Well selected patients over 60 years of age have been shown to have a survival rate similar to that of younger patients.[30]

Improvements in the technical aspects of the transplant procedure have made it feasible to transplant very small infants. The youngest patient to have received a liver is a three week old infant. Children under the age of one can now be successfully transplanted with a good survival rate.[31]

Advances in critical care medicine, anesthesiology as well as other medical specialties have made it possible to maintain and transplant critically ill patients. Although patients who are ventilator dependent, require pressors, dialysis or are in coma preoperatively constitute a high risk population, many of these patients can be salvaged through transplantation and can go on to enjoy long-term survival with excellent quality of life.

PREOPERATIVE MANAGEMENT

The increased success of orthotopic liver transplantation has led to expansion of its indications and efforts to optimize timing for transplantation. The concept that an optimal time exists for transplantation, after which patients suffer increased morbidity or mortality, has now been validated.[32] Clinical and laboratory factors correlated with the success of transplantation have been codified into a risk stratification scoring system. Risk factors include degree of encephalopathy, presence of ascites, degree of malnutrition, serum bilirubin, age, requirement for transfusion during transplantation and degree of coagulopathy. A prospective analysis from the University of Nebraska showed that patients with a low risk score had an actuarial survival of 90.5% for one year. Patients with intermediate and high risk scores had significantly diminished actuarial survivals of 85.2% and 44.5%, respectively.

Although these results indicate that patients should be transplanted prior to the development of a high risk profile, many patients continue to be referred late in the course of their illness and require meticulous management in the preoperative phase to countermand the adverse impact of the complications of terminal liver disease prior to transplantation. Table IV lists the most significant management problems encountered in this preoperative population.

Hepatic Encephalopathy

The degree of portal systemic encephalopathy at the time of transplantation is inversely related with survival. Stratification of 115 adult patients with chronic liver disease transplanted between 1985 and 1988 at the University of Nebraska showed actuarial survival rates of 89.6% in the absence of preoperative encephalopathy. The actuarial survival rate diminished to 78.6% in patients with mild encephalopathy (stages I-III), and 33.6% in patients with severe encephalopathy (stages III-IV).

The initial approach to management requires evaluation of reversible factors that may have precipitated or intensified encephalopathy. These factors include: infection and fever, hypokalemia, metabolic alkalosis, gastrointestinal bleeding, sedatives or narcotic analgesics, and constipation. Once precipitating factors are identified, specific measures should be taken to alleviate them. After treatment of precipitating factors, patients with stage I and II encephalopathy should receive lactulose orally in a dose sufficient to produce two to three semi-soft bowel movements per day.[33] For patients with stage III or IV encephalopathy, lactulose should be administered if intestinal peristalsis is present. Endotracheal intubation is required to protect the airway from possible reflux and aspiration pneumonia in patients with stage III-IV encephalopathy. Oral or nasogastric administration of neomycin may also be utilized. However, the

long-term use of neomycin should be avoided because of the chronic sequella of mid-range hearing loss.

Although reports indicate that the administration of branch chain amino acids may be of benefit in the treatment of chronic portal systemic encephalopathy,[34] studies evaluating this modality in patients awaiting transplant have not been reported. Similarly, studies using flumazenil to antagonize the GABA-benzodiazepine receptor complex have been reported in only a few patients with fulminant hepatic failure prior to transplant.[35] Since these therapies do not improve hepatic function, they should have minimal impact on prognosis following transplantation.

Infection

Localized and systemic bacterial infections are common complications of end-stage liver diseases in adults. Such patients are immunocompromised, both by their liver disease and the commonly accompanying state of malnutrition. Typical signs and symptoms, as well as laboratory tests indicative of infection, may be subtle or absent. Thus, the clinician must be alert to the possibility of infection and prepared to treat promptly with minimal provocation.

Bacterial peritonitis

Recurrent bacterial peritonitis may develop either insidiously or with evidence of fever, sudden hepatic decompensation or onset

or worsening of hepatic encephalopathy.[36] Abdominal findings of tenderness and rebound are infrequently present. Peripheral leukocytosis may also be absent, especially if a patient is leukopenic on the basis of hypersplenism. The clinical diagnosis is made by a diagnostic paracentesis in which $\geq$ 250 mononuclear cells/mm^3 are present.[37] Although a variety of antimicrobial regimens have been advocated, a recent randomized controlled trial indicated a superiority for treatment with a third generation cephalosporin.[38] Subsequent adjustments in coverage can be made on the basis of culture and sensitivity results. In addition, single antibiotic coverage prevents potential nephrotoxicity associated with aminoglycosides.

Response to therapy can be monitored by subsequent paracenteses showing a substantially diminished total white count and a decreasing proportion of polymorphonuclear leukocytes. Since untreated bacterial peritonitis is an absolute contraindication to transplantation, four to five days of antibiotic therapy with evidence of a clinical and ascitic fluid response are required prior to urgent transplantation. Patients transplanted after this abbreviated course should receive antibiotics postoperatively.

Spontaneous bacterial peritonitis must be distinguished from peritonitis secondary to intestinal perforation. Since patients with cirrhosis have a higher prevalence of peptic ulcer disease and may suffer complications associated with stress ulceration, this

consideration is mandatory. Diagnostic evaluation, therefore, should include an upright PA chest film or decubitus abdominal film to identify free intraabdominal air. Features suggestive of secondary bacterial peritonitis[37] include:

1) a rising ascites neutrophil count 48 hours after the initiation of antibiotic treatment;
2) positive bacterial cultures from the ascitic fluid;
3) multiple bacterial organisms;
4) continued culture positivity despite antibiotic therapy; and,
5) the presence of at least two of three chemical findings (ascitic fluid protein greater than 1 g/dl, glucose less than 50 mg/dl, or lactate dehydrogenase greater than the upper limit of normal for serum).

Further radiologic investigations may be required to identify a perforation of the intestinal or biliary tract.

Ascending cholangitis

Ascending cholangitis is an infrequent complication in adult chronic liver disease, except in patients with sclerosing cholangitis, prior biliary tract surgery associated with the development of secondary biliary cirrhosis, and internal or external biliary prostheses. Clinical signs of cholangitis may be

readily apparent with fever, leukocytosis, abdominal pain and worsening liver tests. However, the presentation may be more insidious. Delay in the treatment of cholangitis predisposes to septicemia and hepatic abscesses, which may preclude transplantation. Thus, aggressive empiric antibiotic therapy is warranted for suspected cholangitis following appropriate cultures of ascitic fluid and blood. In patients with a prior history of cholangitis and several courses of antibiotics, the infecting organisms may include gram-positive cocci, gram-negative enteric bacilli, enterococci and anaerobic species. Hence, initial antibiotic coverage should be broad spectrum. Prophylactic regimens of antibiotics for high risk patients following the resolution of ascending cholangitis may be useful for a limited period of time before a donor organ becomes available.

Other infections

The immunosuppressed nature of end-stage liver disease patients renders them susceptible to a variety of other bacterial, viral and fungal infections.[39] It may also be associated with the reactivation of previously quiescent infections, such as mycobacterium tuberculosis or coccidiomycosis. Changes in mental status or stages of encephalopathy may also indicate meningitis, which must be considered. Bacterial infections of the lung, abdominal abscesses and pyelonephritis require a minimum of seven to ten days of therapy before transplantation. Viral infections, such as herpes simplex types I and II and cytomegalovirus, require

antiviral therapy before and after transplantation. Active mycobacterial infections require prolonged therapy, while a history of untreated infection requires prophylactic treatment.

Ascites

Ascites, refractory to medical management, often necessitates recurrent hospitalization prior to liver transplantation. Massive ascites may be associated with respiratory distress and compromise of the cardiovascular hemodynamics. If unrelieved, these situations may predispose to atelectasis, pneumonia, and azotemia. Patients with tense ascites may be safely managed with a moderate volume paracentesis of one to three liters. The role for large volume paracentesis[40] has not been evaluated in patients awaiting transplantation. However, the potential risks of hypotension and azotemia appear unjustified.

Medical management includes sodium restriction, fluid restriction for hyponatremia, and diuretics if renal function is normal. Diuretic regimens often include spironolactone or amiloride augmented with furosemide or bumetanide. The goal of diuretic therapy should be the maximum loss of one-half kilogram in weight per day. More aggressive diuresis may cause azotemia or precipitate hepatorenal syndrome. For patients who cannot be managed with diuretics, periodic mild to moderate paracentesis and/or infusion of salt-poor albumin (75 to 150 g/day) may be used. If repeated paracenteses are performed, appropriate chemical

studies and leukocyte counts should be ordered with each paracentesis to exclude iatrogenic contamination.

Hyponatremia is the principal electrolyte disturbance accompanying refractory ascites and chronic end-stage liver disease.[40] Restriction of free water intake is often necessary to maintain a serum sodium of greater than 130 mEq/L. Electrolyte replacement intravenously may also be required. Severe hyponatremia is to be avoided because of its effects on the mental status of the patient and its association with central pontine myelinolysis.[41]

Renal Insufficiency

Attention to fluid and electrolyte management, gentle diuresis, and avoidance of large volume paracenteses help prevent prerenal azotemia. If rising creatinine, however, does occur in the face of ongoing diuresis or blood loss, intravascular volume should be aggressively replaced and diuretics discontinued. To evaluate suspected prerenal azotemia, patients should receive a fluid challenge of 500 ml of normal saline intravenously. The concentration of urinary sodium should also be measured; the expected concentration being $\leq$ 5 mEq/L. Failure to reverse the creatinine elevation or rapidly increasing creatinine are indicative of hepatorenal syndrome. Since this syndrome is refractory to medical management in the face of deteriorating liver function, patients awaiting transplantation with this

complication should be maintained on hemodialysis. Typically, patients with hepatorenal syndrome recover normal renal function within days or weeks following successful liver transplantation.[42] However, some patients have prolonged postoperative renal insufficiency that can often be attributed to prior nephrotoxic antibiotics, episodes of hypotension or infusion of radiocontrast dyes. A peritoneovenous shunt should not be performed for hepatorenal syndrome prior to transplant because of unacceptable morbidity.

Chronic renal failure may also be evident in patients awaiting transplantation. Chronic renal failure poses an increased risk for early major bacterial infection, and is associated with increased mortality in liver transplantation.[43] Patients with chronic renal failure should undergo appropriate hemodialysis while awaiting transplantation. Selected patients should be evaluated as candidates for a combined kidney and liver transplantation procedure.

Variceal Bleeding

Recurrent variceal hemorrhage is common in patients awaiting liver transplantation. The frequency of hemorrhage and risks of morbidity and mortality increase substantially with worsening coagulopathy and thrombocytopenia. The immediate goals of therapy are maintenance of intravascular volume with fluids and blood transfusion to maintain cardiac output and renal perfusion.

Further attempts to stabilize or prevent recurrent bleeding may employ intravenous vasopressin, direct tamponade with a Sengstaken-Blakemore tube, sclerotherapy, or rubber band ligation. Uncontrolled bleeding or bleeding from gastric, small bowel or colonic varices require urgent transplantation since medical therapy is ineffective. The role for sclerotherapy or rubber band ligation as prophylaxis for recurrent variceal bleeding for inpatients awaiting liver transplantation remains controversial.[44] Studies of beta blocker therapy in patients with end-stage liver disease awaiting liver transplantation have not been reported.[45]

Malnutrition

Malnutrition in adults undergoing OLT is an adverse prognostic indicator of survival.[32] Malnourished patients are particularly prone to infection and poor wound healing. Malnutrition is to be anticipated in 40-60% of liver patients admitted to hospital.[46] Often, the malnutrition adds to the immunocompromised state of the patients, as evidenced by the high frequency of anergy in malnourished patients with end-stage liver disease. Malnutrition in end-stage liver disease may be multifactorial. Many patients are anorexic or unable to prepare adequate meals. Depending upon the type of liver disease, its complications, or necessity for hospitalization, excessive caloric expenditures may also be present. In patients with chronic cholestatic liver disease, fat malabsorption is common and may limit enteral nutritional capacity. Reduction in dietary fat to 40 grams per day or use of medium chain

triglycerides may be of benefit. Such patients should be supplemented with parenteral or water soluble forms of the fat soluble vitamins A, D, K, and E.

The goal of nutritional therapy is to provide adequate calories while maintaining appropriate restrictions of total protein (for patients with chronic encephalopathy) and sodium (for patients with refractory ascites). A full nutritional analysis should be made by a dietician. Enteral nutrition is preferable; however, peripheral venous or central venous parenteral nutrition may be required.

DONOR SELECTION

The transplantation process begins with the finding of a suitable donor. The criteria for donor selection are variable amongst different institutions and are rapidly changing. As liver transplantation becomes more universal and new programs become established, each program will determine their specific criteria for donor acceptance. It is not uncommon for a new program to use more stringent criteria for the blood pressure, arterial oxygenation, use of pressors, liver function tests, cause of death, age, as well as other factors. However, the donor shortage has lead to liberalization of these criteria. In more established programs where the recipient waiting list may be long, it has been

shown that with liberalized criteria, the long-term outcome can be equally successful.[47]

The two major features which are required for appropriate donor-recipient matching are size and blood type; however, even these criteria are not absolute. Appropriate size match requires the following information:

1) recipient height and weight
2) donor height and weight
3) recipient chest circumference
4) donor chest circumference
5) recipient liver volume, calculated via radiologic techniques
6) estimated liver volume of the donor

By using these figures, an appropriate size match can usually be made. One must keep in mind that, depending upon the liver disease, the recipient's liver volume may often be much smaller than the volume that can be placed in the hepatic fossa. A recipient with a small, shrunken liver who has a long history of ascites, can certainly take a larger liver than that calculated by his own volume. In these instances, it is important to have the height, weight and chest circumference of the recipient more closely match those of the donor.

In the case of the stable candidate, one can usually wait for a donor organ of the appropriate size. This becomes more difficult when faced with a critically ill patient or a small child. In these cases, it may be impossible to find an appropriately sized organ prior to further deterioration of the recipient. It is for this reason that size criteria has been liberalized to include the use of segmental livers which will be discussed later in this text.

Although transplantation of ABO incompatible kidneys has been shown in many cases to result in hyperacute rejection, this has not been the case in liver transplantation. Despite the absence of hyperacute rejection, the survival for ABO matched grafts still remains significantly higher than for ABO incompatible or ABO mismatched but compatible grafts.[48] In addition, in the presence of an ABO mismatch, a graft vs. host reaction may develop between two to three weeks post transplantation. This is manifested by a hemolytic anemia which is usually mild and resolves spontaneously. However in some cases, this reaction may be severe enough to warrant retransplantation.

Due to the decreased survival rates and the potential for graft vs. host reactions, blood type remains an important criteria in donor-recipient matching. Once again, this is not an absolute criteria and ABO matching may be waived in the face of a severely ill patient.

Historically, due to the urgency imposed by a short cold storage time, donor-recipient crossmatching has not been possible in liver transplantation. Retrospective review of donor specific crossmatch has, however, revealed no significant effect on graft survival. The presence of a positive crossmatch or a high panel reactive antibody (PRA) has not been shown to correlate with an increased graft loss due to rejection.[48]

HLA matching has also been studied retrospectively and histocompatibility has not been shown to increase graft survival.[48] Clearly, as our ability to preserve grafts for longer periods becomes feasible, it will become increasingly important to re-examine the effects of crossmatching and HLA matching on graft survival.

In the most perfect of circumstances, it would be preferable to use organs from only young hemodynamically stable donors with normal liver function tests. The shortage of donor organs as well as the urgency of transplantation in critically ill patients has made this situation impossible. Fortunately, however through the use of imperfect donor organs, it has been shown that standard criteria for donor selection are not absolute and with some relaxation in the criteria, a good longterm outcome can still be obtained.

Upper age limits are increasing as we find satisfactory function obtained from donors greater than 50 years of age with otherwise satisfactory criteria.[50] Acceptable arterial blood gases, as well as hemodynamic status, vary from institution to institution. In the face of a questionable donor, it is always preferable to assess the liver intraoperatively. Much can be learned by direct examination of the consistency and color of the liver. Furthermore, the bile can be inspected at the time of bile duct transection. With the availability of the University of Wisconsin solution, livers can be preserved for 24 hours. This allows the procurement team to harvest a questionable liver and perform and evaluate a liver biopsy prior to undertaking the recipient operation. Through this method, many otherwise wasted organs can be salvaged and demonstrate good function.

Despite liberalization of donor selection criteria, there do remain absolute contraindications to the use of an organ. These include:

1) absence of heartbeat
2) presence of extracerebral malignancy
3) positive HIV antibody
4) positive hepatitis antigen status
5) systemic sepsis
6) presence of known liver disease
7) presence of specific toxins

Several other variables including liver function tests, fluid and electrolyte status, use of pressors and past medical history must all be considered in donor selection.

In the final analysis donor selection will vary from institution to institution and will depend heavily upon the judgement of the transplantation team. There is currently a search for more objective criteria for the prediction of liver function. One test which is currently being investigated is the Lignocaine Metabolite Formation (MEGX) Test. Preliminary data have demonstrated that levels of MEGX following low dose infusion of Lignocaine can be used as a predictor of liver function.[51] A closer look at this test will be required to determine its reliability. Clearly, a search for objective criteria will certainly be in the future of liver transplantation.

SURGICAL ASPECTS

Donor Hepatectomy

The first step in the performance of a liver transplantation is the procurement of the hepatic allograft. Coordination and cooperation are required among the various surgical teams to ensure the successful procurement of multiple organs from a single donor. Due to significant variations in technique for organ procurement

among different transplant centers, the teams should discuss the methods and time requirements of the individual procedures prior to undertaking the operation, in order to assure optimal procurement of each organ with minimal ischemia and injury. According to the preservation times which each organ can sustain, a priority order has been established for removal of organs once the circulation has been arrested. The heart and lungs are removed first, followed by the liver, and finally the kidneys.

A mid-line incision extending from the suprasternal notch to the pubic symphysis with good retraction provides sufficient exposure and access to the thoracic and abdominal organs. Upon entering the abdominal cavity, the different organs are carefully inspected to assess suitability for transplantation. This comprises evaluation of color, consistency, and size of the various organs. The liver is mobilized by dividing the falciform ligament, left triangular ligament, and gastrohepatic ligament. When dividing the gastrohepatic ligament, it is important to check for the presence of a left hepatic artery arising from the left gastric artery. A left branch is present in approximately 15 percent of donors and if found, must be preserved. The posterior aspect of the porta hepatis should also be inspected for the presence of a right hepatic artery originating from the superior mesenteric artery. Present in approximately 10 percent of the donors, this branch can usually but not always be palpatated and, if present, must be preserved to assure the viability of the liver.

Several techniques have been developed for liver procurement and the choice of technique depends upon the preference and experience of the recovery team as well as the hemodynamic stability of the donor.[52,53] The three techniques currently employed consist of:

1) the classic technique
2) the standard technique
3) the rapid-flush technique

These techniques differ in the amount of dissection, especially of the hepatic hilum, prior to circulatory interruption. A long preliminary dissection may be time consuming and may require blood transfusions. It will, however, require a much less difficult and time consuming extraction once the liver is perfused and cooled after circulatory arrest. Therefore, this is only suitable for a very stable donor. On the other hand, when there is less preliminary preparation, more dissection is needed after the liver has cooled and this requires a greater degree of skill and expertise for safe removal of the liver.

The three procedures have two common principles: the rapid and adequate core cooling of the liver following circulatory interruption, and preservation of all hepatic structures, including anomalous blood vessels.

Classic technique

This original technique is characterized by a thorough dissection of all the hepatic vessels. All the hilar structures, including the bile duct, hepatic artery, portal vein, and branches of the celiac trunk, are dissected. The left gastric and splenic arteries are ligated and divided. The celiac trunk and abdominal aorta are dissected. The superior mesenteric artery is identified and encircled at its origin. The liver is pre-cooled with cold solution through a cannula inserted in the splenic vein. The supraceliac aorta is encircled in preparation for cross-clamping. The infrahepatic vena cava, as well as the renal veins, are isolated. The distal aorta and inferior vena cava are both cannulated after full systemic heparinization. Following circulatory interruption, the liver is rapidly cooled through the cannulae placed in the aorta and the splenic vein. Following cooling, the liver can be removed with a minimum of further dissection.

Standard technique

The standard technique (Figure 1) requires far less dissection than the classic technique. The hilum is freed by dividing the bile duct, and right gastric and gastroduodenal arteries. The left gastric and splenic arteries are ligated and divided distally. The portal vein is identified at its confluence and the splenic vein prepared for cannulation. The supraceliac aorta is identified and prepared for cross-clamping. The distal aorta is dissected and

cannulated after systemic heparinization. Following circulatory interruption, the supraceliac aorta is cross-clamped and the intrathoracic vena cava divided. The liver is then rapidly cooled and the hepatectomy is performed. The superior mesenteric artery is approached by retracting the distal pancreas and, once identified, it is dissected down to the aorta. It is carefully inspected for the presence of a right branch and, depending on the anatomy, is either included or excluded in the aortic patch encompassing the celiac trunk. The infrahepatic vena cava is then divided allowing the liver to be removed.

Rapid flush technique

This technique requires the least time for preliminary dissection and is therefore suitable for unstable donors. The inferior mesenteric vein is dissected and cannulated. The distal aorta is then dissected and cannulated after heparinization (Figure 2). The supraceliac aorta is prepared for cross-clamping prior to cannulation of the distal aorta. The remainder of the dissection is performed after circulatory interruption and cooling. The preparatory steps may take from five to fifteen minutes. However, due to the minimal amount of previous dissection, this technique demands more skill and experience in the performance of the hepatectomy. Following division of the intrathoracic cava and cross-clamping of the supraceliac aorta, the liver is rapidly cooled and hepatectomy undertaken. The right gastric and gastroduodenal arteries are divided to free the hepatic artery and

the bile duct is divided. The portal vein is identified at its confluence, then the splenic vein and superior mesenteric vein are divided to free the portal vein. The left gastric and splenic arteries are divided. The superior mesenteric artery is approached in the same way as in the standard technique and an appropriate patch of aorta encompassing the celiac axis is removed. Once again, the infra-hepatic vena cava is divided and the liver removed with a cuff of diaphragm.

The iliac arteries and veins are routinely recovered after nephrectomy in the event that venous or arterial grafts will be required during the recipient liver procedure. Portions of spleen and mesenteric lymph nodes are removed for the purpose of donor-recipient crossmatching.

The remaining preparations of the donor liver prior to implantation are performed on the backtable at the recipient hospital. The liver is carefully prepared by completing the full dissection of the hepatic vasculature and performing any hepatic arterial reconstruction for anomalies. For livers with anomalous left gastric or superior mesenteric arteries, a single common arterial channel is created using various techniques in order to facilitate anastomosis to the recipient artery.[54,55]

Recipient Operation

The recipient procedure is comprised of the following stages:

1) Hepatectomy
2) Liver implantation
3) Hemostasis
4) Bile duct reconstruction

The completed procedure (Figure 3) consists of four vascular anastomoses and one biliary anastomosis.

Hepatectomy

The vast majority of liver transplants have been performed in an orthotopic position, thus, the first step is the recipient hepatectomy. The recipient surgeon must plan the hepatectomy based on individual considerations. These considerations include: previous upper abdominal surgery, previous episodes of spontaneous bacterial peritonitis with resulting adhesions, the nature of the liver disease, patency of the portal vein, and the presence of portal systemic shunts.

In order to devascularize the liver, the initial dissection is carried out in the hilum. With the exception of malignancies, the bile duct and the hepatic artery should be transsected as proximal to the liver as possible to facilitate their reconstruction. The portal vein is skeletalized and prepared for

veno-venous bypass. The remaining liver attachments can be divided, before or during veno-venous bypass, depending on the presence of coagulopathy and/or diffuse collaterals. A difficult hepatectomy can result in significant blood loss, therefore achieving hemostasis during the hepatectomy is essential in maintaining the stability of the recipient.

Veno-venous bypass

During the final stages of the recipient hepatectomy and ensuing liver implantation, the recipient portal vein and inferior vena cava are cross-clamped, diminishing blood return to the heart. Portal vein occlusion results in splanchnic hypertension, congestion of the bowel, increased lactate concentrations and bleeding in the areas of dissection. Caval occlusion leads to renal hypertension, venous stasis and decreased blood return to the heart. Since 1982, the use of heparin-free veno-venous bypass has significantly improved these problems.[8] Cannulae are inserted into the portal vein and inferior vena cava via the femoral vein. An atraumatic centrifugal pump channels blood through these cannulae back to the heart via a cannula inserted in the axillary vein (Figure 4). Veno-venous bypass has facilitated the maintenance of recipient stability during this very critical time period. Good hemostasis is more readily achieved during the anhepatic phase because veno-venous bypass allows the surgeon time to oversew any raw surfaces created during the hepatectomy. Use of veno-venous bypass reduces postoperative complications, including renal failure

and sepsis, and allows a more rapid return of bowel function. Veno-venous bypass is now used routinely in most adult and pediatric patients weighing over thirty kilograms.

In some instances, the retrohepatic vena cava can be completely preserved. This offers a further advantage in the maintanence of blood return to the heart and can be particularly useful for small pediatric recipients whose size makes the use of bypass practically impossible. Some adult recipients can also benefit from preservation of caval flow, i.e. those with portal systemic shunts who do not require portal bypass, or in cases of significant mismatch in the size of the donor and recipient organs. In the presence of severe portal hypertension in the retroperitoneum, this technique allows this area to remain intact. This is important for older patients and those with cardiac instability. In such cases, only suprahepatic vena cava anastomosis is performed and the donor infrahepatic cava is ligated. This technique has been termed the "piggyback" technique.[56]

Graft revascularization

Anastomosis of the vena cava above and below the liver is performed first. While the lower caval anastomosis is being sewn, the liver is flushed with cold saline solution to remove the highly concentrated potassium contained in the preservation fluid, and air from the major veins. Portal bypass is then interrrupted and the

portal vein anastomosis is performed. It is extremely important to accurately match the lengths of donor and recipient portal veins. This will prevent kinking and possible thrombosis. At this point, the liver is usually revascularized on portal flow only, major bleeding sources are controlled, and the veno-venous bypass is terminated. The hepatic arterial anastomosis is then performed, preferably by anastomosing the recipient common hepatic artery to the donor's celiac trunk, although there are many variations. An accurate match between donor and recipient hepatic arteries is essential. To prevent twisting and assure an adequate arterial blood flow to the liver, the lengths and positions of these arteries must be carefully examined prior to anastomosis.

When the recipient artery is severely diseased, injured, or exhibits poor inflow, an alternative source of inflow must be used. In most cases an aortohepatic graft is employed. A donor iliac graft is anastomosed to the infrarenal aorta, tunneled either posteriorly or anteriorly to the pancreas, and anastomosed to the donor artery in the hilum. Other infrequent alternatives in cases where access to the infrarenal aorta is extremely difficult, include placement of the graft proximal to the celiac trunk on the abdominal aorta, or anastomosis of the donor artery to a common orifice fashioned on the main celiac trunk at the takeoff of the splenic artery. Various techniques and reconstructions have been developed to handle the various hepatic arterial anomalies found in the donor liver. Usually performed on the backtable prior to

implantation, these reconstructions are meant to produce a single orifice for anastomosis.[54,55]

In the past, portal vein thrombosis has been a major contraindication to liver transplantation. Depending on the extent of thrombosis, different methods of venous grafting have been developed and employed with excellent results.[57,58] If the clot obstructs only the main portal vein, the donor iliac vein graft is anastomosed to the confluence of the splenic and superior mesenteric veins. If the extension of the thrombosis includes the confluence, a jump graft is placed on the anterior surface of the superior mesenteric vein below the transverse mesocolon. This vein graft is brought anteriorly to the pancreas through the transverse mesocolon and into the hilum.

Careful collaboration between the surgeon and anesthesiologist is then required to achieve appropriate hemostasis. This includes correction of coagulopathy and careful inspection of all surgical sites.

Bile duct reconstruction

Standardization of bile duct reconstruction has markedly reduced the incidence of postoperative complications, i.e. biliary tract leaks and strictures. There are two predominant methods of bile duct reconstruction:[59]

1) choledochocholedochostomy over a T-tube stent

2) hepaticojejunostomy over an internal stent

The preferred method is a choledochocholedochostomy over a T-tube stent (Figure 5a). The simplest of the two techniques, it provides an access for easy inspection of the bile and radiologic evaluation of the biliary tree. It can only be used in the absence of malignancies, bile duct diseases, i.e. sclerosing cholangitis, or significant discrepancies in the size of donor and recipient ducts. The T-tube is left in for approximately three months after the procedure.

The alternative procedure is a hepaticojejunostomy over an internal stent (Figure 5b). A Roux-en-y loop of jejunum is fashioned and brought up into the hepatic hilum either anti- or retrocolically. This is the anastomosis of choice in pediatric cases because of its reliability and extremely low complication rate.

A third alternative, the so-called "Waddell-Calne" technique, uses the gall bladder as an interpositional conduit between donor and recipient bile ducts.[60] This technique is rarely used, but can be employed when technical difficulties make it impossible to fashion a Roux-en-y loop of jejunum.

Size Mismatched Donors

In order to overcome the shortage of small donors in the pediatric liver transplant population, surgeons are currently exploring technical variations that would allow transplantation of grafts procured from size mismatched donors. Such techinques may be needed when fulminant hepatitis or graft failure necessitates urgent transplantation and no appropriate donor can be found.

Reduced-size liver technique

The first such method to be used on a large scale is the reduced-size liver technique.[61-63] Reduced-size liver transplantation allows a weight ratio of one to six, making possible a weight differentiation of 300 to 500 percent between donor and recipient. The transplantation of a liver harvested from a large donor into a smaller recipient is accomplished by backtable resection of the right lobe, either by a bisegmentectomy using the left lobe or, more commonly, a trisegmentectomy using the left lateral segment. Both procedures require careful backtable dissection of the hilar structures and ligation of all of the structures transected in the liver parenchyma. Usually the left (and occasionally the middle) hepatic vein is preserved in continuity with the entire retrohepatic vena cava. The implantation is similar to that of an entire hepatic allograft, with exact positioning crucial to prevention of vessel torsion (Figure 6). In some cases, the recipient's retrohepatic vena cava can be preserved and the hepatic segment implanted in "piggyback"

fashion (see above). This avoids the need for cross-clamping of the vena cava in recipients who are typically too small for veno-venous bypass.

Split liver technique

The so-called split liver technique involves the division of the liver parenchyme and the partition of vascular and biliary structures. This technique addresses the shortage of suitable donor livers by allowing two viable grafts to be obtained from a single donor for implantation in different recipients. The split-liver techique continues to evolve with time and with the expanding, accumulative experience of transplant teams.[64-66]

Living-related donor technique

Without considering, in the present text, the ethical implications that have arisen, it is technically feasible to obtain a liver segment from a living relative for implantation into a pediatric recipient. The living-related transplant procedure has been successfully performed in numerous cases.[67] The technique for donor segmentectomy includes hilar dissection, parenchymal transection, and isolation of the hepatic vein included with those segments. Once the vessels to this segment have been clamped, the hepatectomy is performed, and the organ is flushed and cooled on the backtable.

Auxiliary liver transplantation

Until recently, the technique of auxiliary liver transplantation was abandoned in favor of orthotopic transplantation. However, a few high-risk patients have recently undergone auxiliary transplantation with reports of some success.[68] In auxiliary liver transplantation, a segment of donor liver is implanted beneath the recipient's liver, which remains in place (Figure 7). The usefulness of the procedure requires further evaluation and, in the future, may be considered under very special circumstances.

POST OPERATIVE CARE

Graft Function

For purposes of postoperative evaluation, hepatic function can be divided convienently into three general categories: synthetic, excretory and metabolic. Synthetic function includes the production of coaguation factors, albumin and other proteins such as transferrin and haptoglobin. Excretory function includes the excretion of bilirubin as well as the detoxification and excretion of drugs. Metabolic function includes glucose and lactate metabolism (including glycogenolysis and gluconeogenesis) and the intermediary metabolism of fat and protein. When evaluating the postoperative function of a hepatic allograft it is important to

note that specific functions of the liver recover from cold preservation at different rates.

Synthetic Function

Immediate hepatic synthesis of coagulation factors is necesary for hemostasis and successful completion of the transplant operation. With the addition of coagulation factors, in addition to the factors produced by the newly implanted liver, hemostasis can be attained. In the operating room, thromboelastography is used to assess to the status of the interaction of platelets and coagulation factors.[69] In the post-operative period, platelet count, prothrombin time and partial thromboplastin time are usually sufficient to monitor the coagulation status. The prothrombin time, which reflects ongoing synthesis of specific factors by hepatocytes, is an early indicator of graft function. Although normalization is a encouraging sign, occasional prolongation occurs despite good graft function as a result of vitamin K deficiency. With the exception of vitamin K administration, aggressive correction of coagulation abnormalities with exogenous factors in the early post-operative period should be avoided so that graft function can be monitored by changes in the prothrombin time. Prothrombin times of even 20 to 25 seconds may not require treatment with fresh frozen plasma as long as there is no evidence of bleeding or serious hypertension. If graft dysfunction requires factor supplementation, substantial improvement in prothrombin time with infusion of 7-10cc/kg of fresh frozen plasma indicates the

likely recovery of synthetic function with time. If no improvement in the prothrombin time occurs, a severe preservation injury or technical complication should be suspected and investigated. Once the prothrombin time has corrected to within 2 seconds of normal, it is no longer a useful guide to graft function. Thus, it is unnecessary to measure this parameter daily after the first week unless other signs of graft dysfunction are present. Activated partial thromboplastin time is rarely abnormal, and marked prolongation of APTT suggests the contamination of the specimen with heparin.

Excretory Function

The production of bile in the operating room is the first indication of resumed excretory function. Because of the load of hemoglobin that accompanies transfusion during the procedure, increases in bilirubin in the first few days after the transplant are common, regardless of the function of the graft. Thus increases are not indicative of graft dysfuction. Paradoxical falls in bilirubin immediately after transplantion can result from dilution resulting from blood loss and fluid and blood replacement. However, such changes are limited to the first 24 to 48 hours and subsequent changes in serum bilirubin are indicative of graft function.

If an end-to-end reconstruction of the biliary system has been performed, the bile excreted through the T-tube is an excellent

gauge of liver function. The experienced clinician can derive a considerable amount of useful information about the graft from examination of recently produced bile. Both quality and quantity of bile produced are of considerable clinical value. Typically, bile is dark golden brown and very viscous and up to 300 cc may be produced in per day. As the quantity of bile produced increases, the color may become lighter due to the increased content of water. Because the amount of bile passing into the gut rather than through the T-tube is unknown, a low quantity of bile output may not be a serious finding if the bile is of appropriate color and viscosity. Light colored or water-clear bile indicate severe graft injury, most commonly due to preservation injury, primary nonfunction or rejection.

Another important hepatic excretory function is the detoxification and clearance of anesthetic agents as well as removal of the toxins of hepatic encephalopathy. Awakening from anesthesia is an encouraging sign. To minimize confusion regarding the sensorium immediately after transplantation, analgesics are administered sparingly, if at all. Fortunately, most patients experience a tolerable degree of discomfort during this stage without a significant analgesic requirement. Once the patient is fully recovered from anesthesia and encephalopathy has cleared, narcotics can be given with caution.

Metabolic Function

Metabolic function of the liver is evident immediately post implantation. Two parameters which can be followed clinically both in the operating room and in the ICU are serum lactate concentration and temperature. Liver metabolism produces significant heat, and rewarming frequently begins shortly after unclamping. Inablilty to rewarm or slow rewarming after closure of the wound raises concern about poor graft function. Similarly, the metabolism of lactic acid is an early sign of graft function.[70] Generally, serum lactate concentration is normal within 6 to 12 hours post transplant. Increasing or persistent elevation of lactate indicates graft dysfunction. Glucose metabolism is an insensitive index of graft function; glucose levels generally remain high regardless of graft function. Hypoglycemia occurs only in circumstances of severe graft injury.

Preservation Injury

Some degree of injury occurs in the preservation of all hepatic allografts. Transaminase levels during the first 48 hours are generally thought to reflect the degree of preservation injury. Interpretation of transaminase levels is not absolute and requires consideration of all clinical information. AST levels less than 2000 and ALT levels less than 1500 suggest moderate preservation injury, while levels less than 600 indicate minimal preservation injury. With severe preservation injury, additional clinical indices of graft dysfunction can be expected. These include

decreased clearance of bilirubin, delayed normalization of prothrombin time, slowed awakening and persistent encephalopathy. In severe cases, lactic acidosis and persistent hypothermia are observed. If the AST is over 4000, the survival of the graft is questionable. After careful serial evaluation and observation, retransplantation may be required.

Immunosuppression

Immunosuppression after liver transplantation requires continuous monitoring and adjustment. Although most centers follow a standardized immunosuppression protocol, great latitude in treatment is required to respond to the needs of individual patients. Thus, immunosuppression protocols serve primarily as guidelines for the individualized prescription of immunosuppression. The need for immunosupression is greatest during the first weeks after transplantation when the probability of rejection is the greatest.[71] After 2 to 3 months, the immunosuppressive regimen can be moderated as the host immune system accomodates to the graft. Cyclosporine and steroids as the mainstays of maintenance immunosuppression in most centers.

The need to provide adequate immunosuppression to prevent rejection must be weighed against the increased risk of subsequent infections.[72,73] Unfortunately, the adverse effect of immunosuppression on host resistance is cumulative, and the onset of infections resulting from over-immunosuppression may

occasionally be delayed by many months. Alternatively, insufficient immunosuppression resulting in rejection may require so much additional immuosuppression that the risk of unnecessary infectious complications is increased.

Cyclosporine

The introduction of cyclosporine in 1980 coincided with spectacular improvement in the results of liver transplantation. The acceptance of liver transplantation as standard therapy for end-stage liver disease has accompanied the clinical introduction of cyclsporine.[74,75] The dominant mechanism of action of cyclosporine is the inhibition of mitogen induced production of interleukin 2. Additional effects may include reduced production of interleukin 1, gamma interferon and interleukin 2 receptor.

Adverse effects of cyclosporine include renal impairment, hepatic dysfunction, hypertension, hyperkalemia, CNS dysfunction, hirsutism and gingival hypertrophy.[76]

The dosage of cyclosporine is ordinarily determined by measurement of cyclosporine levels in blood or serum. Many assays are available, and the desired target levels vary between centers. Furthermore, dosage may be limited by toxic effects. Unfortunatley, manifestations of cyclosporine toxicity do no necessarily indicate achievement of an adequate therapeutic effect. Indeed, rejection and cyclosporine toxicity may coexist.

Steroids

Corticosteroids are the second major component of standard immunosuppression in liver transplantation. The action is primarily anti-inflamatory although other specific activities have been proposed. Generally, high dose steroids are the initial treatment and are rapidly tapered during the first 7- 14 days, followed by maintenance doses which are slowly tapered during the ensuing 3-6 months.

The usual side-effects of steroid therapy are reduced by this initial early pulse and subsequent tapering. Specifically, glucose intolerance, catabolism, susceptibility to infection and fat accumulation are minimized, although they still remain substantial problems when the steroid requirements of individual patients remain high.

Azathioprine

Azathioprine is frequently used as an additional immunosuppressive agent in liver transplantation. It plays an important role in patients who are unable to tolerate adequate doses of cyclosporine due to side effects, primarily renal failure or CNS disturbances. At sub-therapeutic doses it facilitates reduction of cyclosporine dosage while minimizing the adverse effects associated with full therapeutic doses of azathioprine.

The mechanism of azathioprine is primarily cytotoxic, particularly on rapidly dividing cells. Thus, proliferating, activated immune cells are susceptible to its action. Granulocytopenia, and occasionally thrombocytopenia, manifestations of toxicity, may require reduction of the dose. The dose may be reduced further when hypersplenism results in leukopenia or thrombocytopenia. Because of its relatively non-specific mode of action, the dose of azathioprine is generally reduced or the drug discontinued when infection is present. There is also concern regarding long-term hepatotoxic effects and predisposition to lymphoproliferative disorders.

Rejection

While the aim of maintenance immunosuppression is to prevent rejection, this is achieved in only about 30% of liver transplant recipients.[71,77] Once rejection has developed, intensification of maintenance immunosuppression is insufficient to reverse the process and specific regimens of anti-rejection therapy are required. Generally, these regimens consist of high dose steroids or specific T-cell cytotoxic therapy.

Virtually all rejection seen early after liver transplantation is acute cellular rejection mediated by the T-cells. Acute cellular rejection is rarely seen in the first few days after transplantation. Most commonly, the onset of rejection occurs between the fourth and fourteenth post operative day. There are

few typical symptoms of hepatic rejection. Although fever is not uncommon, and patients may report malaise on the first day of rejection. These nonspecific signs and symptoms often have alternative explanations. Because the organ is free within the abdominal cavity, swelling does not usually cause pain as seen with renal transplant rejection.

Antibody mediated hyperacute rejection, more commonly seen in kidney transplantation, is extremely uncommon in liver transplantation. This is corroborated by the finding that cytotoxic cross-matching does not predict outcome in liver transplantation.[78] Although there are a few reports of hyperacute liver rejection,[79,80] it has been speculated that some cases of primary graft non-function may also represent hyperacute rejection.

Vanishing bile duct syndrome[19] may develop at virtually any time after transplantion, although it is rare during the first one or two months. Characteristically, there is a paucity or disappearance of bile ducts associated with nonsuppurative destructive cholangitis and degenerative changes of bile duct epithelial cells attributed to cytokine-mediated injury or ischemia. There are several effective therapeutic options for acute cellular rejection, but standard regimens are ineffective for hyperacute or vanishing bile duct syndrome.

The first signs of rejection are elevations of liver function tests.[77] Bilirubin usually increases, and aminotransferases and biliary enzymes may also increase. Fever and malaise as well as leukocytosis may also occur. The graft may become enlarged and firm on physical examination. Perhaps most important, the bile, if available for inspection, will be lighter and less viscous. Many centers perform routine biopsy on about the seventh post operative day because of the frequency of rejection at this time.

The typical biopsy findings of rejection are expansion of the portal tracts by mononuclear cells, activated lymphocytes and frequently eosinophils.[81] Polymorphonuclear leukocytes may also be present. The critical finding is invasion and damage of the bile ducts by the lymphocytes.[82] These findings can be spotty throughout the liver and should be noted in multiple portal tracts if the diagnosis of rejection is to be confirmed. Cholangitis may exhibit similar findings, but the predominance of polymorphonuclear leukocytes often provides the correct diagnosis.

Many laboratory tests have been proposed as aids to the diagnosis of rejection, but none has gained widespread acceptance or validation. Clinical judgement, standard laboratory tests of liver function and liver biopsy remain the standard modalities for the diagnosis of rejection.

Steroid therapy of rejection generally consists of a brief course of very high doses of intravenous corticosteroids for 1-3 days or a bolus followed by tapering doses of corticosteroids.[19,71,77] A response is often seen within several hours of bolus injection. If there is no response to the steroid therapy or if rebound rejection should occur after the steroid therapy, OKT3, a murine monoclonal antibody against T cells may be given daily for 7 to 14 days. This drug binds to the CD3 component of the CD3-T cell receptor complex present on all mature T cells and causes T cell inactivation which interrupts the rejection process.[83] Other antibody preparations that act similarly by binding to T cells include antilymphocyte, antilymphoblast and antithymocyte antibodies.

Once rejection is controlled, maintenance immunosuppression is often intensified for several weeks or months to prevent recurrence. This may take the form of additional steroids or the conversion from dual drug (cyclosporine and steroids) to triple drug (addition of azathioprine) therapy. In some cases, rejection cannot be controlled by maximuim therapy and retransplantation is required. Although the result of retransplantation for rejection is not as good as with the initial transplant, rejection does not necessarily recur.[84]

Renal Function, Fluid, and Electrolytes

There is a close relationship between liver and kidney function, and many patients with end-stage liver disease have significant renal impairment. In the setting of impaired renal function, the insult of operation, substantial blood loss, temporary occlusion of the vena cava and large doses of intravenous cyclosporine results in some renal injury in the majority of liver transplant recipients. Fortunately, this injury is usually transient and dialysis is rarely needed. Oliguria is a common finding in the first two post operative days and requires aggressive fluid administrationd guided by pulmonary artery pressure monitoring and hemodynamic evaluation. Once adequate volume expansion is achieved, as indicated by a pulmonary capillary wedge pressure of 14 to 17 torr, large doses of loop diruetics are indicated if urinary output does not improve. Typically, the BUN and creatinine will rise for 48 to 72 hours regardless of urinary output. The first sign of recovery from the perioperative renal injury is a decline in creatinine. The BUN usually rises for another 24 to 48 hours before declining. Severe cyclosporine toxicity may sustain the elevated BUN despite improvement of creatinine and urine flow. As discussed below, post-operative bleeding may further impair urine output and cause oliguric acute renal failure in extreme instances.

Preoperative hepato-renal syndrome has prompted some centers to advocate simultaneous liver and kidney transplantation. Others

have expected the prompt return of renal function with restoration of hepatic function and have deferred kidney transplantation for those who fail to respond to liver replacement alone.[85] In those patients with pre-existing renal failure, hepatorenal syndrome or perioperative renal failure, the timing of dialysis after liver transplantation is critical. It is wise to delay hemodialysis for as long as possible in order to avoid anticoagulation, platelet destruction and subsequent bleeding. Continuous arterio-venous hemofiltration or veno-venous hemofiltration can provide alternatives to hemodialysis for fluid removal as well as a very mild dialysis with minimal anticoagulation in the perioperative period. This is particularly useful in cases of severe volume overload or hemodynamic instability and can achieve significant volume losses over a period of several days.

Positive intraoperative fluid balance is expected during liver transplantation and a gain of 10% or more of the preoperative weight is not unusual even after significant losses of ascitic fluid. If subtantial blood loss is encountered, weight gain of up to 20% may be anticipated. Most or all of this volume is sequestered in the interstitial space and in the "third space." Much of this fluid can be mobilized and excreted in the third to fifth post-operative days if renal function is adequate. Removal of this fluid usually requires the use of diuretics even in the absence of renal injury. The addition of albumin to the diuretic regimen may increase the response if the serum albumin is low. As

mentioned above, ultrafiltration is an option for fluid removal if the renal function is poor but hemodialysis is otherwise not needed. If interstitial fluid is not removed as it is mobilized into the vascular space, pulmonary edema may ensue. Careful management of volume status with central pressure monitoring may be necessary to manage difficult cases.

The common use of diuretic therapy in the first week after transplant often causes electrolyte imbalance with hypokalemia, hypomagnesemia and alkalosis. Metabolic alkalosis may result from many causes.[86,87] The transfusion of large volumes of blood products supplies substantial amounts of citrate which are converted by the liver to bicarbonate for several days after transplantation. Acidosis during the hepatectomy and the anhepatic phase may occur because of accumulation of lactate and require infusion of sodium bicarbonate. Once the liver is reperfused and lactate metabolism is restored, the residual bicarbonate may also contribute to post-operative alkalosis. Naso-gastric suction further aggravates alkalosis because of the loss of chloride, as does diuretic therapy which results in losses of potassium and chloride. The ensuing alkalosis may be quite severe and stimulate compensatory respiratory acidosis. This may result in small tidal volumes and, theoretically, may contribute to atelectasis. Systemic alkalosis also alters oxyhemoglobin dissociation and impairs oxygen availability to the tissue, a potentially serious problem if arterial oxygenation is poor or tissue perfusion is impaired. This

could theoretically contribute to further damage of grafts compromised by severe preservation injury.

Treatment of alkalosis usually begins with aggressive replacement of potassium deficits with potassium chloride. At the same time, ventilation is adjusted to normalize pH and optimize oxygen delivery. Severe alkalosis constitutes a relative contraindication to extubation because of the risk of compensatory respiratory acidosis, hypoventilation and atelectasis. Some patients maintain normal PACO2 despite severe alkalosis rather than compensating with hypoventilation. In this case there is no contraindication to extubation in the face of metabolic alkalosis. If hypoventilation delays extubation, may result in atelectasis or impaired tissue oxygenation, or if alkalosis results in pH above 7.5, treatment with intravenous hydrochloric acid is appropriate. Risks associated with infusion of concentrated hydrochloric acid include hemolysis and tissue injury resulting from extravasation. Carbonic anhydrase inhibitors are generally inadequate and may alkalinize the urine and enhance reabsorption of ammonia from the urine, potentially aggravating encephalopathy. Ammonium chloride is contraindicated to minimize the ammonia load requiring conversion to urea by the newly implanted liver.

Potassium deficits are common with the aggressive use of loop diuretics to maintain urine flow and achieve negative fluid balance. Because of the risk of oliguria or anuria during the early

postoperative period, replacement has usually been given by intermittent infusions of potassium chloride. Addition of potassium to the maintenance fluid has traditionally been avoided because of potentially severe hyperkalemia that might result from sudden graft failure and concommittant renal failure. This complication is now rarely seen, and addition of potassium to the maintenance fluid is probably safe if urine flow is adequate.

Maintenance of magnesium concentrations is particularly important because of the correlation between seizures during the early postoperative period of cyclosporine infusion and low or low-normal magnesium levels. Prior to aggressive replacement of magnesium deficits, postoperative seizures were common while patients were receiving intravenous cyclosporine. Once the magnesum levels were regularly maintained at 2 meq/dl or more, seizures became quite rare.

Cardiovascular

Cardiovascular complications of liver transplantation are fortunately quite rare. Significant cardiovascular disease has been considered a compelling contraindication to liver transplantation. With improvement in anesthesia, post operative management and relaxation of formerly rigid age limits, patients with preexisting cardiovascular disease have more commonly become liver transplant candidates. Relatively mild degrees of cardiac

impairment are acceptable among candidates, and satisfactory results have been obtained.

Pulmonary artery catheterization, thermodilution cardiac output and intra-arterial monitoring have become standard practice in liver transplantation. Cardiac function is easily evaluated in the intensive care unit using standard techniques in those patients with preexisting cardiac dysfunction or complications resulting from perioperative events. The effect of liver failure on altered hemodynamics must be appreciated. One should be aware of the reduction in afterload. Typically, cardiac output is high, resistance is low, ejection fraction is supranormal and mixed venous saturation is high. These changes are the result of marked peripheral shunting. After liver transplantation, the shunts persist for a considerable period of time before resolving. The rapidity of this change is uncertain since hemodynamic monitoring is ordinarilly withdrawn within the first few days after transplantation and the hyperdynamic state persists beyond this time.

Pulmonary

Pulmonary function is of paramount importance in the first few postoperative days. Pulmonary complications are frequent, but with careful management they are infrequently serious.[88] In contrast, minor respiratory complications, if not managed aggressively, can result in death.

The typical postoperative patient returns to the intensive care unit intubated and requires several hours to several days of mechanical ventilation. The awakening process is delayed compared to other major surgical procedures, probably because of slow hepatic metabolism of anesthetic agents and muscle relaxants and residual hepatic encephalopathy. Accordingly, prolonged awakening results in a substantial period during which the patient would be at risk for aspiration unless intubated.

All patients have impaired pulmonary mechanics resulting from the extensive upper abdominal incision which transects abdominal oblique muscles on the right as well as both rectus muscles. Many will have concommitant muscle atrophy resulting from malnutrition and prolonged hepatic failure. Finally, right, left or bilateral phrenic nerve injury occasionally results from clamp placement or hemostatic sutures in the diaphragm.

Renal dysfunction, common in the first week after transplantation, often requires aggressive volume expansion which may contribute to pulmonary compromise because of volume overload with decreased pulmonary compliance, alveolar collapse and increased respiratory effort.

Premature extubation of debilitated or encephalopathic patients may result in respiratory failure due to atelectasis or

aspiration pneumonia. Careful evaluation of mental status, chest roentgenogram and pulmonary mechanics prior to withdrawal of mechanical ventilatory support and airway protection can minimize these complications. Once pulmonary mechanics are adequate, the patient is evaluated for the ability to voluntarily cough and deep breathe. A simple, standardized test of cognitive function is performed to assess residual encephalopathy or persistent effects of anesthesia. If all criteria are satisfied, the patient can be confidently weaned and extubated. This practice rarely prolongs by more than a few hours the period of intubation and permits detection of those patients at highest risk for aspiration, atelectasis and pneumonia following premature extubation.

Right pleural effusion is a routine finding after liver transplantation.[89] Left-sided effusions are less common but not unusual. Effusions are transudative and may attain considerable volumes. If the volume of effusion impairs pulmonary mechanics or contributes to atelectasis, therapy is indicated. Although diuresis may reduce the volume of the effusion, thoracentesis provides a more rapid effect. Such drainage often allows earlier weaning and extubation, thus reducing the risk of nosocomial pneumonia.

Atelectasis is also a common postoperative pulmonary complication. The incidence of basilar atelectasis is probably no more common after liver transplantation than after other major

upper abdominal procedures and resolves with mobilization of the patient and close attention to pulmonary toilet. Lobar or whole lung collapse is infrequent but requires aggressive management. Turning, bagging and suctioning are important in prevention and treatment of atelectasis and may be sufficient treatment for minor collapse. More extensive collapse may result from major airway complications including malposition of the endotracheal tube, large mucous plugs and blood clots. Such problems may be evaluated at the bedside and by portable chest roentgenogram and can frequently be treated appropriately without delay. Positive pressure maneuvers can rapidly reinflate collapsed lung once obstruction is relieved. If pulmonary lavage, suctioning and bagging with positive pressure do not promptly inflate the lung, prompt bronchoscopy is necessary.

Pneumonia is currently an infrequent complication of liver transplantation if the above precautions are observed. Pneumonia is most frequently bacterial in origin during the first two weeks. Subsequently, protozoal, fungal and viral pneumonias are more common, with cytomegalovirus and pneumocystis seen most frequently.

With improvement in anesthetic management and a more stable intraoperative course, adult respiratory distress syndrome (ARDS) has also become an infrequent complication of liver transplantation. Treatment of ARDS resulting from liver transplantation is no different from the treatment of ARDS

resulting from other causes. However, the adverse effects of PEEP on hepatic blood flow must be appreciated when treating ARDS. This may be particularly important when preservation injury or rejection produces edema of the graft and further reduction in blood flow resulting from PEEP may exacerbate graft ischemia.[90]

Late pulmonary complications are most commonly infectious and, as mentioned, cytomegalovirus and pneumocystis are the most frequent organisms.[91] Adequate prophylaxis with sulfamethoxazole-trimethoprim or pentamidine has virtually eliminated pneumocystis pneumonia. CMV remains a substantial problem but progress in the prevention and treatment of CMV has substantially reduced the clinical impact of this organism. Both CMV and pneumocystis can present with a frank pneumonia, but more commonly the initial signs are subtle and may consist of isolated fever, mild dyspnea or tachypnea. Hypoxemia on room air has been a useful early sign of opportunistic infection and should prompt thorough evaluation of possible pulmonary infection. Broncho-alveolar lavage provides the diagnosis most consistently with minimal morbidity, and open lung biopsy is now rarely necessary. Other possible etiologies for pneumonia should also be considered including tuberculosis, legionella and fungi. With aggressive and appropriate early detection and management, severe pulmonary compromise and intubation and mechanical ventilation are usually unnecessary.

Infection and Prophylaxis

Broad spectrum antibacterial prophylaxis is given intravenously prior to operation and for 2 to 5 days afterward. There has been a trend to shorten the duration of perioperative antibacterial therapy in an effort to minimize the selection of resistant organisms. The addition of oral antibacterial and antifungal therapy may decrease the colonization of the gut by yeast and opportunistic gram negative organisms.[92] Patients recieving lactulose preoperatively, those undergoing prolonged operations (greater than 12 hours), those undergoing second operations and those cared for in the intensive care unit for more than 24-48 hours prior to transplant have also recieved short courses of low dose amphotericin B in an effort to reduce colonization and minimize fungal infections.

Pneumocysitis carinii pneumonia has virtually disappeared with the introduction of low dose trimethoprim-sulfamethoxazole therapy for 3 to 6 months after transplantation.[93] For those allergic to sulfa drugs, inhaled pentamidine is advocated.[94] The prevention of cytomegalovirus infections has been less successful, although acylovir has proven to be an effective prophylactic agent.[95] Intravenous human IgG has also shown promise in the prevention of CMV infections.[96] Finally, gancyclovir, a potent treatment for established CMV infections has markedly reduced morbidity and mortality.[97]

Surgical Complications

Bleeding

As noted earlier, initial graft function must be adequate for completion of the procedure with satisfactory hemostasis. The abdomen is not usually closed until the surgical team is satisfied that the entire surgical site is dry. Postoperative bleeding is most often the result of poor surgical hemostasis unless the graft is severely injured. Some blood loss from the surgical site is acceptable, but ordinarily drainage from the abdomen consists primarily of ascites and the hematocrit of such drainage is usually less than 5%. Intrabdominal drains are not infallible indicators of bleeding and a significant hematoma may develop without excessive drainage. Computerized tomography may identify a large hematoma when clinical findings are equivocal.

Significant bleeding is frequently associated with oliguria and, if the urine output is poor, the need for more than 1 or 2 units of transfusion in the first 12 hours is cause for concern. If significant bleeding occurs, reoperation is often required to evacuate the blood clot even though active bleeding is infrequently observed at operation.

Hepatic Artery Thrombosis

The parenchymal tissue of the liver is capable of surviving on portal blood flow alone, making the early clinical detection of thrombosis of the hepatic artery difficult. In addition, the

infrequent nature of hepatic artery thrombosis makes detection all the more challenging. Routine doppler ultrasound can be used as a screening test for hepatic arterial flow.[98] The test is very sensitive for detection of reduced or absent flow, but relatively non-specific. Thus, if the sonographer is unable to demonstrate arterial flow, a confirmatory angiogram is necessary before corrective therapy is undertaken. If detected early, reoperation may restore flow and prevent the need for retransplantation. Alternatively, if flow is demonstrated, one can be confident of hepatic artery patency.

Several syndromes have been associated with untreated thrombosis of the hepatic artery.[99] The earliest, and least common occurs in those rare grafts which depend on arterial flow for survival. In such grafts, hepatic artery thrombosis produces a sudden graft failure with severe coagulopathy, renal failure, hyperkalemia, encephalopathy and hypoglycemia. Urgent replacement of the graft is necessary if the patient is to survive. The other three syndromes result from dependency of the bile duct on hepatic artery blood flow. If the arterial thrombosis occurs early, the bile duct anastamosis fails to heal and leakage develops. Should the artery thrombose later, multiple ischemic intrahepatic bile duct strictures may develop. Finally, intrahepatic bile ducts may undergo ischemic necrosis with formation of multiple bile lakes or abcesses. Most of these complications are irreversible and require retransplantation. While waiting for a donor organ, abcesses or

cholangitis should be treated by appropriate drainage and antibiotics.

Bile Duct Complications

The blood supply of the common bile duct is quite tenuous and may explain the tendency of bilary anastamoses to scar and stricture when immunosuppression is withheld.[100] Steroids and other immunosuppressive drugs prevent biliary sclerosis wich may explain the relatively low incidence of biliary stricture in the transplant population. Biliary tract leaks usually result in signs and symptoms of an abdominal infection.[101] Diagnosis is usually made by cholangiogram. A cholangiogram is simple to perform via a T-tube or a transjejunal stent; a percutaneous transhepatic cholangiogram carries more risk. Leaks of the bile duct anastamosis usually require surgery when detected as they rarely heal without reconstruction. If such a leak remains undetected until an abcess develops, immediate reconstruction is quite perilous. Cholangiography is also useful for detection of obstruction of the biliary system. Early on, ductal dilation is not always present, and a normal sonogram does not exclude biliary obstruction.

Simple strictures may be percutaneously dilated with a balloon catheter, although the beneficial effect can be transient.[102] Conversion of an end-to-end anastamosis to a roux-en-y or reconstruction of a roux-en-y provides a more durable result. It

is important to note that bile duct strictures can be misinterpreted as rejection on percutaneous liver biopsy. The presence of increased numbers of polymorphonuclear leukocytes around the bile ducts may be the only indications of biliary obstruction. When rejection is unresponsive to standard therapy, a bile duct complication should be suspected and evaluated. Since bile leak or stricture may also result from hepatic artery thrombosis, discovery of a bile duct complication warrants an investigation of the hepatic artery.

It is possible for the T-tube or internal stent to occlude the bile duct producing chemical abnormalities. This is detected by cholangiogram. Removal of the T-tube or percutaneous removal of a retained stent can resolve this problem.[101]

Intraabdominal Infection

Prolonged operation, perforation of the intestine, and immunosuppression all increase the risk for intraabdominal infection in the liver transplant recipient. Poor nutritional status of the candidate preoperatively also increases the risk for infection. Bacterial infections are the most common and are most frequently associated with biliary complications.[101] These infections usually occur during the first few weeks after transplantation with fever, leukocytosis or failure to thrive. Because of immunosuppression, patients may have minimal signs of infection despite large infected abdominal collections. For this

reason, CT scanning and diagnostic aspiration of intraabdominal fluid collections is important in those patients who appear to be failing without obvious cause.

Late intraabdominal infections such as cholangitis and intrahepatic abcess are likely to be the result of occult occlusion of the hepatic artery or stricture of the bile duct. Diagnosis is based on appropriate imaging procedures and cultures obtained at the time of drainage. The surgical principle of adequate drainage coupled with appropriate antibiotics may be accomplished by percutaneous techniques, but open drainage may be neccessary if a safe percutaneous route is unavailable or the response to percutaneous drainage is not prompt or complete. Caution should be exercised before routinely draining perihepatic fluid colletions, since loculated perihepatic ascites is quite frequent and most often benign. Only if infection is clinically suspected and other sources of infection have been eliminated, should perihepatic fluid collections be aspirated.

Ascites

Ascites is almost universal after liver transplantation, even if none was present before the operation. This ascites has been attributed to open lymphatic vessels in the porta hepatis and the surface of the diaphragm. The ascites is usually worse in those patients with severe ascites prior to surgery. During the first

few days after transplantation, the ascites is ordinarily drained by closed suction drainage systems. The amount of fluid which can be removed by these systems can be substantial and result in significant volume depletion.

Formation of ascites can increase dramatically when the graft is injured by rejection or portal vein thrombosis. A substantial increase in ascites should prompt an investigation of possible causes of graft dysfunction. Losses of ascites may require replacement with an appropriate solution, since fluid removed from the abdominal cavity is quite promptly replaced by the formation of new ascites at the expense of extracellular fluid and ultimately plasma volume. The protein losses associated with ascitic drainage can be formidable and some form of replacement either by colloid infusions or parenteral nutrition is necessary.

Occasionally, ascites will persist for more than 4 weeks and constitute a demanding patient management challenge with related problems of intravascular dehydration and renal failure. In rare cases, a permanent peritoneovenous shunt may eliminate the need for invasive monitoring and large volume replacements, simplify the care of the patient and hasten ICU or hospital discharge.

Portal Vein Thrombosis

Portal vein thrombosis is a rare technical complication of liver transplantation.[103] If the anastamosis is technically adequate, and thrombosis occurs, intrahepatic obstruction of portal flow may sometimes be responsible. This may be due to edema resulting from severe preservation injury or less commonly, early severe cellular rejection. It has been suggested that portal vein thrombosis arising in the first few hours after implantation may be a manifestation of hyperacute rejection.

Another possible cause of portal vein thrombosis is clot forming within the donor portal system. Such thrombus may form within the portal system after a thrombectomy performed upon a clotted portal vein during the preparation for hepatic implantation. Alternatively, unsuspected pre-existing clot within the portal system may be a nidus for thombus propagation within the portal system and subsequent portal vein thrombosis.

Finally, thrombosis due to poor flow in the portal system may be the result of high flow portal-systemic shunts arising spontaneously or surgically created prior to transplantation. Such a situation may be detected if portal vein flow is measured intraoperatively, and corrective action taken prior to closure.

The clinical findings associated with portal vein thrombosis are quite characteristic and should rapidly lead to the correct

diagnosis after urgent doppler study and confirmatory angiography, if necessary. The patient with complete thombosis of the portal vein will suddenly become desperately ill, with hypotension, sudden and massive ascites, profound hypotension, shock and sepsis. Severe coagulopathy, marked elevation of aminotransferases, lactic acidosis and hypoglycemia are associated laboratory findings. Urgent retransplantation is the only opportunty to salvage the patient with portal vein thrombosis and survival for more than 24 hours is unusual after the diagnosis is made.

RESULTS

Liver transplantation has proven to be a successful treatment for end stage liver disease since the introduction of cyclosporine in the early 1980's. Introduction of this immunosuppressive agent was coincidental with other improvements in surgical techniques, anesthesiology, critical care medicine and hepatology. Currently, the one-year survival rate for all indications is approximately 70-85 percent.[32,104,105] The five year survival rate, similarly for all indications, is 60-70 percent.[104] Survival rates for different disease indications, based on the University of Pittsburgh series, are outlined in Figure 8. Survival rates for pediatric and adult recipients have been similar. The variations noted between centers is most likely attributable to differences in patient selection. Those centers which have been more aggressive in transplanting

patients with difficult anatomical situations and with more problematic indications (ie malignancy, hepatitis B), have lower survival rates than those centers transplanting carefully selected, good risk patients.

The best survival is achieved for those adult patients transplanted for post-necrotic cirrhosis, primary biliary cirrhosis, sclerosing cholangitis without concomitant tumor and inborn errors of metabolism. In the pediatric group of patients, the best results have been achieved for children transplanted for biliary atresia, post-necrotic cirrhosis, and inborn errors of metabolism. The indications for which survival is decreased are those diseases which can recur after transplantation. These include patients with hepatitis B surface antigen positivity and hepatic malignancies. Furthermore, patients with acute fulminant hepatic failure have shown a decreased survival following liver transplantation, most likely due to the advanced state of disease and coma with which these patients are often transferred to transplant centers.[14] Clearly, early referral for patients with acute fulminant failure would improve the outcome and long-term survival.

Those patients transplanted for chronic hepatitis-B who are surface antigen positive preoperatively, have, for the most part, developed recurrence of their disease following transplantation. The one-year survival rate has been reported to be approximately

60 percent, and the five-year survival rate, approximately 50 percent.[106] In comparison, patients transplanted for fulminant hepatic failure who are hepatitis B surface antigen positive have had 75-80 percent one and five year survival rates.[106] There are currently clinical trials underway in various centers exploring adjuvant therapy to prevent recurrent disease. These trials have included the use of large doses of hepatitis B hyperimmune globulin during the anhepatic phase and postoperatively, the use of hepatitis-B vaccine in the perioperative period, the use of monoclonal antibodies, and the use of interferon. Long term follow-up of these patients is required before recommendations can be made as to the best perioperative treatment.

Transplantation for malignant disease has been, for the main part, disappointing. In the presence of hepatocellular carcinoma, survival has been poor with only occasional long-term survivors.[10] For the fibrolamellar variant of hepatoma, survival has been better with many patients surviving for prolonged periods despite recurrence of the disease. Transplantation, in the face of cholangiocarcinoma, has been uniformly disappointing. The cluster operation, also termed the upper abdominal exenteration[11], is currently being evaluated for this very difficult and frustrating indication. Epitheliod hemangioendothelioma has a 90 percent one year and 50 percent five year survival rate.[106]

Although many centers have abandoned transplantation for hepatic malignancies, other centers continue to offer transplantation to these patients who have no other option for cure. However, most centers that continue to transplant patients for primary hepatic malignancies have instituted protocols employing perioperative chemotherapy to reduce the incidence of recurrence. The best survival can be obtained in those patients who undergo very careful preoperative assessment to exclude extrahepatic disease. This includes extensive radiologic evaluation, radionuclear scans, pre-transplantation laparotomy and lymph node sampling.

Patients transplanted for other indications and found to have small incidental tumors can attain similar survival rates as patients without tumor.[10,106] With improvements in radiologic techniques, small intrahepatic tumors can be diagnosed more readily than in the past. Therefore, what were previously considered incidental tumors may be diagnosed preoperatively. Clearly, it can be expected that results for liver transplantation for patients diagnosed with tumor will improve in such situations.

Following liver transplantation, over 80 percent of patients return to their normal life-styles. Patients return to school, to their family responsibilities, to their employment, and to their normal social activities. Despite the use of long-term immunosuppressive therapy, many male patients have successfully

fathered children, and many females have become pregnant and given birth to healthy children. In one report, 20 children were born to 17 female patients who had received a wide variety of immunosuppressive agents including cyclosporine, imuran, steroids, polyclonal antibodies, and monoclonal antibodies.[107] Despite the increased incidence of Caesarian section and premature births, most of the children have done well.

IN THE FUTURE

Despite the excellent results which have been obtained with liver transplantation, the field continues to evolve. Although various diseases can be cured with liver transplantation with an excellent survival, other diseases will require development of efficacious adjuvant therapies before achieving equal survival rates. Research is in progress for those diseases which demonstrate recurrence following transplantation including hepatitis B surface antigen positive cirrhosis and primary liver malignancies. A close collaboration between transplantation surgeons, hepatologists, virologists and immunologists is required to devise perioperative management protocols for patients with hepatitis B. A major effort must be directed towards the definition of adjuvant therapy to prevent or at least significantly alter recurrent disease.

The efforts directed towards the management of patients with primary hepatic malignancies are multifactorial. The available data suggests that better results can be achieved through better patient selection, recognition of favorable tumor types, modification of the postoperative immunosuppressive regimen, administration of adjuvant chemotherapy and the development of new operative approaches to these diseases. In the presence of hepatic malignancies that cannot be resected by conventional techniques, liver transplantation continues as the only hope for cure. Despite the occasional longterm survivor, the results for most hepatic malignancies remain poor. Carefully conducted trials of perioperative chemotherapy will be one area of focus to improve this situation.

Future research must address the supply of suitable and adequate donor organs. Improved preservation techniques and the development of segmental liver transplantation have alleviated a small part of the problem. The feasibility of organ transplantation across species has been demonstrated.[108] The survival is short, because these allografts succomb to an accelerated rejection process. It is anticipated that with improved techniques of immunosuppression and further studies to achieve tolerance, xenograft transplantation can become a reality. Although frought with ethical and emotional issues, the ability to transplant across species would resolve the issue of the organ

shortage and would render liver transplantation an elective procedure.

Although cyclosporine helped revolutionize extrarenal organ transplantation, rejection and infection remain amongst the most common postoperative complications. Efforts are currently underway to produce and identify new immunosuppressive agents. Ideally, an immunosuppressive agent should be specific for allograft rejection while sparing the host from infection. Preliminary data demonstrates the effectiveness of a new immunosuppressive agent, FK-506, in decreasing rejection episodes and prolonging graft survival.[109,110] FK-506 and cyclosporine appear to have a similar mechanism of immunosuppression. However, FK-506 appears to be a more potent immunosuppressive agent requiring markedly decreased adjuvant immunosuppressive agents. One major advantage is the ability to wean the recipient from steroids in the early postoperative period. Clinical trials are currently underway to test and confirm the efficacy and safety of this new drug.

Over the past 27 years, the field of liver transplantation has made great strides. It has progressed from an experimental procedure to an accepted therapeutic modality for many patients with end-stage liver disease. Survival rates and the quality of life have made this the treatment of choice for most patients with end-stage liver disease and it can be anticipated that with further

developments survival rates as well as quality of life will even improve even further.

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LEGEND

TABLE I History of Immunosuppression

TABLE II a. Liver Transplantation in the United States
b. Liver Transplantation in the United Kingdom

TABLE III Indications for Orthotopic Liver Transplantation

TABLE IV Pretransplantation Management Problems

FIGURE 1 Procurement of the Hepatic Allograft - Standard Technique
Common bile duct transected, splenic and left gastric arteries ligated, cannula in splenic vein for cold perfusion.

FIGURE 2 Procurement of the Hepatic Allograft - Rapid Flush Technique
Cannulae in inferior mesenteric vein (I.M.v.) and aorta beneath the inferior mesenteric artery (I.M.a.).

FIGURE 3 Completed Liver Transplant Including Four Vascular Anastomoses and One Biliary Anastomosis
IVC = inferior vena cava

FIGURE 4 Heparin-Free Veno-Venous Bypass

FIGURE 5 Biliary Tract Anastomoses -
a. Choledochocholedochostomy over a T-tube stent
b. Choledochojejunostomy over an internal stent

FIGURE 6 Segmental Liver Transplant
IVC = inferior vena cava
HA = hepatic artery
PA = portal vein anastamosis to confluence of superior mesenteric vein and splenic vein
Ao = aorta

FIGURE 7 Auxiliary Liver Transplant
IVC = inferior vena cava
Ao = aorta

FIGURE 8 Survival Rates for Liver Transplantation
a. Adult
b. Pediatric
Adapted from LIVER TRANSPLANTATION A 31-YEAR PERSPECTIVE by Thomas E. Starzl, M.D., Ph.D. and Anthony J. Demetris, M.D., a Year Book Medical Publishers, Inc. 1990 publication.

TABLE I

History of Immunosuppression

Agent	Year Reported
Azathioprine	1962
Combined Azathioprine-Steroids	1963
Polyclonal Antibodies Antilymphocyte Globulin	1966
Cyclophosphamide	1970
Immunosuppressive Properties of Cyclosporine Identified	1972
Cyclosporine used in Humans	1978
Combined Cyclosporine-Steroids	1980
Monoclonal Antibodies Developed	1981
Cyclosporine Approved in U.S. for Liver	1983

Table IIa

LIVER TRANSPLANTATION IN THE UNITED STATES

Before 1982	119
1982	62
1983	164
1984	308
1985	602
1986	924
1987	1199
1988	1680

Table IIb

LIVER TRANSPLANTATION IN THE UNITED KINGDOM

1983		20
1984		51
1985		88
1986		127
1987		175
1988		244
1989	(est)	300

Table III

INDICATIONS FOR ORTHOTOPIC LIVER TRANSPLANTATION

I. Chronic Active Hepatitis
    A. Viral
    B. Drug Induced
    C. Autoimmune
II. Alcoholic Liver Disease
III. Primary Biliary Cirrhosis
IV. Sclerosing Cholangitis
V. Biliary Atresia
VI. Cholestatic Syndrome
VII. Budd-Chiari Syndrome
VIII. Unresectable Hepatic Malignancies
IX. Fulminant Hepatic Failure
    A. Viral
    B. Drug-Induced
    C. Metabolic Liver Disease
X. Inborn Errors of Metabolism
    A. Wilson's Disease
    B. Alpha-1-antitrypsin Deficiency
    C. Tyrosinemia
    D. Glycogen Storage Disease Type I
    E. Glycogen Storage Disease Type IV
    F. Hemochromatosis
    G. Homozygous Hyperlipoproteinemia Type II
    H. Crigler-Najjar Syndrome I
    I. Neville's Syndrome
    J. Protein C Deficiency
    K. Hemophilia
    L. Urea Cycle Deficiency
    M. Cystic Fibrosis
    N. Protoporphyria

TABLE IV

PRETRANSPLANTATION MANAGEMENT PROBLEMS

Hepatic Encephalopathy

Infection

Refractory Ascites

Renal Failure

Variceal Hemorrhage

Malnutrition

FIGURE 1

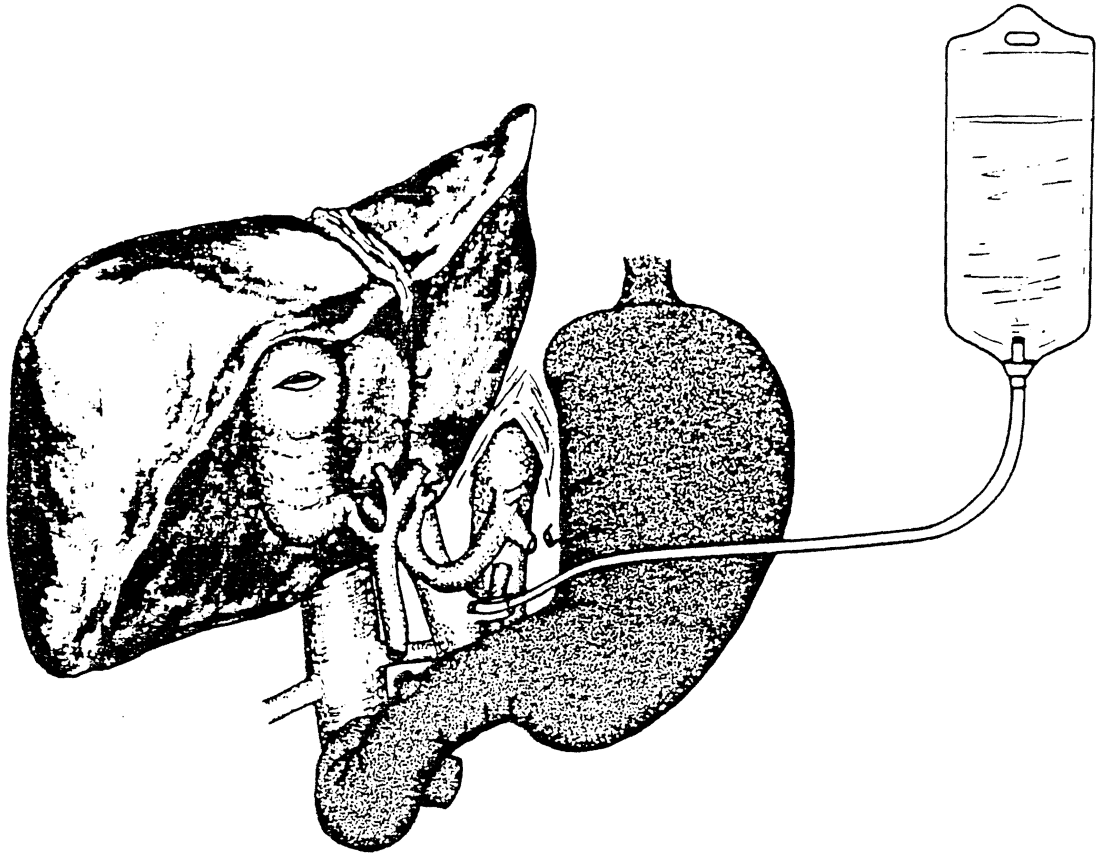


FIGURE 2

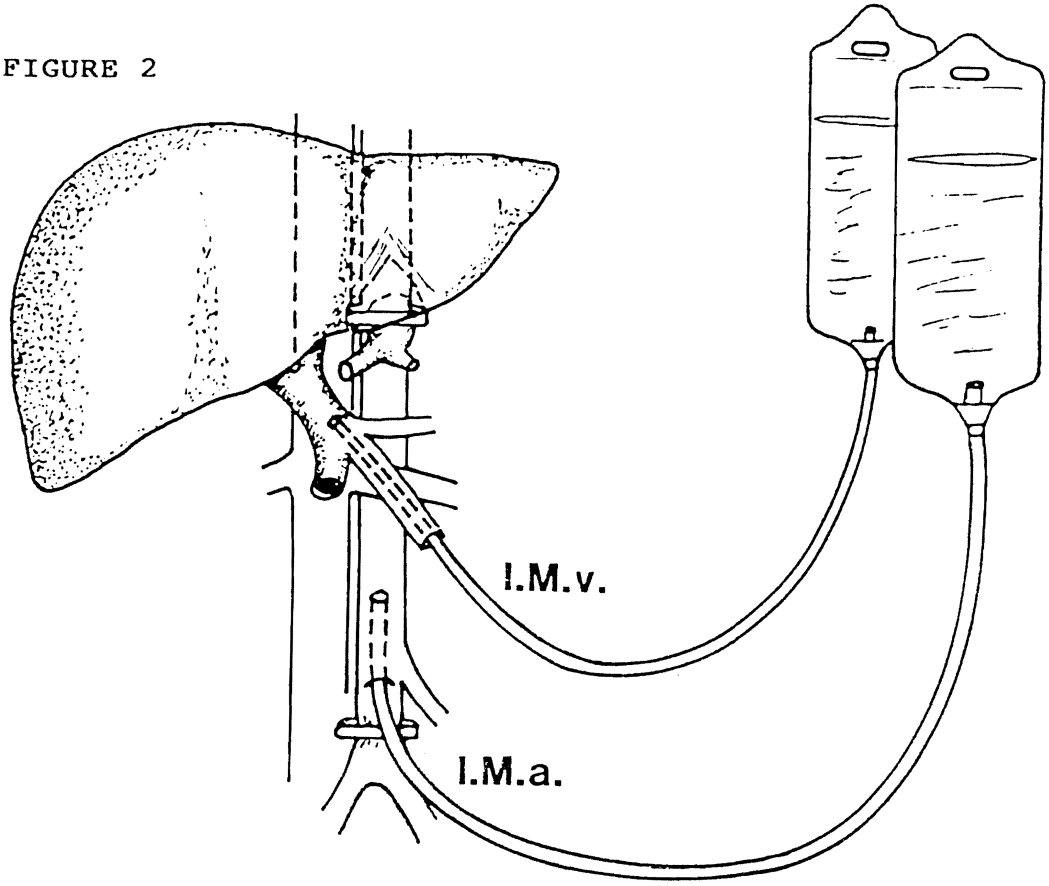


FIGURE 3

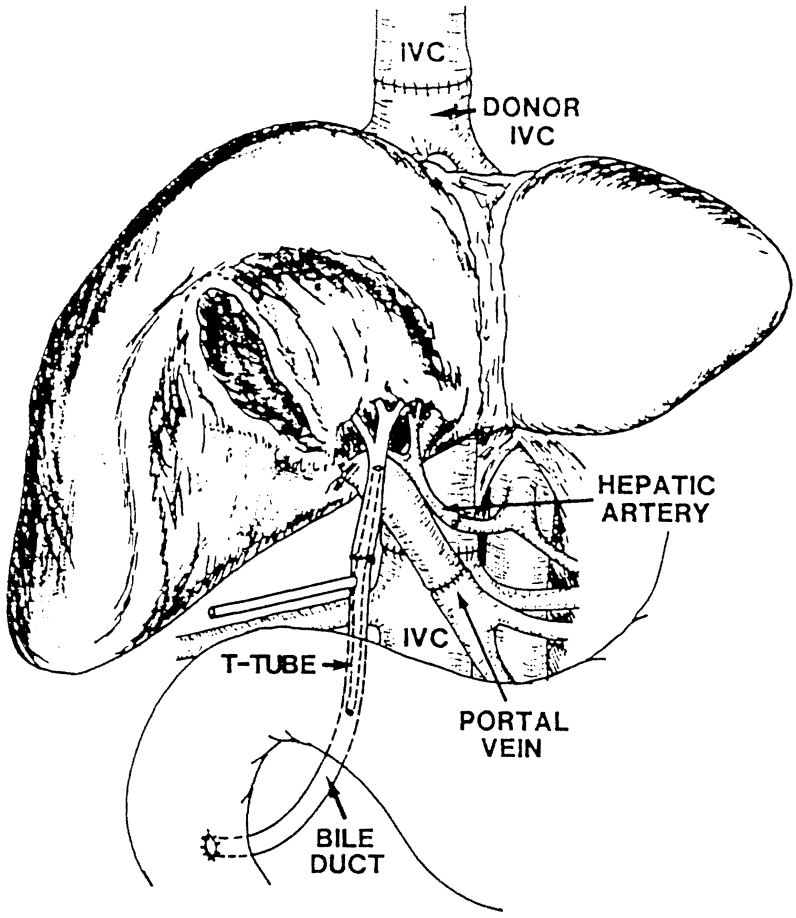

IVC
DONOR
IVC
HEPATIC
ARTERY
IVC
T-TUBE
PORTAL
VEIN
BILE
DUCT

FIGURE 4

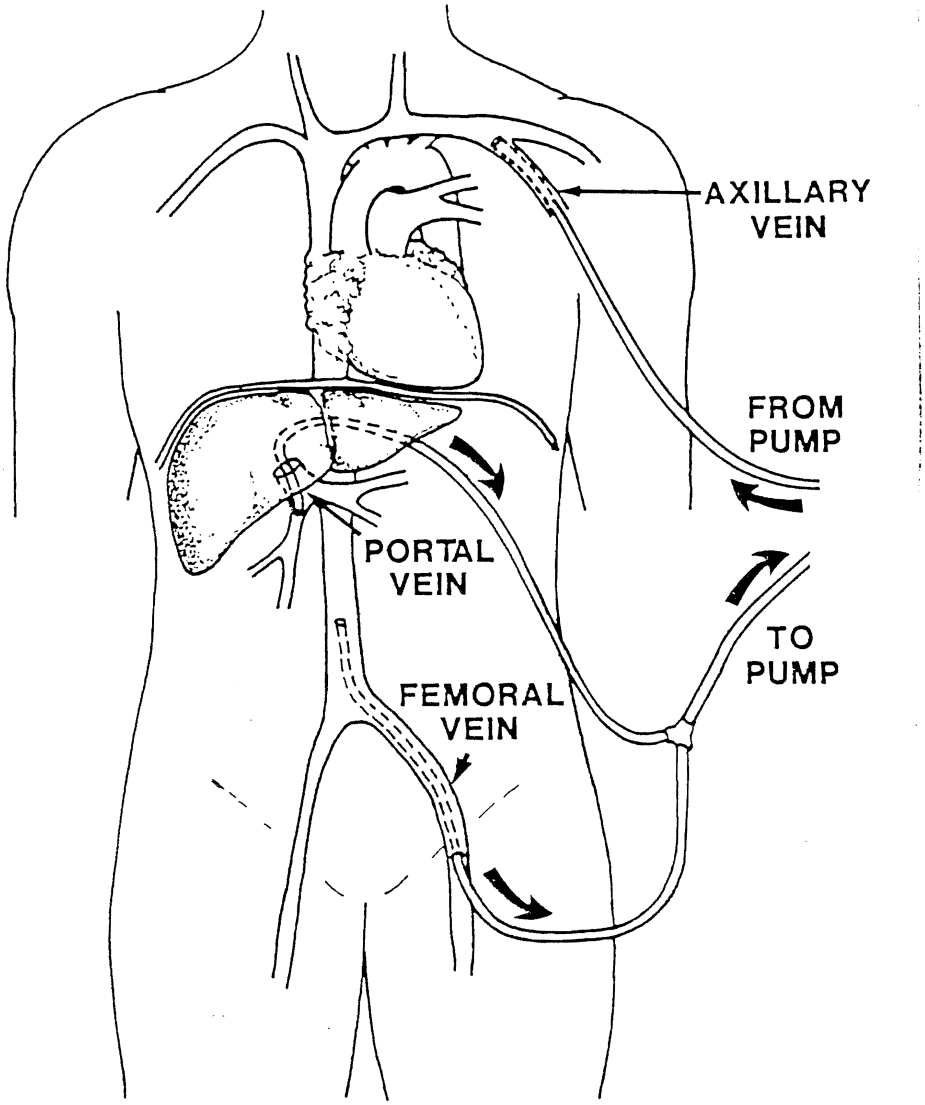


FIGURE 5

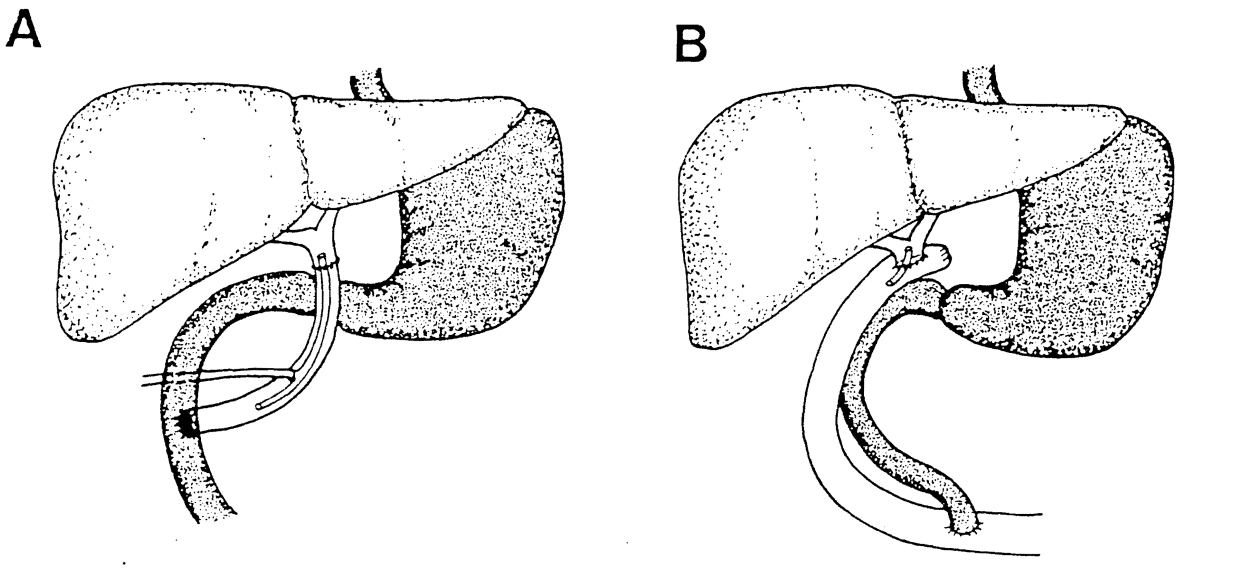


FIGURE 6

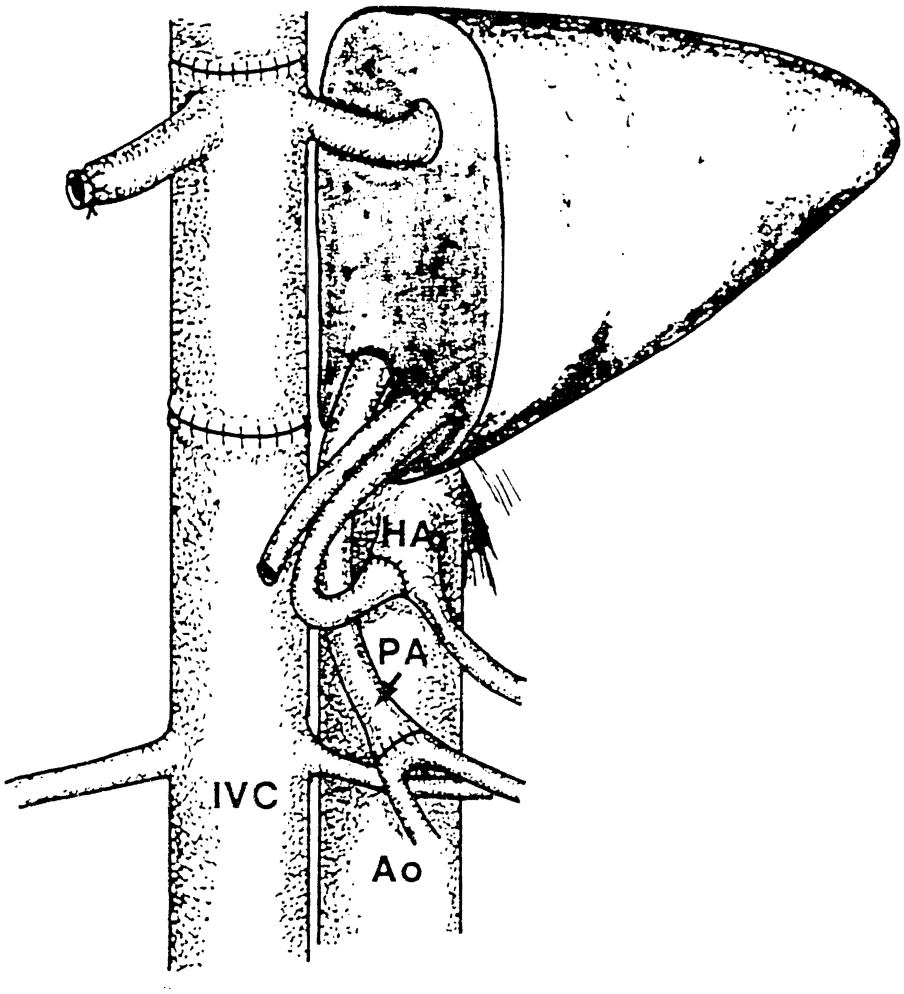


FIGURE 7

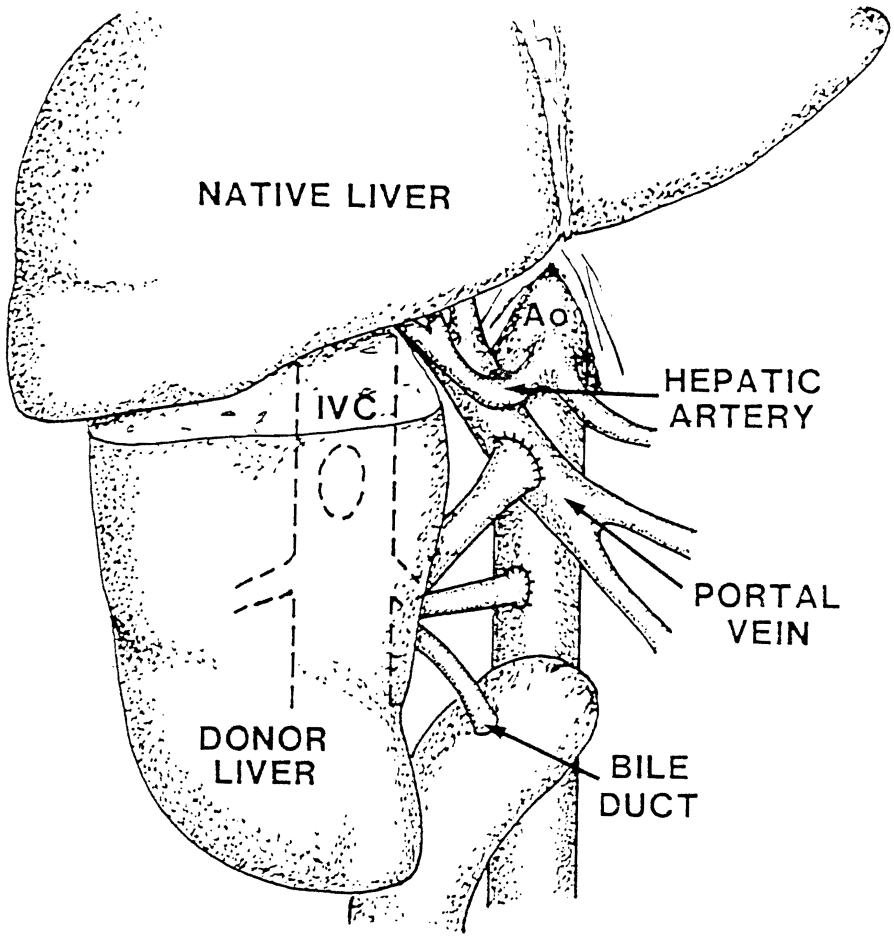
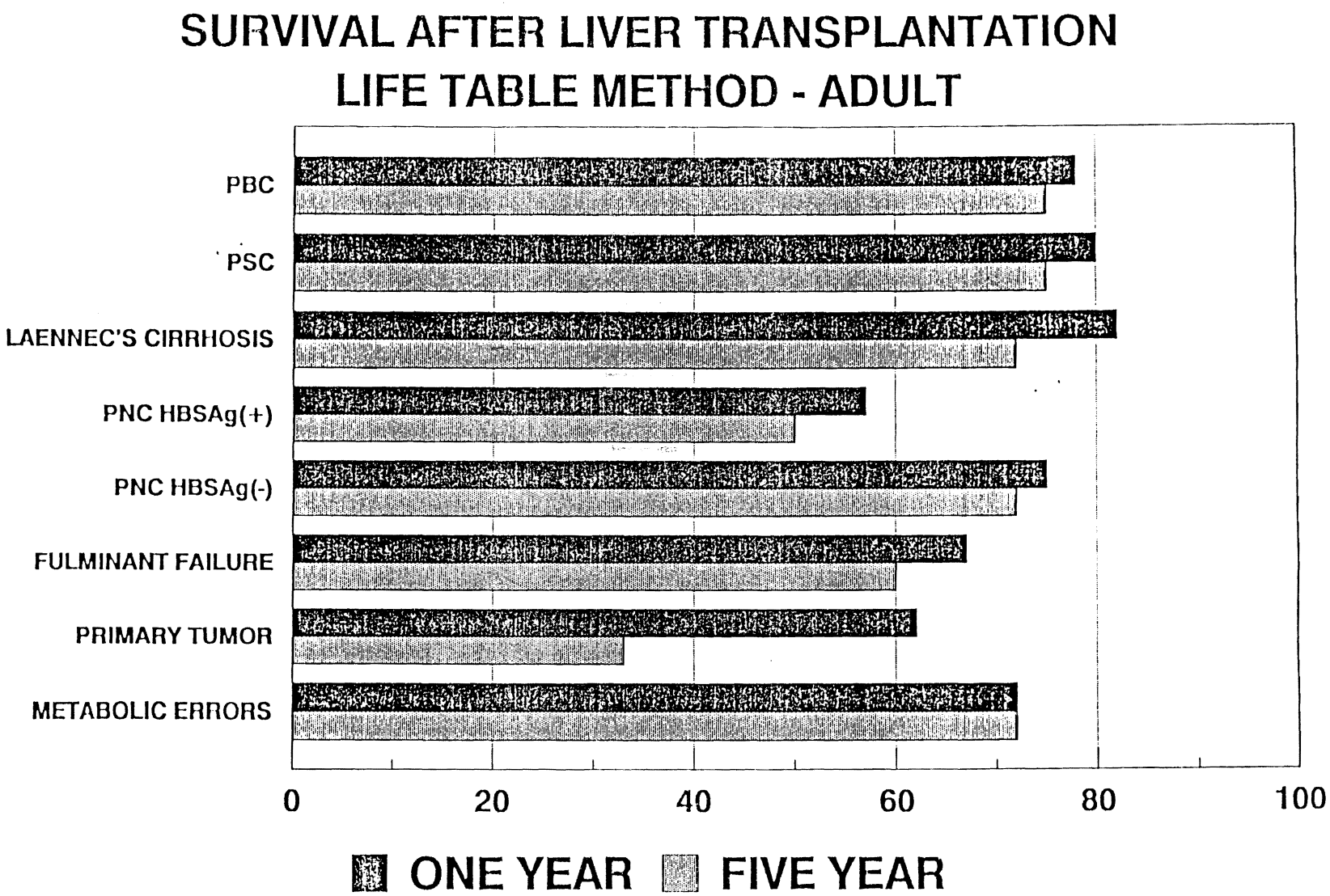

NATIVE LIVER
Ao
IVC
HEPATIC ARTERY
PORTAL VEIN
DONOR LIVER
BILE DUCT

FIGURE 8a



PBC = PRIMARY BILIARY CIRRHOSIS, PSC = PRIMARY SCLEROSING CHOLANGITIS, PNC = POST NECROTIC CIRRHOSIS

FIGURE 8a

FIGURE 8b

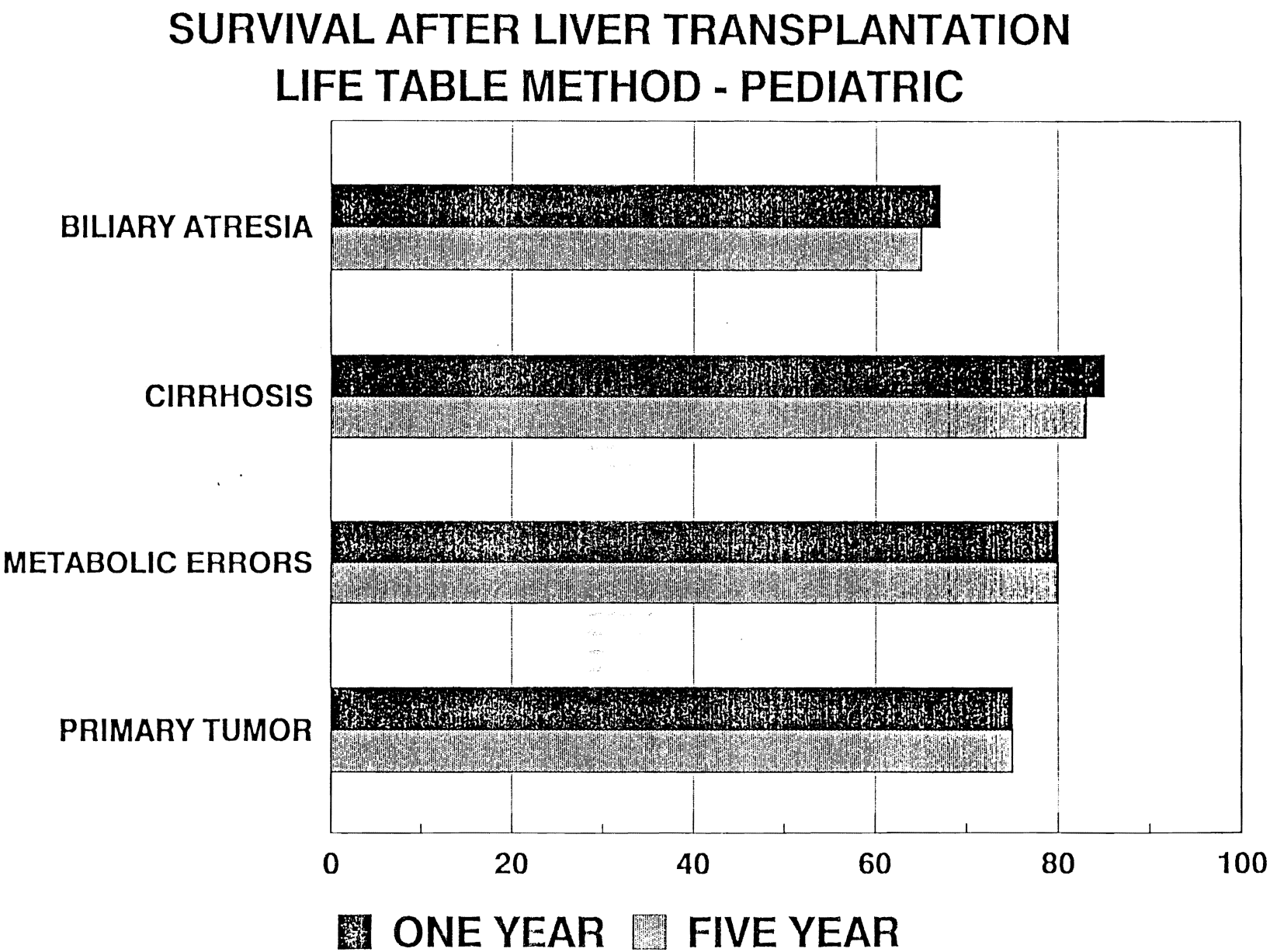


FIGURE 8b