1032

60. Orthotopic Liver Transplantation

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The dramatic increase in orthotopic liver transplants performed in the United States and Europe since the introduction of cyclosporine for maintenance immunosuppression bears witness to the international acceptance of this operation for the treatment of end-stage liver disease. In the first 17 months of reporting to the UNOS, the national organ sharing network for the United States, 1636 liver recipients from 51 transplant centers in 25 states were registered (Fig. 60–1). The first summary from the European liver registry, published in 1987, reported 1238 recipients from 32 transplant centers (Fig. 60–2). By mid-1988 this had increased to 2414 recipients from 49 centers.

INDICATIONS FOR LIVER TRANSPLANTATION

Today any patient with an irreversible and progressive liver disease that is intractable to other medical or surgical therapy and who does not have a contraindication to transplantation is a potential candidate for liver replacement. The diverse conditions for which liver transplantation has been performed at the University of Pittsburgh are summarized in Table 60–1. Most conditions are diseases that lead to liver failure, but occasionally liver transplantation is performed to correct a genetic error based in the liver that produces life-threatening disease in other organ systems. Examples are oxalosis, which results in renal failure and usually recurs soon after renal transplantation, and familial hyperlipoproteinemia, which results in severe premature coronary artery disease and may necessitate heart transplantation as well.

In considering the indications for liver transplantation, it is convenient to allocate patients into three groups based on body weight at the time of transplantation: adults (>20 kg), children (7 to 20 kg), and infants (less than 7 kg). Actuarial (life-table) patient survival rates after liver transplantation for 728 adults, 240 children, and 37 infants for nonmalignant indications are summarized in Figure 60–3. The 30-day, 1-year, and 3-year survival rates for adults are 89.0, 75.3, and 70.1 percent, respectively. For children, these rates are 84.6, 68.3, and 67.3 percent. The survival rates for infants are 78.4, 55.8, and 44.0 percent. The poorer results in infants are primarily accounted for by technical considerations, as will be discussed later in this chapter.

Indications in Infants and Children

Figure 60–4 summarizes the indications for liver transplantation in 281 patients who weighed less than 20 kg at the time of operation. Biliary atresia is the predominant indication for transplantation in this group (67.6 percent). Because of the scarcity of organ donors for these patients, many die waiting for transplantation, and many of those fortunate enough to receive a transplant have waited until they are critically ill. Technical complications, especially vascular thrombosis, are also more frequent in this group and carry substantial morbidity and mortality.

Most patients have extrahepatic biliary atresia and have had at least one prior surgical attempt to establish biliary drainage. Portoenterostomy (Kasai procedure) is successful in establishing biliary drainage in only one fourth of patients. Thus for most patients with biliary atresia, liver transplantation is the only viable solution.

A single attempt at biliary diversion is worthwhile since it can permit normal growth and development. Even if transplantation is later required for intractable cholangitis or eventual biliary cirrhosis, donor organ scarcity and technical hazards are less for older children. However, multiple forays into the hepatic hilum and intestinal reconfigurations make liver transplantation much more difficult. Reoperation should be limited to those patients in whom bile flow is lost after an initially successful operation and can be reestablished by simple correction of a technical flaw or removal of biliary stones.

Inborn errors of metabolism, hereditary cholestatic syndromes, fulminant hepatic failure, chronic active hepatitis, and neonatal (giant cell) hepatitis account for most of the other transplantations performed in children. Survival rates for these indications are similar to survival in adults receiving transplants for benign diseases.

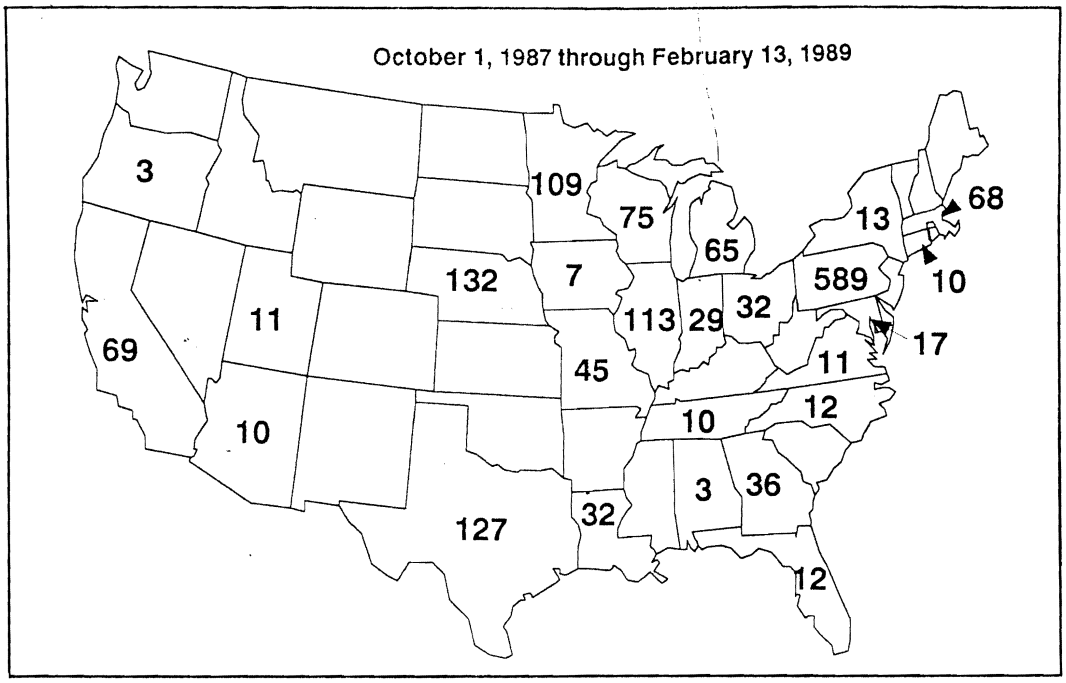

Figure 60–1. Liver transplantations registered with UNOS, the national organ sharing network in the United States during the first 17 months.

Indications in Adults

Figure 60–5 summarizes the principal indication for liver transplantation in 770 patients who weighed more than 20 kg at the time of transplantation. Cryptogenic cirrhosis, which is presumed in most cases to be the nonA–nonB type of viral hepatitis but also includes a small percentage of patients with idiopathic autoimmune hepatitis, is the most common indication for transplantation in adults. This is followed by primary biliary cirrhosis, alcoholic cirrhosis, genetic errors of metabolism, sclerosing cholangitis, and chronic active hepatitis B.

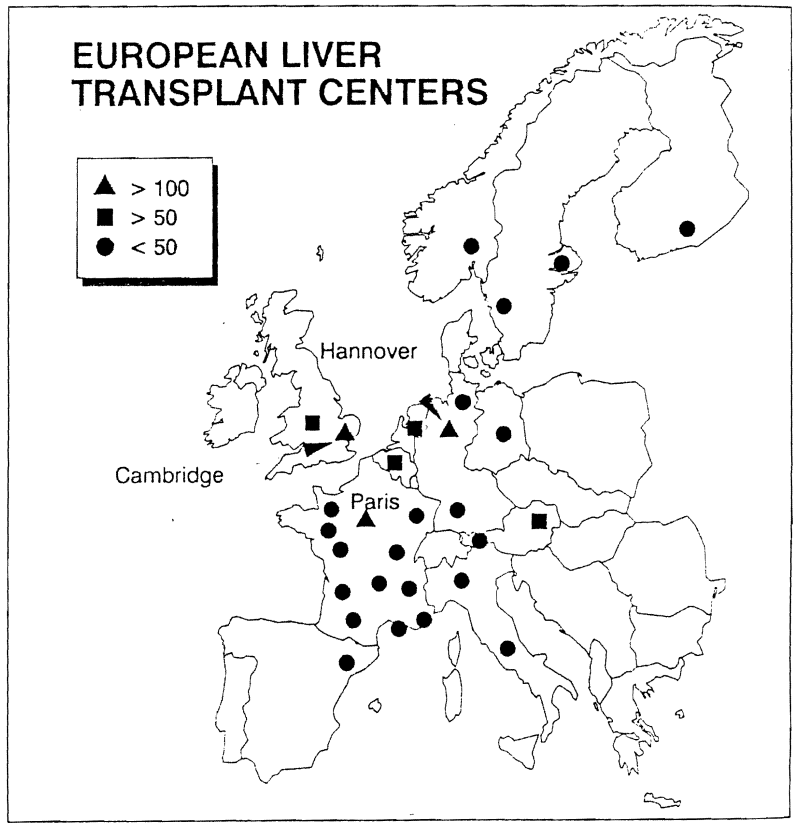

Figure 60–2. Liver transplant centers registered in the first report of the European Liver Transplant Registry.

(Source: From Bismuth H, Caistaing D, et al, 1987, with permission.)

TABLE 60–1. INDICATIONS FOR LIVER TRANSPLANTATION

Fulminant Hepatic Failure	**Advanced Chronic Liver Disease**
Viral hepatitis	Cholestatic diseases
A, B, D, nonA–nonB, EBV, CMV, others	Primary biliary cirrhosis
Drug-induced liver disease	Primary sclerosing cholangitis
Halothane	Biliary atresia
Gold	Familial cholestatic syndromes
Dilsulfiram	Hepatocellular diseases
Acetaminophen	Chronic viral hepatitis
Others	Chronic toxic hepatitis
Metabolic liver disease	Chronic alcoholic cirrhosis
Wilson disease	Idiopathic autoimmune hepatitis
Reye syndrome	Vascular disease
Organic acidurias	Budd-Chiari syndrome
Massive trauma	Venoocclusive disease
Unresectable Hepatic Tumors	**Genetic Errors of Metabolism**
Hepatocellular carcinoma	α-1-antitrypsin deficiency
Rare nonhepatocellular or bile duct tumors arising in the liver	Wilson disease
	Homozygous type II hyperliproteinemia
Isolated hepatic metastatic disease	Crigler-Najjar syndrome type I
Carcinoid	Urea cycle deficiencies
Pancreatic islet cell tumor	Glycogen storage disease types I and II
Others	Tyrosinemia
	Protein C deficiency
	Hemophilia
	Oxalosis

EBV, Epstein-Barr virus; CMV, cytomegalovirus.

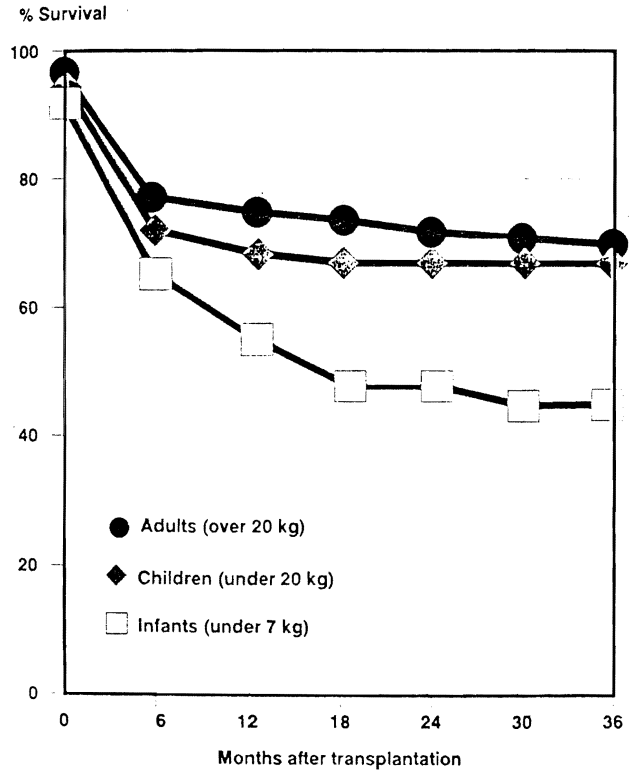

Figure 60–3. Actuarial (life-table) survival rates after liver transplantation for 728 adults, 240 children, and 37 infants. The survival rate for infants is signficantly below those for adults and children ($P < .01$).

Figure 60–6 compares survival rates after liver transplantation for 698 adults with benign chronic disease (cryptogenic cirrhosis, primary biliary cirrhosis, inborn errors of metabolism, etc.) to 52 adults with chronic active hepatitis B, and 60 adults with hepatobiliary cancers. Although early survival is high in all three groups, longer survival for patients after transplantation for chronic active hepatitis B or for unresectable cancer is characterized by high mortality from recurrent disease.

Hepatic and Biliary Tract Cancer

When orthotopic liver transplantation was first attempted in humans, primary liver malignancy was thought to be an excellent indication. Many patients when first seen did not have severe portal hypertension, and total hepatectomy offered an opportunity to extend the limits of resectability. Table 60–2 summarizes the 30-day and 1-year survival rates after transplantation for malignant and benign disease in the University of Pittsburgh and the Cambridge/King's College Hospital (England) experiences. In the first European Liver Transplant Registry report, survival at 2 years after transplantation for patients with hepatocellular carcinoma was 30 percent. These series demonstrate the high longer-term mortality after transplantation for cancer, with many patients developing recurrence within 18 to 36 months of transplantation. The liver graft and the lungs are frequent sites of first recurrence. Several factors are important in determining prognosis, including the histologic type, the presence of cirrhosis, and regional lymph node involvement.

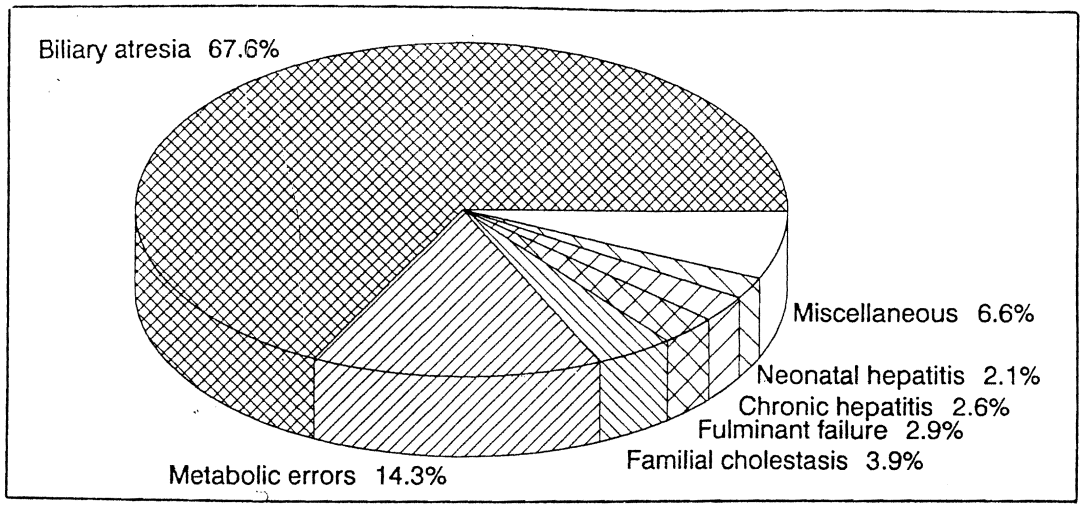

Figure 60–4. Indications for liver transplantation in 281 pediatric recipients treated at the University of Pittsburgh with cyclosporine-prednisone therapy.

Hepatocellular Carcinoma. Hepatocellular carcinoma is the most common primary liver cancer and is particularly prevalent in the Far East where it is associated with the high rate of chronic HBV. Many patients with concurrent cirrhosis are initially seen with advanced tumors. Thus recurrence is common and tends to occur early. Better survival is obtained in patients without concurrent cirrhosis or in patients who received a transplant for benign indications with small incidental hepatomas discovered at operation or on subsequent pathologic examination of hepatectomy specimen. Only 1 of 14 patients in the Pittsburgh series who had an incidental tumor has developed a recurrence.

Fibrolamellar Hepatoma. Fibrolamellar hepatoma is a histologic variant of hepatocellular carcinoma that tends to afflict younger patients and behaves less aggressively than conventional hepatoma. Although eventual recurrence has been common, it has tended to occur later; mean survival in the Pittsburgh series is 30⅓ months.

Bile Duct Cancers. Bile duct cancers have tended to behave aggressively after liver transplantation, and recurrence within the first year after operation has been common. Approximately 10 percent of the patients who came for transplantation for sclerosing cholangitis have subsequently been found to have malignant lesions in the bile ducts.

The Hannover group (Germany) found that survival is significantly better in patients with tumor-free regional lymph nodes. None of the patients in their series with positive regional nodes survived more than 2 years, but 83 percent of those with tumor-free nodes were alive at 2 years.

Epithelioid Hemangioendothelioma. Epithelioid hemangioendothelioma originates in the endothelial cell and is not unique to the liver. Although it grows slowly, it eventually metastasizes to lymph nodes, bones, and pleura. Multiple lesions in both lobes of the liver are often found, thus necessitating removal by total hepatectomy and transplantation.

Six patients with this lesion who received a transplant

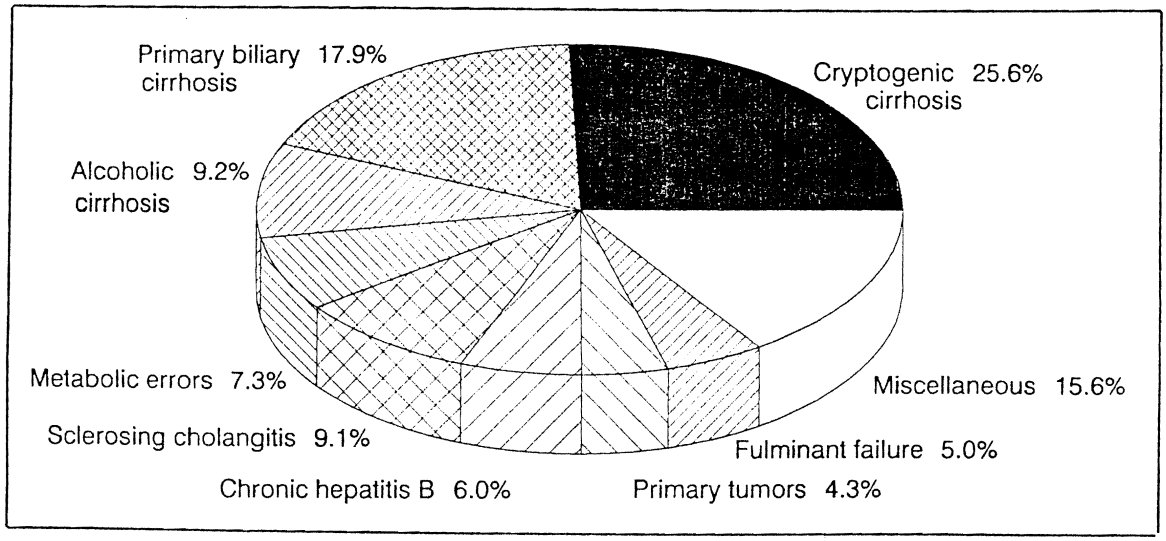

Figure 60–5. Indications for liver transplantation in 770 adult recipients treated at the University of Pittsburgh with cyclosporine-prednisone therapy.

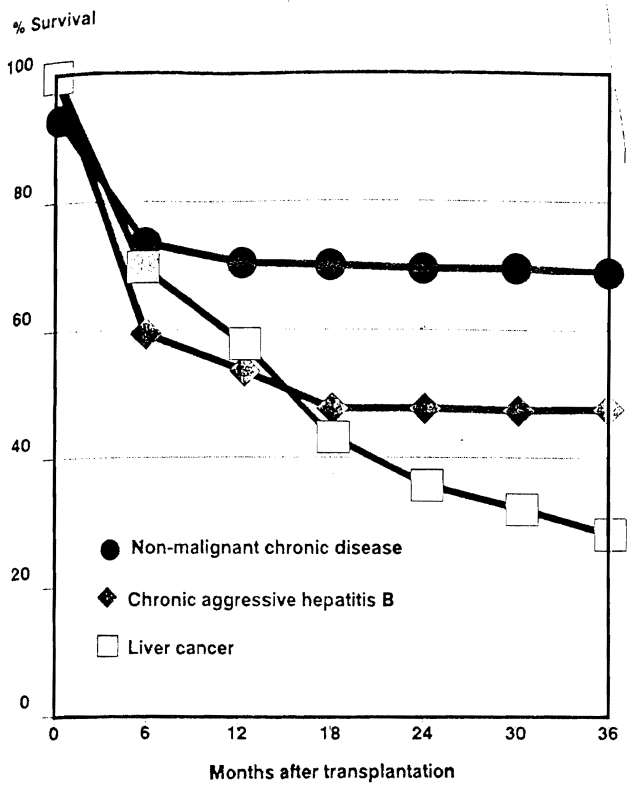

Figure 60–6. Actuarial survival rates (life-table method) after liver transplantation for 698 adult patients with benign chronic diseases (e.g., cryptogenic cirrhosis, primary biliary cirrhosis, alcoholic cirrhosis, inborn errors of metabolism, sclerosing cholangitis) compared to 52 patients with chronic active hepatitis-B and 60 patients with liver cancer.

in Pittsburgh have survived, including two patients with known distant metastases that remained stable after operation. Although this tumor has recurred, it progresses slowly, as is typical of hemangioendothelioma, and long periods of effective palliation have been achieved. More experience is needed to determine the ultimate role for liver transplantation in the management of this lesion.

Angiosarcoma. Angiosarcoma is an aggressive tumor. Transplantation has been attempted in a small number of patients but recurrence has been early and quickly fatal. Currently, it is a lesion that is not effectively treated by transplantation.

Metastatic Cancer. Transplantation for adenocarcinoma metastatic to the liver has had poor results in most instances. The role of liver transplantation for metastatic neuroendocrine tumors is still being investigated. Recently, Starzl has performed a radical hepaticopancreatectomy in which the liver and the contiguous pancreas, duodenum, right colon, and stomach are removed en bloc and replaced either by a composite "cluster graft" of liver, pancreas, and duodenum, or a liver graft alone in an effort to remove both the regional metastases and the primary tumor. It is not yet known how this approach will affect recurrence.

Liver transplantation is of limited benefit for most patients with liver or biliary tract cancer. Although it is still premature to remove liver transplantation from the list of therapeutic options for such patients, its role needs to be redefined in the context of other advances in the therapy of cancer.

Chronic Active B-virus Hepatitis

A chronic carrier state develops in approximately 10 percent of patients after infection with hepatitis B-virus (HBV), and half of these will progress to chronic active hepatitis with end-stage cirrhosis. After liver transplantation, most patients remain surface antigen–positive (HBsAg+). Although clinical reinfection is common, the ultimate clinical course is unpredictable. A significant proportion of patients are first seen with a persistent low-grade hepatitis that may or may not progress to end-stage liver disease.

Several approaches have been taken in the effort to reduce the risk of reinfection, including active and passive immunization protocols with HBV vaccines and hyperimmune globulin and trials of α-interferon therapy. Although a few patients have been reported to develop antibody and become antigen free after such treatments, overall results have been unimpressive. Recently, a human monoclonal antibody to the HBV surface antigen has been developed by the Sandoz Corporation (Basel, Switzerland). This antibody is 50,000 times more potent than conventional hyperimmune globulin and has a relatively long half-life in serum. Limited clinical trials with this agent were recently begun, and it has effectively cleared detectable surface antigen for up to 6 months. Further study is needed to determine whether this agent can alter the course of reinfection and clinical hepatitis after liver transplantation for chronic HBV.

Since the outcome after transplantation for chronic HBV is unpredictable and no other effective therapy is available to those patients with end-stage cirrhosis, continued efforts to offer liver transplantation to these patients appear justified.

Fulminant Hepatic Failure

Fulminant hepatic failure may be caused by acute viral infection (hepatitis A, hepatitis B, nonA–nonB hepatitis, Epstein-Barr virus, cytomegalovirus, herpes hepatitis), toxic agents including drugs (acetaminophen, organic solvents, halothane, mushroom poisoning), or metabolic disorders, especially acute Wilson disease. The decision to proceed with transplantation

TABLE 60–2. PATIENT SURVIVAL RATES AFTER LIVER TRANSPLANTATION FOR BENIGN AND MALIGNANT DISEASE

	30-Day Survival		1-Year Survival	
	Malignant	Benign	Malignant	Benign
Pittsburgh	92%	88%	59%	72%
Cambridge/King's College	80%	70%	30%	50%

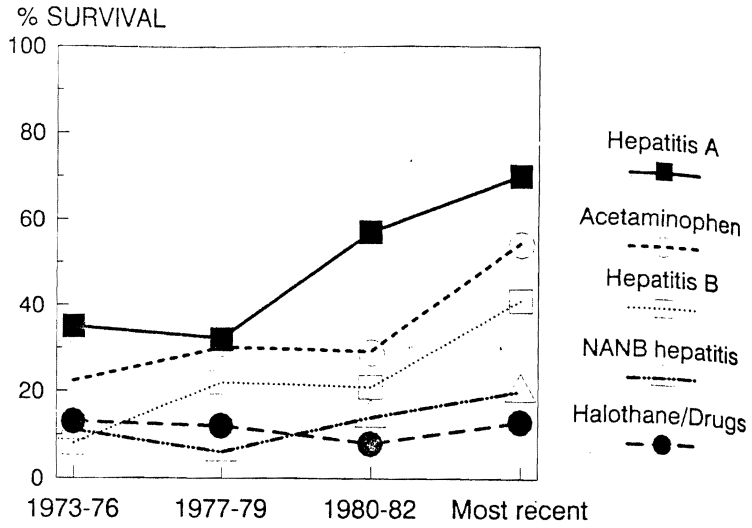

Figure 60–7. Survival rates for medical management of fulminant hepatitic failure according to etiology.

(Source: Adapted from O'Grady JG, Gimson AES, et al, 1988, with permission.)

can be difficult since many patients recover, but delay greatly increases the risk for patients who will not recover without a new liver. The traditional liver chemistry profile (bilirubin, alanine aminotransferase, aspartate aminotransferase, and prothrombin time) is often an unreliable guide to prognosis since extreme abnormalities may be seen in patients who eventually recover. Acetaminophen and mushroom poisoning typically present with extreme abnormalities in liver function studies, but these are not predictive of outcome.

Fortunately, some guidelines are available. Figure 60–7 is adapted from a recent study of the medical management of fulminant hepatic failure by the King's College Hospital liver service in England. In recent years, survival rates for acute hepatitis A (66.7 percent) and acetaminophen poisoning (52.9 percent) have improved significantly, and with proper management many of these patients will recover without transplantation. Survival for other forms of drug-induced or toxic hepatitis and for fulminant nonA–nonB hepatitis remain poor. Early transplantation is probably the best hope for most of these patients. Outcome for acute hepatitis B is variable; it may be necessary to take the patient to the operating room for open liver biopsy with a liver graft available. If biopsy results show severe hepatocellular injury, transplantation should be performed. If results of biopsy show preservation of hepatic lobules consistent with recovery, the liver can be used for someone else.

Rapid shrinkage of liver size on serial imaging studies, progressive mental deterioration with cerebral edema, and elevated cerebrospinal fluid pressure, renal dysfunction, or metabolic acidosis suggest a poor prognosis and can be regarded as indications for transplantation. Plasmapheresis or hemofiltration may be valuable to maintain fluid balance and reduce cerebral edema, lessen the severity of jaundice, and control coagulopathy until a liver donor can be found.

Survival rates after liver transplantation at the University of Pittsburgh are shown in Figure 60–8. Included in this series are 7 patients with drug-induced failure, 10 patients with acute hepatitis-B, 29 cases of acute nonA–nonB hepatitis, 4 cases of acute hepatitis A, and 13 cases of unknown cause. The poor results for patients with toxic hepatitis or unknown types of fulminant failure are indicative of late referral of severely ill patients with a high early postoperative mortality. Since most patients with hepatitis A are expected to recover, these few referrals have also been advanced cases. Early survival for hepatitis B and nonA–nonB patients has been much higher, possibly because these patients are not expected to do as well with medical therapy and transplantation has been aggressively pursued. In all groups, patients who survive the first 6 months after transplantation have an excellent long-term prognosis.

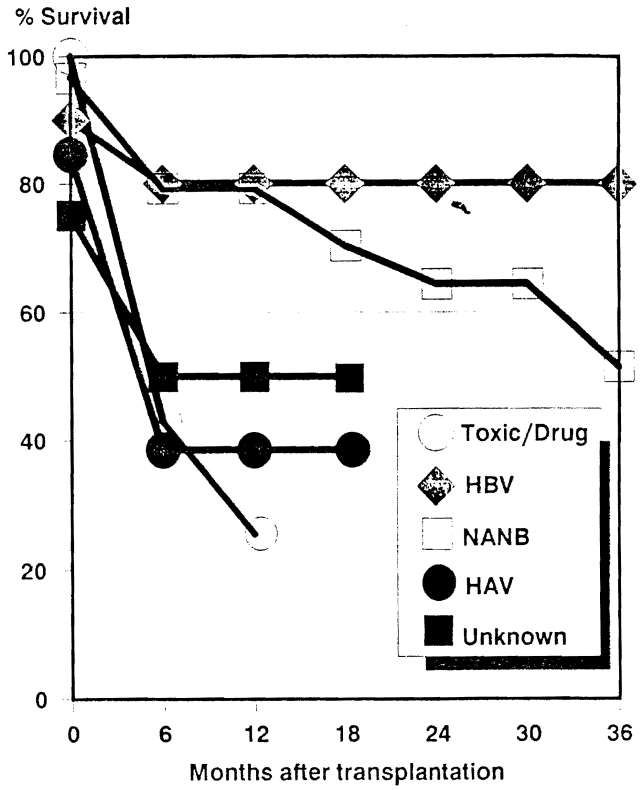

Figure 60–8. Actuarial survival rates (life-table method) after liver transplantation at the University of Pittsburgh for 7 patients with drug-related acute hepatic failure, 10 patients with acute hepatitis-B, 29 patients with fulminant nonA–nonB hepatitis, 4 cases of acute hepatitis A, and 13 cases of unknown cause.

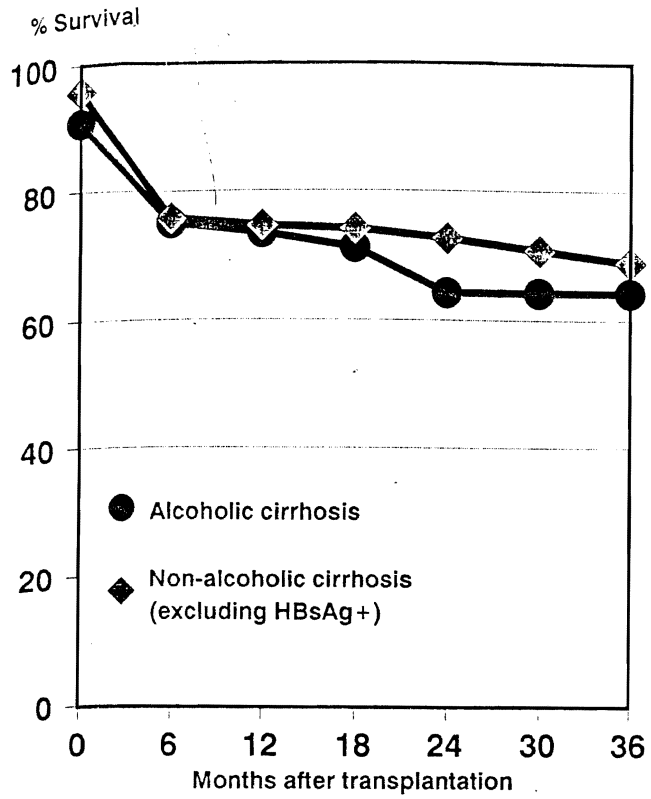

Figure 60–9. Actuarial survival rates (life-table method) after liver transplantation at the University of Pittsburgh for 76 adults with alcoholic cirrhosis compared with 256 adults with other forms of cirrhosis, excluding HBsAg-positive patients and patients with hepatobiliary cancers. There is no significant difference in the survival rates.

Since the prognosis is at best guarded for many patients presenting in fulminant hepatic failure, early consultation with a liver transplant center is an important component of modern management.

Alcoholic Cirrhosis

The role of liver transplantation in the management of alcoholic cirrhosis has been controversial. The disease carries a social stigma and is regarded by some as a form of errant behavior rather than a health problem. Because of the relative shortage of organ donors, it has been argued that patients with self-inflicted disease and willful misbehavior should be at the end of the waiting list for a scarce and vital resource. Furthermore, patients with alcoholic cirrhosis have been considered to be a high medical risk group, since they often present with serious acute complications such as massive variceal hemorrhage, encephalopathy, or severe ascites and malnutrition.

Figure 60–9 presents the survival rate for 76 adults who had liver transplants at the University of Pittsburgh for alcoholic cirrhosis compared to the survival rate for 256 patients with other forms of cirrhosis (excluding HBsAg-positive patients and patients with primary liver cancer). There is no significant difference in early or late survival between these groups. Alcoholic cirrhosis is the most common cause of advanced liver disease in Western society. In the absence of objective contraindications to transplantation such as uncorrectable cardiomyopathy, irreversible central nervous system degeneration, or deliberate refusal by the patient to cooperate despite appropriate medical and psychiatric support, there is no rational basis for denial of transplantation to these patients.

Portal Hypertension and Variceal Hemorrhage

Operations such as esophageal devascularization procedures or nonselective or selective portosystemic shunts for the patient with an acute hemorrhage from esophageal varices are designed to prevent rebleeding but do not correct the underlying liver disease. In recent years, endoscopic sclerotherapy has been widely used for control of acute hemorrhage, and in experienced hands, sclerotherapy alone can prevent rebleeding. However, most of the patients with advanced cirrhosis who have variceal hemorrhage will die within 3 months of liver failure, not rebleeding. Although control of diet and abstinence from hepatotoxic substances such as alcohol may produce transient improvement in liver function, cirrhosis is typically a relentless process of progressive hepatic fibrosis, hepatocellular failure, and worsening portal hypertension.

Child's classification of liver functional status, shown in Table 60–3, remains a useful guide to management of the patient with variceal hemorrhage. Patients in class A have good hepatic reserve, are unlikely to die of liver failure in the near future, and remain excellent candidates for sclerotherapy or a selective shunt to prevent rebleeding. However, most patients in class B and virtually all patients in class C are at high risk of early death from hepatic failure. Liver transplantation is the only procedure that can effectively treat cirrhosis, and such patients should be considered for transplantation. In most of these patients, sclerotherapy can be used for initial control of bleeding. If an interventional surgical procedure is required because of failure of sclerotherapy and an unavailability of transplantation, a selective splenorenal (Warren) or mesocaval (Drapanas) shunt is recommended. These shunts avoid dissection in the hepatic hilum and can be interrupted easily at transplantation.

CONTRAINDICATIONS TO LIVER TRANSPLANTATION

The list of contraindications to liver transplantation has grown shorter as management and operative techniques have improved. Active infection outside the hepatobiliary tree, unresectable cancer, advanced cardiopulmonary disease, clinical AIDS-related complex (ARC) or acquired immune deficiency syndrome (AIDS), or any morbid condition that is a major

TABLE 60–3. CHILD'S FUNCTIONAL CLASSIFICATION OF LIVER DISEASE

Clinical and Biochemical Measurements	Child's Class		
	A	B	C
Encephalopathy	None	Mild-moderate	Severe
Ascites	None	Slight	Moderate
Bilirubin (mg/dl)	<1.5	1.5–3.0	>3.0
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged)	1–4	4–6	>6

impairment to improvement after liver transplantation are the only absolute contraindications. There is no absolute age limit for liver transplant candidates. Neonates and patients in the eighth decade have been successfully transplanted.

Relative contraindications include advanced age, portal vein thrombosis, severe hypoxemia with intrapulmonary right to left shunts, prior complex hepatobiliary surgery, and positive-HIV serology without clinical AIDS. In experienced transplant centers, many of these relative contraindications can be overcome.

PREPARATION FOR SURGERY

When serious complications of advanced liver disease are present, such as advanced ascites, encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis, hepatic osteodystrophy, or intractable pruritus, serious consideration must be given to candidacy for liver transplantation. The object of medical care should be to put the patient in the best possible condition for operation.

Infections must be aggressively treated. Four to five days of therapy with appropriate antibiotics is sufficient for patients who need urgent transplantation, except when deep-seated soft tissue infection (pneumonia, intraabdominal abscess, pyelonephritis) is present. At least a week of therapy is preferable in cases of deep infection. Standard medical therapy including oral neomycin or lactulose, transfusions of blood or albumin, diuretics, and control of diet are instituted for correction of blood volume, fluid abnormalities, and to clear encephalopathy if present. Dialysis may be necessary in patients with hepatorenal syndrome. In severe cases, plasmapheresis may be helpful. Attention to tracheobronchial toilet is essential since early postoperative respiratory infection has a high mortality.

Immunological Considerations

Although the liver is relatively resistant to the hyperacute rejection observed in renal transplantation when grafts are placed in violation of the rules for ABO blood groups or in the presence of preformed antidonor lymphocytotoxic antibody, there is mounting evidence that risks do exist.

ABO Blood Groups. Although liver transplantation performed across an ABO-compatible mismatch (e.g., O to A, O to B, B to AB, etc.) or an ABO incompatibility (e.g., A to B, B to A, A to O, etc.) are often successful, there is a 10 to 15 percent increased mortality associated with such transplants. In the case of an ABO-compatible but mismatched graft, there is frequently a graft-versus-host reaction characterized by a hemolytic anemia, usually in the first 12 to 21 days after transplantation. This is often self-limited but in some cases has been severe, requiring donor ABO blood group red cell transfusion, plasmapheresis, and even retransplantation with an ABO-compatible graft.

The consequences of transplantation of an ABO-incompatible liver are unpredictable and can occasionally be disastrous. There is a significantly higher incidence of acute graft failure with widespread hemorrhagic necrosis after transplantation of an ABO-incompatible liver. For this reason it is currently recommended that only ABO-compatible liver transplantation be performed except in urgent situations and that ABO-incompatible grafts are best avoided altogether.

Preformed Lymphocytotoxic Antibody. To date there is no evidence that liver transplantation in the presence of a high-percentage panel reactive antibody or a positive anti-donor-specific antibody crossmatch has any adverse effect on the outcome of liver transplantation. Preoperative antibody crossmatching is not required.

HLA Typing. The importance of HLA typing in liver transplantation is not clear. Recent single-center studies have shown better results in patients with the poorest grades of HLA match. However, these data must remain suspect until confirmed by larger multi-center studies. Similar results were reported in the early days of renal transplantation and were later proved to be wrong.

THE LIVER DONOR

Donor Selection

The most common explanation for transplantation of an inadequately preserved liver is preexisting hepatic injury, rather than poor harvesting technique. Thus removal of a satisfactory liver begins with careful screening of donors. There is no single reliable test to assess liver viability in the donor, on the back bench in the operating room, or immediately after reperfusion in the recipient. Moderate abnormalities in the liver chemistry profile, especially if there is improvement in serial measurements, should not discourage procurement, but severe profile abnormalities, a need for excessive levels of pressor support, a long period (several days) between injury and the pronouncement of brain death, or deterioration of renal function that suggest poor perfusion of other organ systems, are cause for caution.

Severe coagulopathy is often seen in brain-injured donors and an elevated prothrombin time by itself should not disqualify a donor. Serology results positive for human immunodeficiency virus (HIV) or viral hepatitis, extracranial malignancy, and severe systemic sepsis are contraindications to procurement.

Severe diabetes insipidus is common in the brain-injured donor. It is important to maintain the serum sodium level in the normal range by infusions of solutions containing free water if the serum sodium level is rising. There is a high incidence of primary graft failure for livers procured from severely hypernatremic donors.

It may be necessary to support blood pressure with moderate amounts of vasoactive drugs. Central venous pressure should be monitored to prevent overhydration.

Donor Hepatectomy

Liver grafts are usually procured as part of a multiple-organ procurement, and frequently multiple teams of surgeons participate. The usual order of removal of the organs is heart or heart and lungs first, liver or liver and pancreas next, followed by the kidneys.

The standard technique for donor hepatectomy required several hours of meticulous dissection of the hepatic hilum.

Prolonged manipulation of the liver can result in intermittent interruption of the blood supply and warm ischemic injury. The technique was also unsuitable for use with unstable donors, and the length of the procedure was not conducive to collaboration with other procurement teams. The procedure has been modified in recent years to allow more rapid retrieval.

Modified Rapid Donor Hepatectomy

A midline sternal-splitting incision is used to expose the mediastinum and abdomen. The liver is examined, and the fluid status of the patient is assessed. A swollen, firm organ is indicative of overhydration, and diuretics or phlebotomy should be used. The falciform and left triangular ligaments are divided.

Variations in the liver arterial supply are encountered 40 percent of the time and must be looked for (Fig. 60–10). A palpable pulse in the gastrohepatic ligament suggests an artery to the left lateral segment from the left gastric artery. It should be preserved in continuity with its left gastric origin from the celiac axis. If not present, the gastrohepatic ligament may be divided and the supraceliac aorta exposed.

The hilar dissection is performed next (Fig. 60–11). An arterial pulse posterior to the portal vein in the foramen of Winslow suggests a right hepatic artery originating from the superior mesenteric artery. If such is the case, pancreas procurement is usually abandoned since it is difficult to safely preserve the arterial supply to both liver and pancreas in this circumstance. It is not necessary and may be imprudent to dissect this artery since arterial spasm may result. The common hepatic artery should be identified in the groove between the superior border of the pancreas and the large lymph node always present there. Absence of a vessel there indicates that the entire arterial supply to the liver originates from the superior mesenteric artery. The hilar structures are then dissected free, with care being taken to stay as far from the liver as possible. The gastroduodenal artery is ligated and divided. The common bile duct is divided close to the duodenum. The gallbladder fundus is incised, and the gallbladder and ducts are flushed with saline solution to prevent autolysis of the mucosa by bile.

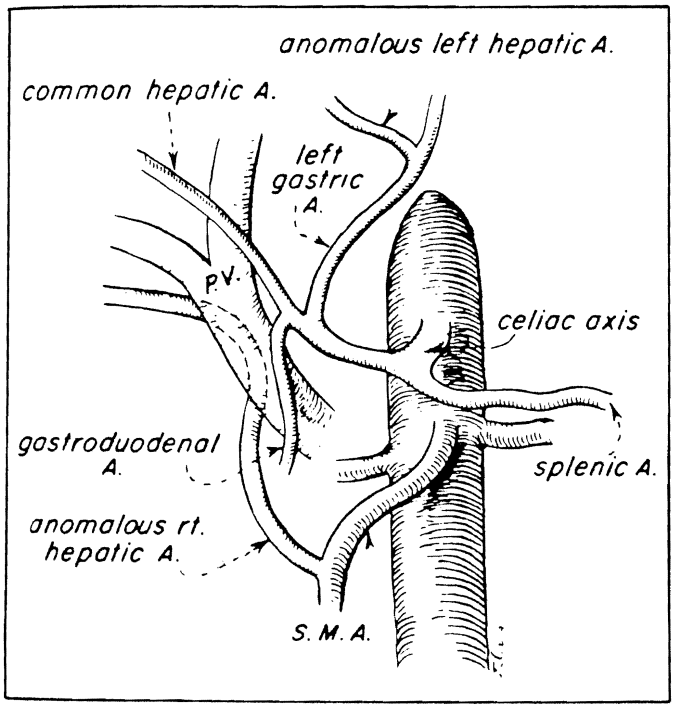

Figure 60–10. Anomalies of hepatic arterial supply.

(Source: From Shaw BW Jr, Hakala T, et al: Combination donor hepatectomy and nephrectomy and early functional results of allografts. Surg Gynecol Obstet 155:321, 1982, with permission.)

The splenic vein is prepared for cannulation. A plane is developed below the hepatic artery and pancreas for access to the splenic vein. If the coronary vein is encountered, it may be divided. The confluence of the superior mesenteric vein and the splenic vein constitute the limits of dissection.

Next, the infrarenal aorta is dissected for a short length just above the bifurcation of the common iliac arteries. The inferior mesenteric artery is divided. The patient is then ready for cannulation, and 300 USP U/kg of heparin is given intravenously. Cannulae are placed in the aorta and in the portal vein via the previously prepared splenic vein. The superior mesenteric vein is tied as soon as the organs are flushed.

The aorta is crossclamped at the supraceliac level, and the suprahepatic vena cava is cut at the level of the right atrium to vent the venous system and prevent outflow obstruction of the liver. The portal vein is perfused with 2 to 3 L of cold (4° C) Ringer's lactate solution. The aorta is perfused with cold Ringer's, Euro-Collins solution, or University of Wisconsin (UW) solution, depending on the preference of the host institution.

Iced Ringer's lactate slush may be placed in the abdomen for additional topical cooling. If the organs are properly flushed and cool, it is not necessary to mobilize them immediately. After cardiectomy is completed by the thoracic surgical team, the thoracic aorta may be reclamped above the diaphragm, and the supraceliac clamp may be removed to facilitate exposure.

The splenic artery is then divided and tied if this has not previously been done. A length of 3 to 4 cm should be preserved with the liver since it can be useful in reconstruction of an anomalous hepatic arterial supply. The splenic vein and portal vein are divided at the junction with the superior mesenteric vein. If the pancreas is not to be removed, the pancreas may be split to facilitate the dissection of the origin of the portal vein.

Preservation of the hepatic arterial supply requires removal of a cuff of celiac origin and, when a right hepatic branch is present, superior mesenteric artery (SMA) origin. A modified Kocher maneuver is performed and the SMA is palpated just superior to the pancreas. Dissection is kept to the left side of this vessel to avoid injury to an anomalous right hepatic artery. The dissection is carried down to the origin of the SMA from the aorta. The aorta is entered on the left side and a cuff containing the origin of the SMA and celiac arteries is separated from the aorta. A clamp can then be placed on the upper end of the aorta if continued cold perfusion of the kidneys is desired.

The infrahepatic vena cava and the origin of the renal veins are identified. The cava is divided above the renal veins. A large piece of diaphragm containing the suprahepatic vena cava is excised. The right kidney is retracted downward to

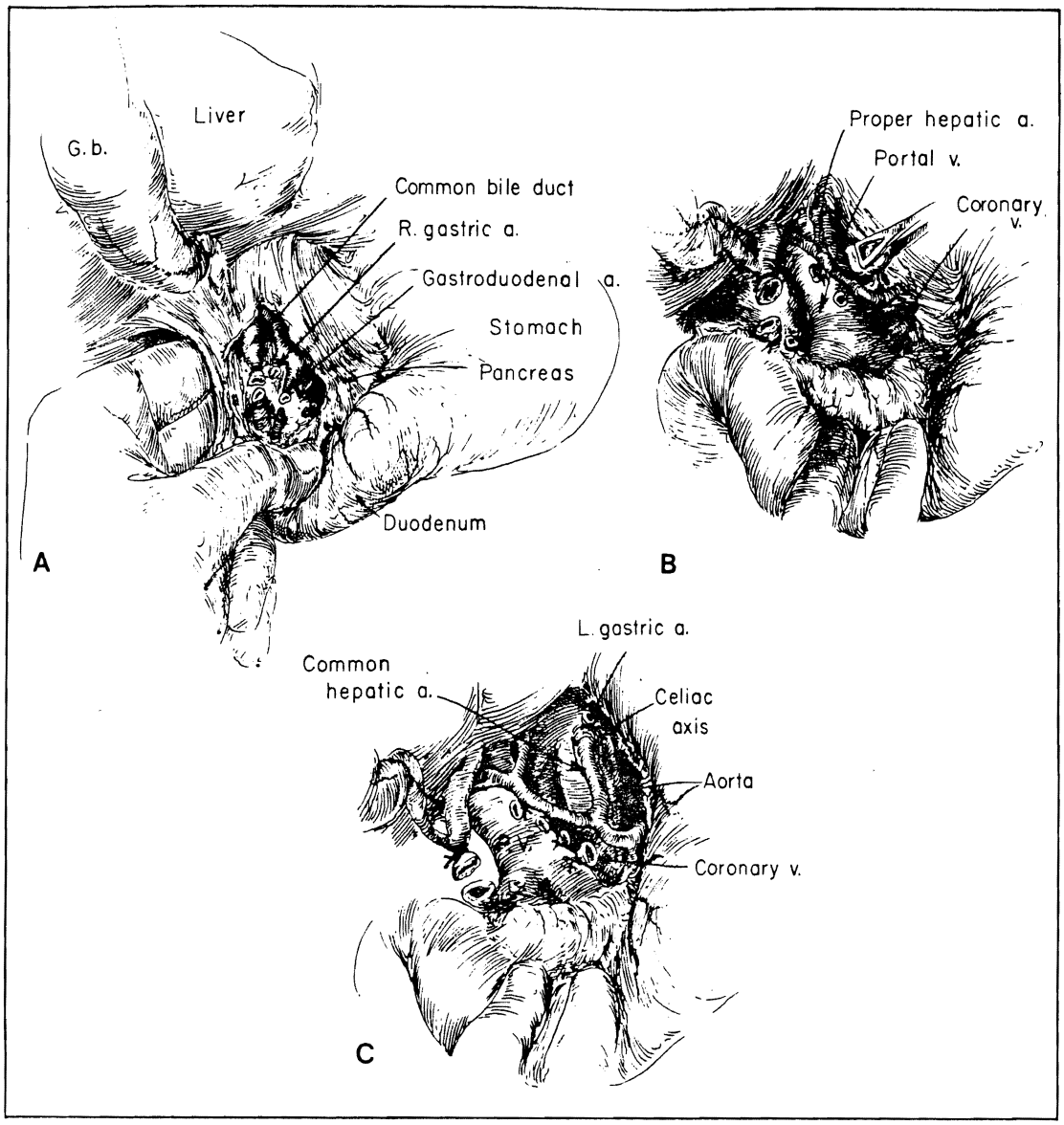

Figure 60–11. Dissection of the portal triad during donor hepatectomy. **A.** The common duct and the gastroduodenal and right gastric arteries are tied and divided. **B.** The hepatic artery has been mobilized far enough so that the anterior surface of the portal vein is uncovered. The coronary vein entering the left side of the portal trunk, or into the splenic vein as shown, is almost always found; this tributary is ligated and divided. **C.** The portal vein has been freed and the celiac axis mobilized. The splenic artery has not yet been ligated and divided. When the liver is removed, all of the celiac axis is usually retained with the specimen, and it may be advisable to include a segment of aorta as well.

(*Source: From Starzl TE [with the assistance of CW Putnam], 1969, with permission.*)

protect it from injury during dissection of the diaphragm. The liver is now entirely free except for its medial attachment to the diaphragmatic crura along the aorta. These remaining attachments are cut to remove the graft.

The liver is placed in a sterile plastic bag, and 1200 to 1500 ml of UW solution is infused in the portal vein. The effluent from the vena cava should be clear. The celiac axis is also perfused with 300 to 500 ml of UW solution. The liver is packed in the cold UW solution and placed in an ice chest for storage and transport to the recipient operating room. The liver can be safely stored for at least 24 hours if UW solution is used.

Rapid Donor Hepatectomy

This technique requires a higher degree of skill than the modified method and is used for unstable donors. There is minimal preliminary dissection except for encirclement of the supraceliac aorta and cannulation of the infrarenal aorta and portal vein via the inferior mesenteric vein. The aorta is crossclamped, and the portal and aortic lines are flushed with cold solution. The suprahepatic cava is divided in the chest to provide for fluid egress. Dissection continues in the flushed, bloodless field. The left gastric artery is identified and divided. The splenic artery is divided, preserving 3 to 4 cm with the hepatic arterial supply. The right gastric and

gastroduodenal arteries are divided. The common bile duct is divided, and the gallbladder is incised and flushed. The pancreas is split above the portal vein, and the SMV and splenic veins are divided. Care is taken to preserve an anomalous right hepatic artery if present. A modified Kocher maneuver is then performed, and dissection proceeds in the same manner as the modified method described above.

Accessory Vascular Grafts

Iliac artery grafts may be needed to reconstruct the recipient arterial inflow in cases in which the native recipient hepatic artery cannot be used. Donor iliac vein is also useful in reconstruction of the portal vein. Approximately 15 percent of recipients require use of accessory grafts to reconstruct arterial or portal inflow.

THE RECIPIENT OPERATION

The operation is performed through either a bilateral subcostal incision with upper midline extension or through an upper midline incision extended to the right at the level of the umbilicus to the midaxillary line. It is rarely necessary to enter the chest.

Recipient Hepatectomy

The strategy of recipient hepatectomy depends on the findings after the abdomen has been entered. The standard approach is to begin dissection in the hepatic hilum with division of the hepatic artery and bile duct and skeletonization of the portal vein. The patient (except for smaller children) is then placed on venous bypass, the suspensory ligaments are taken down, and the vena cava is freed above and below the liver. However, in cases in which the hilum is badly scarred, it may be necessary to clamp the hepatic hilus en masse, divide it, and identify the hilar structures in the cut end (Fig. 60–12). In extremely difficult cases, initial access to the hilum is impossible and the liver must be approached from above by dividing the suprahepatic cava and peeling the organ out from above.

It is not necessary to dissect the infrahepatic vena cava prior to dividing the infrahepatic and suprahepatic vena cava. In fact, an expeditious strategy is to clamp and divide the vena cava above and below the liver and cut up the vena cava along the base of liver, leaving a portion of the back wall of the infrahepatic vena cava in the recipient as the liver is removed. The adrenal vein orifice can be easily identified and oversewn after the liver is removed.

Development of an adequate cuff of upper vena cava requires care. The suprahepatic cava is divided at the level of the hepatic veins staying as close to the liver as possible (Figure 60–13). The confluence of the hepatic veins is then cut to form a cloaca for anastomosis to the graft.

Venovenous Bypass

The anhepatic phase of the recipient operation can be a precarious time. The obligatory interruption of the splanchnic and systemic venous circulations sequesters large volumes of blood in the gastrointestinal tract and lower body, produces renal venous hypertension, and may promote additional bleeding from the numerous thin-walled collateral vessels commonly found in patients with long-standing portal hypertension.

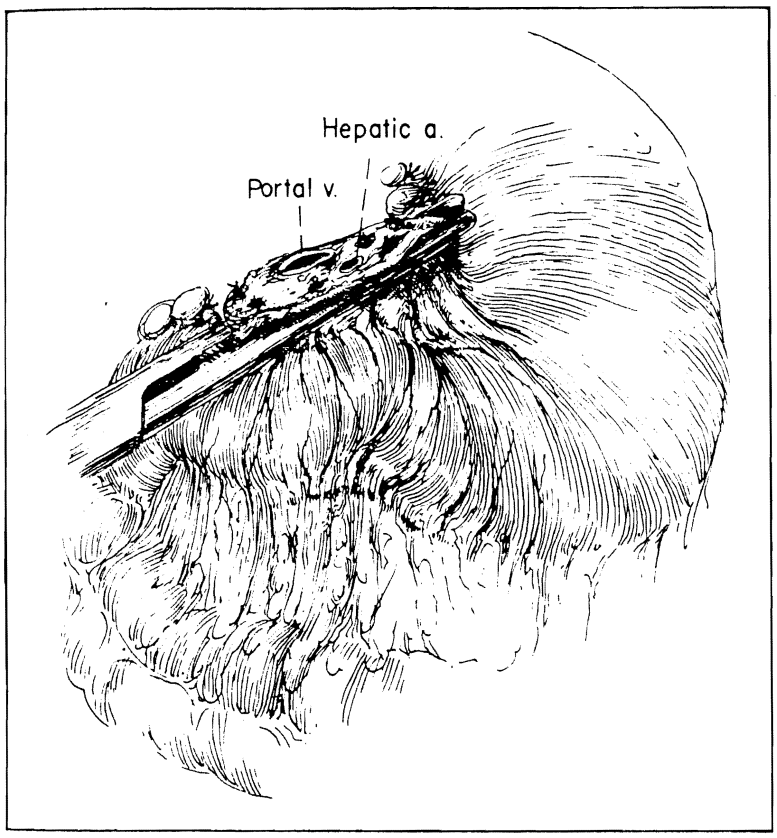

Figure 60–12. Incision en masse of the portal triad. This maneuver has been necessary on several occasions when the individual structures could not be dissected free. After the transection, the portal vein and hepatic artery can be liberated enough to permit the vascular anastomoses to be performed.

(Source: From Starzl TE [with the assistance of CW Putnam], 1969, with permission.)

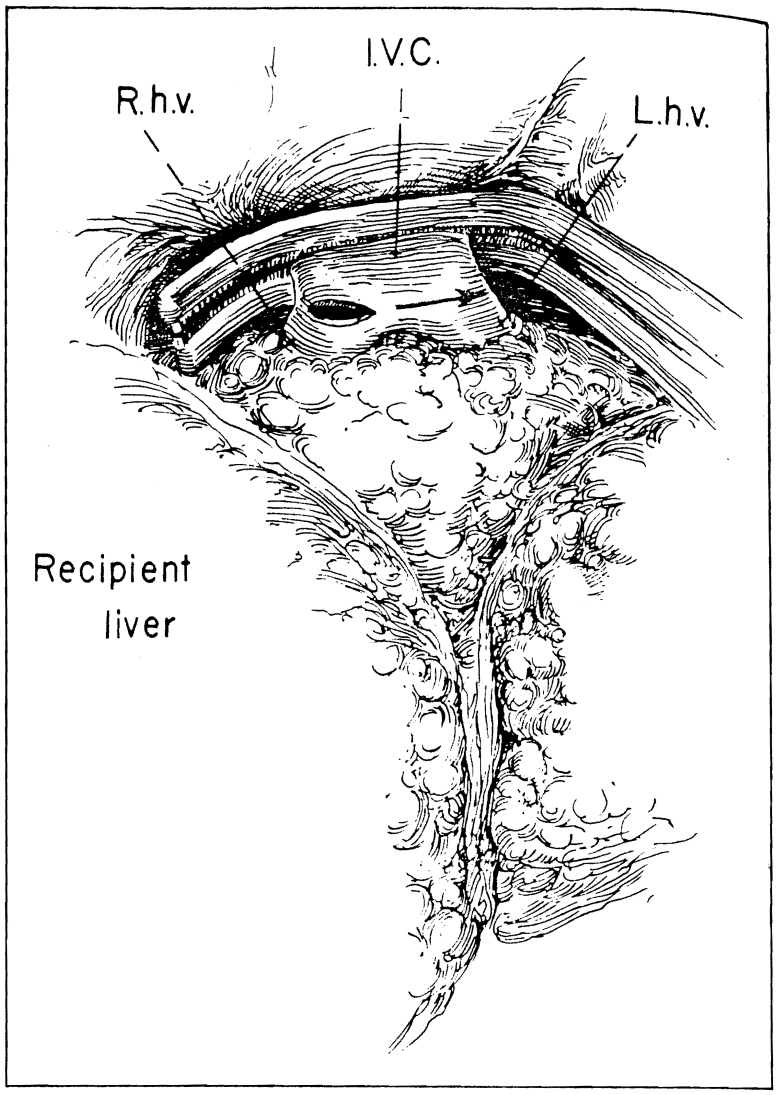

Figure 60–13. Transection of the suprahepatic inferior vena cava. Note that the line of incision is kept as close to the liver as possible to retain the maximum vessel length for subsequent anastomosis. R.h.v. = right hepatic vein; L.h.v. = left hepatic vein; I.V.C. = inferior vena cava.

(*Source: From Starzl TE [with the assistance of CW Putnam], 1969, with permission.*)

Use of a pump-driven venovenous bypass shown in Figure 60–14 can avoid many of the difficulties during this period of operation. The iliofemoral system is cannulated by cutdown on the saphenous vein near the saphenofemoral junction. The portal vein is divided high in the hilum, and a large-bore cannula is inserted to the level of the confluence of the portal, splenic, and superior mesenteric veins. Blood is returned through a cannula placed in the axillary vein. When the size of the veins permits, heparin-bonded Gott shunts are used for cannulation. If the axillary vein will not accept a 7-mm Gott shunt, a 16 or 12 French chest tube is used instead. Systemic heparinization is avoided. A flowmeter on the axillary return line is used to monitor flow through the bypass.

The bypass is started after completion of the hilar dissection and before beginning exposure of the vena cava. This permits unhindered manipulation of the native liver without compromising systemic venous return. After completion of the hepatectomy, attention can be given to hemostasis in the bare areas denuded by removal of the liver. The implantation can then begin in a controlled field.

Use of the bypass prevents renal venous hypertension, reduces blood loss, prevents intestinal congestion, and maintains hemodynamic stability. It has permitted liver transplantation to be performed in higher risk patients with reduced morbidity and mortality.

If cardiac instability, hypotension, or severe reduction in bypass flow occurs, the bypass should be clamped and removed. It is dangerous to maintain the system in patients experiencing severe circulatory problems. Fortunately, this rarely occurs.

Graft Implantation

Venous Anastomosis

The supracaval anastomosis is performed first (Fig. 60–15). A traction stitch is placed in each corner. A temporary traction suture (not shown in the figure) is placed at the midpoint of the back wall to help in lining up the vessel and to evert the ends of the vein. The far-sided suture is tied and brought to the inside. The back wall is completed by running the suture to the near corner, at which point the suture is brought to the outside and is continued around the corner and for a few bites. The other end is then sewn from the far corner to join its mate to complete closure of the anterior wall.

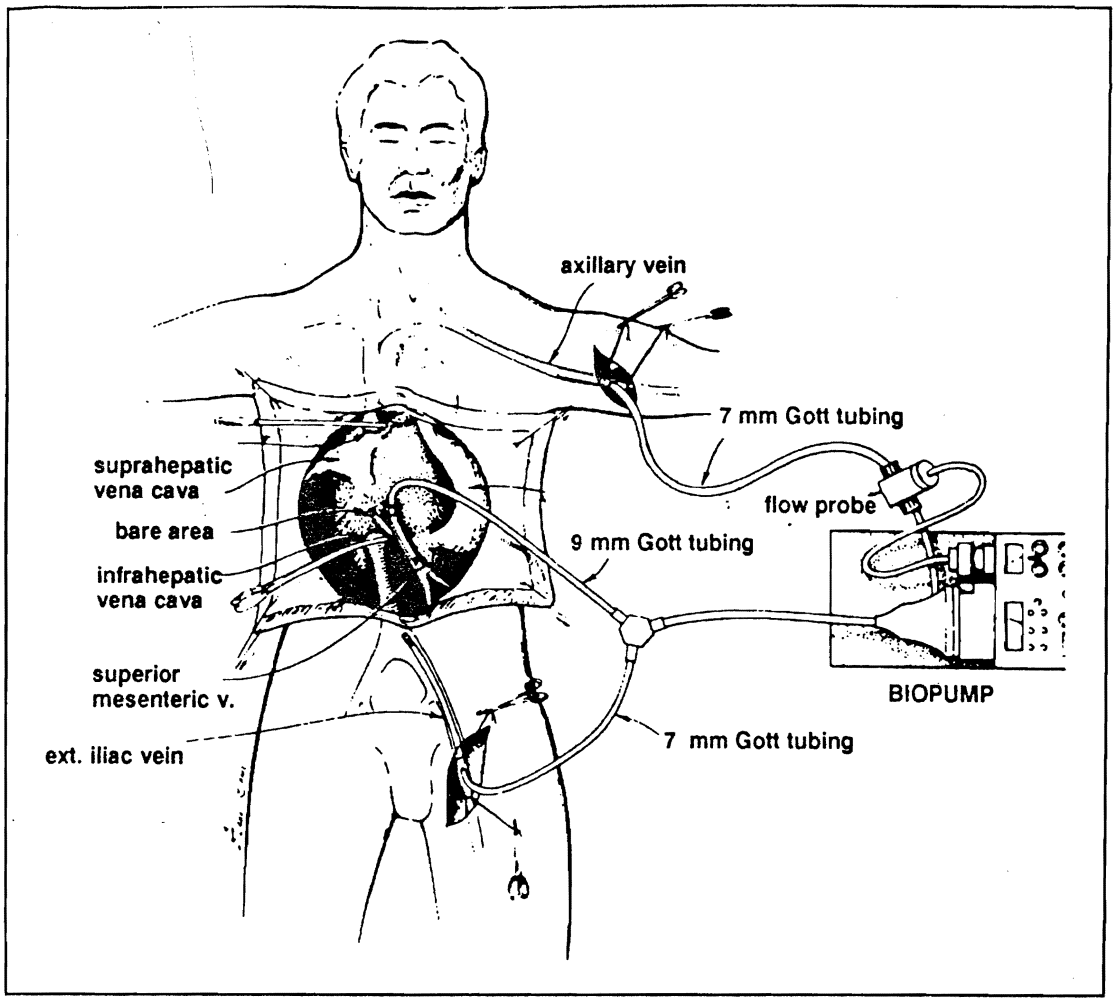

Figure 60–14. Pump-driven venovenous bypass.

(Source: From Griffith BP, Shaw BW Jr, et al: Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. Surg Gynecol Obstet 160:270, 1985, with permission.)

The infrahepatic cava anastomosis is then performed with similar technique (Fig. 60–16). Before completion of the anastomosis the graft is instilled with 200 to 300 ml of Ringer's lactate solution through the portal vein to flush out residual preservative solution and potassium and to eliminate air in the hepatic veins and vena cava.

The portal bypass line is clamped and removed. There is usually little change in bypass flow when the line is removed. The technique of portal anastomosis is similar to the technique used for the vena cava (Fig. 60–17). The running suture is tied near the corner stay suture and the knot is left 1 to 2 cm from the wall of the vein to allow expansion of the anastomosis with restoration of flow. This "growth factor" technique is shown in Figure 60–18. The stay suture adjacent to the running suture is also tied to prevent separation of the vessel at this point.

If the recipient portal vein is thrombosed, atretic, or otherwise diseased, it may be necessary to place an iliac vein graft from the donor on the confluence of the portal vein and splenic vein and anastomose the donor portal vein to this interposition graft. If the portal vein is thrombosed proximal to the confluence and thrombectomy is not possible, a donor iliac vein graft can be jumped from the superior mesenteric vein over the pancreas and sewn to the donor portal vein (Fig. 60–19).

After completion of the portal anastomosis, the venous clamps are removed, and the liver is allowed to perfuse with portal blood. The remaining bypass lines are then removed. If hemostasis permits, the arterial anastomosis is then performed.

Arterial Anastomosis

The arterial anastomosis is demanding and requires a compulsive dedication to technique. The preferred method is to anastomose the celiac axis of the donor to the proximal hepatic artery. In some cases it is necessary to perform the anastomosis at the level of the recipient celiac artery. The end-to-end technique is used. Beveling of the ends is unnecessary and may be harmful. A generous "growth factor" is left to avoid stricture, similar to the method used for the portal vein (Fig. 60–18).

In 10 to 15 percent of cases, the recipient arterial supply is unsuitable for anastomosis to the donor. In this situation an iliac artery graft from the same donor is anastomosed to

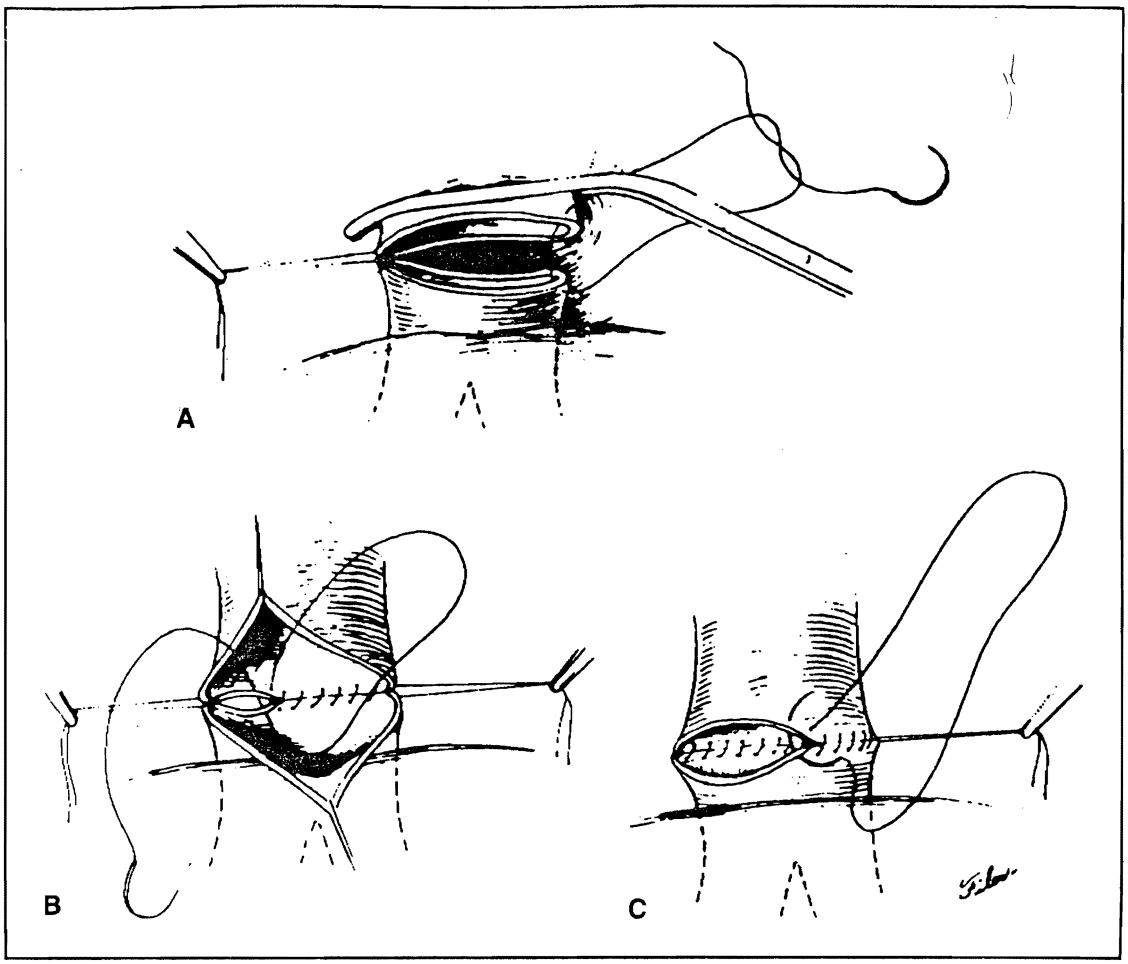

Figure 60–15. Anastomosis of the suprahepatic vena cava.

(Source: From Makowka L, Stieber AC, et al: Gastroenterol Clin North Am 17:33, 1988, with permission.)

the donor celiac artery and is then passed to the aorta, just below the left renal vein in a tunnel created by finger dissection anterior to the vena cava and left renal vein and posterior to the portal vein, duodenum, and superior mesenteric artery (Fig. 60–20). If the tunnel is kept posterior to the SMA, there is little danger of encountering venous collaterals in this tunnel. If the finger is passed anterior to the SMA, the tunnel is more medial and shorter, but there is greater risk of encountering large venous collaterals, the coronary vein, and the splenic vein.

In small children the donor aorta is sometimes left in continuity with the celiac axis and is used as a conduit to the recipient aorta. In some cases, this may be the only feasible way to reconstruct the arterial supply to liver, but there is a significant incidence of thrombosis associated with the use of such aortic conduits; their use is best avoided if possible.

If an anomalous right hepatic artery is present, the preferred method of reconstruction is to join the proximal end of the right hepatic artery to the stump of splenic artery. The celiac axis is then used for anastomosis, as in the case of a conventional arterial anatomy. If the splenic artery is unsuitable, the origin of the donor SMA is sewn to the origin of the donor celiac axis, and the cut end of the SMA distal to the origin of the right hepatic artery is then used for anastomosis to the recipient (Fig. 60–21).

Biliary Reconstruction

A variety of methods of biliary reconstruction have been used in liver transplantation, but two methods are used in most cases today (Fig. 60–22). When possible, direct duct-to-duct reconstruction over a T-tube stent is the preferred method and preserves the sphincter of Oddi (Fig. 60–22A). However, this method cannot be used in patients with disease of the extrahepatic bile ducts, such as patients with sclerosing cholangitis or extrahepatic biliary atresia, and should not be used if there is a major size discrepancy between the donor and recipient ducts. In such cases, Roux-en-Y choledochojejunostomy over an internal stent is used (Fig. 60–22B). Although this is a more complex reconstruction, it has the lowest overall complication rate.

Reduced Liver Transplants

To meet the critical need for organs for infants with biliary atresia, several transplant centers have begun using reduced-size liver grafts, a technique first used by Starzl in 1975.

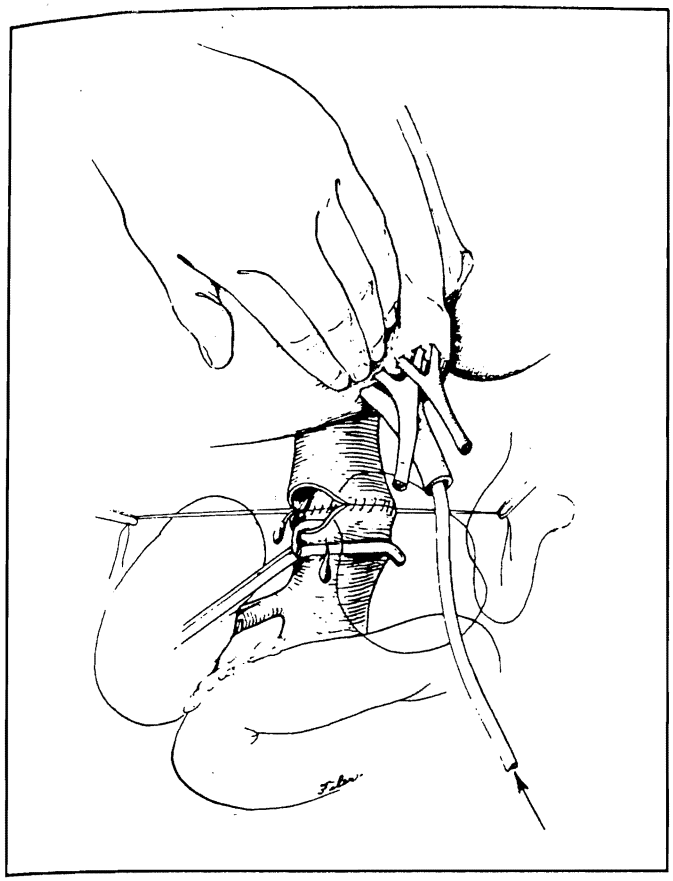

Figure 60–16. Anastomosis of the infrahepatic vena cava. The liver is flushed with cold Ringer's lactate solution through the portal cannula to flush out residual preservation solution and potassium and to evacuate air from the vena cava.

(Source: From Makowka L, Stieber AC, et al: Gastroenterol Clin North Am 17:33–51, 1988, with permission.)

Successful series of reduced-size liver transplants in pediatric patients have been reported from transplant centers in Brussels, Chicago, Hannover, and Paris. The segmental anatomy of the liver provides considerable flexibility for the surgeon in tailoring the graft (Fig. 60–23).

POSTOPERATIVE CARE

The postoperative care of liver transplant patients is in many respects similar to that of any patient who has had an extensive abdominal operation. In the immediate postoperative period, close attention is given to intravascular fluids, electrolytes, pulmonary toilet, liver and renal function, and cardiovascular stability. Excessive crystalloid is avoided because most patients leave the operating room with a significant fluid excess. Plasma protein fraction or fresh frozen plasma are given to support oncotic pressure and maintain intravascular volume. Potassium must be administered cautiously until it is certain that renal function is adequate and acute graft failure is unlikely. Medications that cloud the sensorium are avoided because assessment of mental status is an important part of the initial evaluation of graft function.

Hypertension is common after liver transplantation and should be treated aggressively. Hydralazine and β-adrenergic blocking agents such as labetalol and propranolol are good first choices. In acute emergencies, nifedipine, 10 mg sublingually, is often effective. In refractory hypertension, labetalol can be given as a 20-mg bolus over 2 minutes and repeated as needed every 20 minutes up to a maximum total dosage of 300 mg. Minoxidil, clonidine, and captopril are alternative agents for maintenance antihypertensive treatment.

Antacids are given by nasogastric tube every 4 hours to maintain gastric pH above 5. As soon as gastrointestinal motility returns, oral intake is permitted.

The most common early difficulties have been pulmonary insufficiency requiring prolonged mechanical ventilation, renal failure at the same time that large fluid shifts are occurring, and persistent clotting abnormalities. If the liver functions well, recovery can be dramatic, but if graft function is marginal or poor, these problems can quickly become life threatening.

Attention to tracheobronchial toilet is essential. Frequent suctioning, turning, and manual hyperinflation of the lungs are important. Many patients can be weaned from the ventilator within 12 to 24 hours of surgery, but if prolonged mechanical ventilation is required, early consideration should be given to tracheostomy.

Antibiotic prophylaxis consists of coverage for biliary tract pathogens (*Klebsiella, Escherichia coli,* and enterococcus) during the perioperative period: nystatin (Mycostatin) orally (and vaginally in women), single-stength trimethoprim-sulfamethoxazole (Bactrim) daily, and acyclovir 200 mg twice a day.

Hypoglycemia, hyperkalemia, oliguria or anuria, rising serum lactate levels, encephalopathy, and persistent coagulopathy are indications of primary graft failure. If a T-tube is present, the quantity and quality of bile produced is also an excellent index of liver function. The liver should begin making normal-looking bile shortly after revascularization. Plasmapheresis is valuable in supporting patients with primary graft failure until another donor can be found.

IMMUNOSUPPRESSION

All the methods used to prevent reverse rejection of whole-organ transplants have been developed with the simpler procedure of renal transplantation. These are summarized in Table 60–4.

Although there was discontent with the immunosuppressive agents available from 1963 to 1978, improved drug therapy was not possible until the discovery of cyclosporine. Cyclosporine is an extract from the fungi *Cylindrocarpon lucidum* and *Tolypocladium inflatum Gams* (formerly designated *Trichoderma polysporum*). It was discovered and characterized by scientists at the Sandoz Corporation, Basel, Switzerland, who showed that it was immunosuppressive in mice, rats, and guinea pigs. The drug depressed humoral and cellular immunity with a quickly reversible action. These effects were not accompanied by the bone marrow depression that had frequently limited the doses of azathioprine and cyclophosphamide.

When cyclosporine was first used by Calne at Cambridge, it was hoped that no other drug would be routinely required.

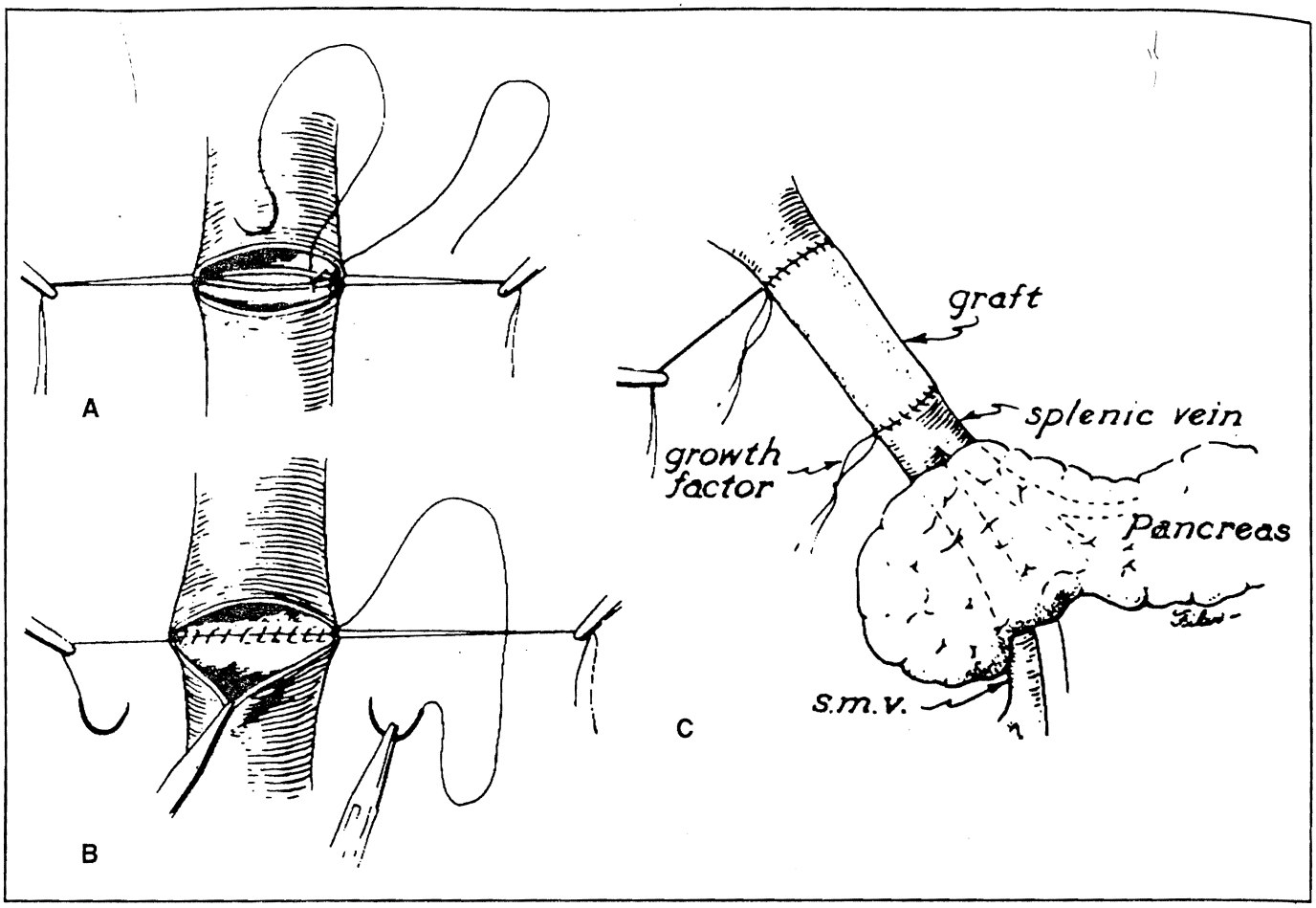

Figure 60–17. Anastomosis of the portal vein.

(Source: From Makowka L, Stieber AC, et al: Gastroenterol Clin North Am 17:33–51, 1988, with permission.)

However, cyclosporine is best when used from the outset with steroids, although smaller doses of steroids are needed than in the past.

Nephrotoxicity is the most serious side effect of cyclosporine. A significant fall in glomerular filtration rate is observed soon after administration of cyclosporine, which persists with continued administration of the drug. Studies of renal function in Stanford heart transplant patients have shown a high incidence of irreversible pathologic changes in the kidneys of these patients, although only a small percentage of patients have required renal transplantation. Serious hepatotoxicity has been uncommon, but moderate elevations in liver function tests are commonly seen and respond to adjustments in dosage. Some centers have adopted quadruple drug regimens that combine cyclosporine and prednisone with azathioprine and monoclonal or polyclonal antilymphocyte globulin (ALG) to reduce dependence on higher, nephrotoxic dosages of cyclosporine early after transplantation.

Hypertension is another frequent and troublesome side effect of cyclosporine, and many patients require multiple drug therapy to control it. Other side effects, including hirsutism, gum hyperplasia, tremors, regional flushing, paresthesias in hands and feet, perioral numbness, postnasal drip, and vague abdominal discomfort just after drug ingestion have rarely been serious.

Lymphoproliferative lesions, usually in the gastorintestinal tract, mesenteric lymph nodes, or the liver itself and frequently associated with Epstein-Barr virus infections have been seen in a small but significant percentage of patients. Development of these lesions is a consequence of overall immunosuppression rather than a specific effect of cyclosporine. Treatment consists of reduction or withdrawal of immunosuppression and administration of acyclovir. Localized lesions in the gastrointestinal tract are amenable to surgical resection. Antitumor chemotherapy rarely is necessary to control more aggressive, disseminated lesions, but prognosis is poor with this stage of disease.

Cyclosporine is administered intravenously, 2 mg/kg twice a day beginning in the operating room. Oral cyclosporine, 17.5 mg/kg per day in two divided doses, is begun as soon as gastrointestinal motility permits. Intravenous therapy is overlapped with oral drug until absorption is stable and consistent blood levels can be maintained. Children have a higher cyclosporine clearance and usually require higher doses per kilogram of body weight than adults. Adult patients are also given a 5-day burst of prednisolone, starting at 200

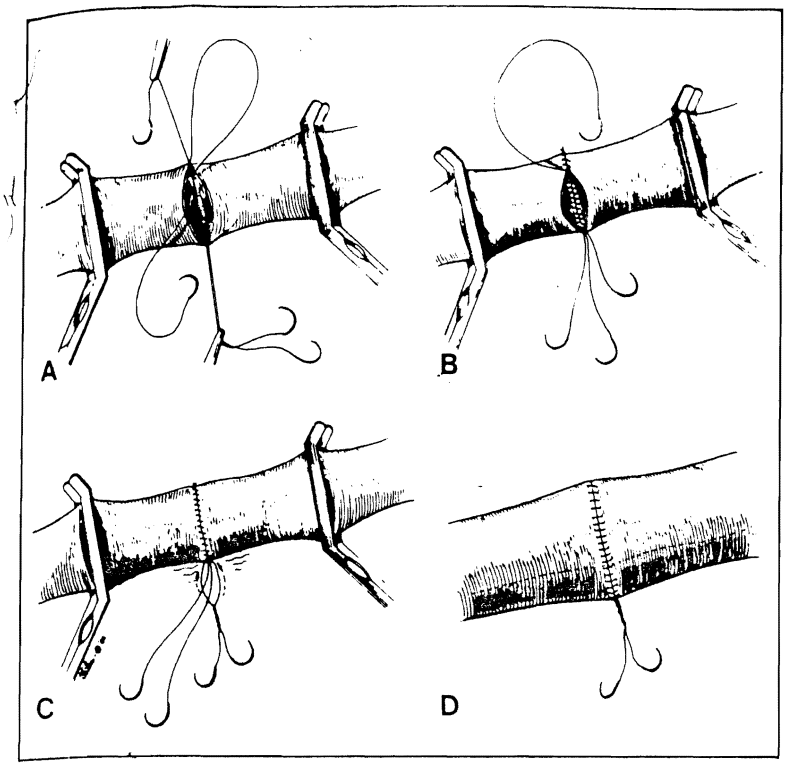

Figure 60–18. Method of avoiding strictures of small vascular anastomoses.

(*Source: From Starzl TE, Iwatsuki S, et al: A "growth factor" in fine vascular anastomoses. Surg Gynecol Obstet [in press], with permission.*)

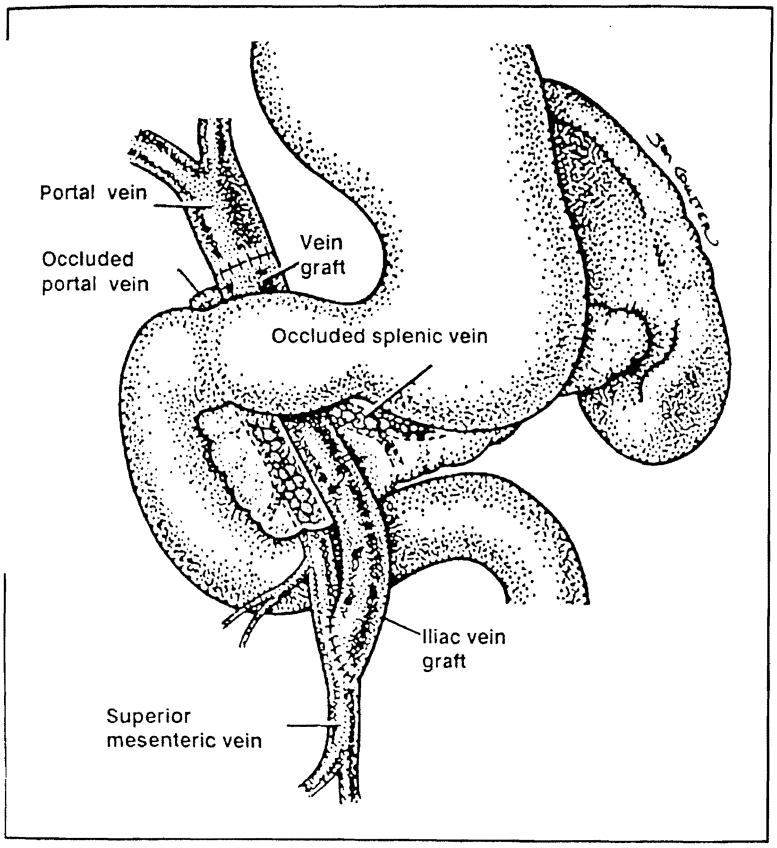

Figure 60–19. Donor iliac vein graft from the superior mesenteric vein below the transverse mesocolon to the donor portal vein in a liver recipient with a thrombosed portal vein and portal-mesenteric-splenic vein confluence.

mg tapered to a maintenance dose of 20 mg per day. Lower doses are used for children based on body weight. Further reductions of cyclosporine and steroid dosages are made on an individualized basis.

Rejection is commonly manifested by a disturbance in the liver chemistry profile, fever, malaise, lethargy, myalgias, or arthralgias. Percutaneous biopsy is frequently performed to confirm the diagnosis. Initial treatment is administration of a large bolus of methylprednisolone and repetition of the 5-day high-dose steriod taper. If response is poor, treatment with Orthoclone OKT3 (Ortho Pharmaceuticals, Raritan, N.J.), a mouse antihuman antibody active against the antigen receptor on T lymphocytes, is given daily for 10 to 14 days and is highly effective. However, patients may develop antibodies to the mouse protein and become refractory to further treatment or subsequent retreatment with OKT3.

COMPLICATIONS AFTER LIVER TRANSPLANTATION

Pulmonary Complications

Pulmonary complications including atelectasis and pleural effusion are common and require aggressive treatment. Pleural effusions are drained by percutaneous insertion of a small pig-tailed catheter using guidewire technique, since compromised expansion of the underlying lung in an immunosuppressed patient can rapidly lead to pneumonia. Flexible fiberoptic bronchoscopy is frequently performed in patients with retained secretions. During application of the vascular clamp to the suprahepatic cava, it is possible to injure the phrenic nerve. Paralysis of the hemidiaphragms can be easily evaluated at the bedside with an ultrasound examination.

Hemorrhage

Careful attention to hemostasis during surgery is essential to minimize the risk of postoperative bleeding. The highest risk of bleeding is in the first 48 hours after transplantation. Patients who demonstrate hemodynamic instability and require five or more units of blood in a 24-hour period should be evaluated for bleeding. Exploration to remove accumulated clot is worthwhile even if no active bleeding point is found. Abdominal computed tomography (CT) scans are useful to confirm significant accumulations of clot. In patients with marginal graft function, it may be prudent to delay exploration for 24 to 48 hours until liver function and coagulation have improved.

Late hemorrhage may occur as a result of disruption of a vascular anastomosis (usually a result of mycotic infection), gastrointestinal ulceration from cytomegalovirus infection, or from hematobilia that occurs as a complication of percutaneous needle biopsy or percutaneous cholangiography. Common sites of gastrointestinal bleeding are the jejunojejunostomy or the tip of the Roux-en-Y limb in patients with a choledochojejunostomy reconstruction. In some cases these sites are ulcerated by infection with cytomegalovirus (CMV). CMV colon ulcers may also present with bleeding.

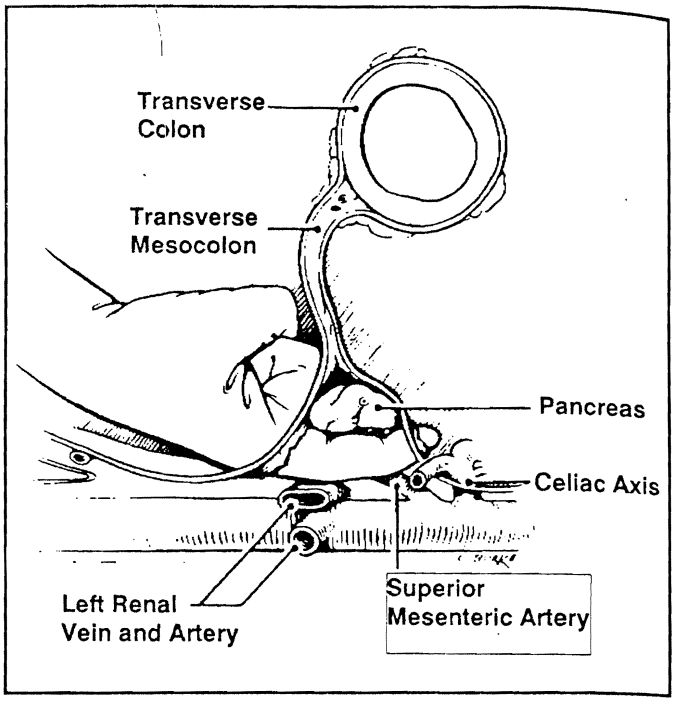

Figure 60–20. Finger dissection at the base of the mesocolon anterior to the left renal vein and vena cava and posterior to the pancreas and splenic vein to create a tunnel for an iliac artery graft from the recipient aorta to the donor hepatic artery. In the figure, the finger is shown passing medial to the vena cava directly over the renal vein and superior mesenteric artery. In practice, it is often easier and safer to pass the finger more to the right side of the patient so that it enters the clean plane under the superior mesenteric artery. This avoids any encounter with collaterals in the area of the splenic or coronary veins. The tip of the finger will emerge behind and slightly lateral to the portal vein and anterior to the infrahepatic vena cava.

(Source: From Makowka L. Stieber AC, et al: Gastroenterol Clin North Am 17:33–51, 1988, with permission.)

Primary Graft Failure

Primary graft failure, the most dreaded early complication after liver transplantation, occurs in 5 to 10 percent of cases and requires urgent retransplantation. Recognition and supportive management were previously discussed in the section on postoperative care.

Vascular Complications

Hepatic Arterial Thrombosis. Hepatic arterial thrombosis is the most common major vascular complication after liver transplantation, and is most prevalent after transplantation in infants. Although technical flaws are an important factor in this complication, physiologic factors also contribute. Children have been shown to have a hypercoagulable state characterized by a severe deficiency of protein C and antithrombin as well as defective fibrinolysis in the first 10 days after liver transplantation. There is evidence that cyclosporine is involved in prostanoid metabolism and in mechanisms of endothelial cell injury. Allograft rejection can produce a severe endotheliitis in the venous and arterial systems of the liver, which may promote thrombosis of involved vessels.

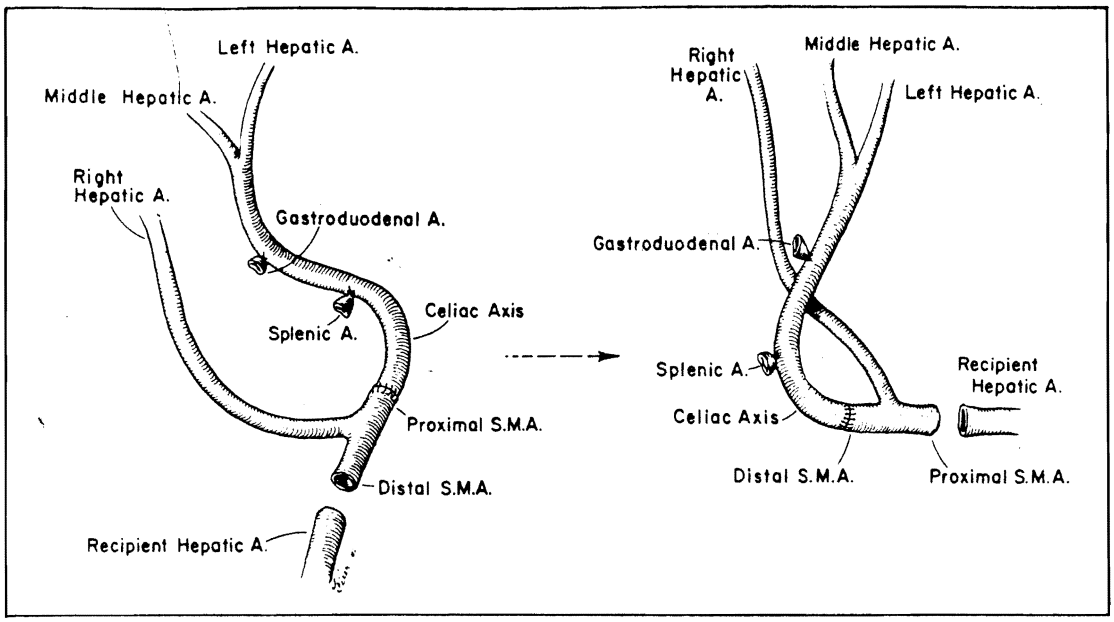

Figure 60–21. The management of a common graft anomaly in which part of the liver blood supply is derived from the superior mesenteric artery. Note that the celiac axis is anastomosed to one end of the main superior mesenteric artery and the other end is used for anastomosis to a recipient vessel.

(Source: From Shaw BW Jr, Iwatsuki S, et al: Alternative methods of hepatic graft arterialization. Surg Gynecol Obstet [in press], with permission.)

e clinical presentation of hepatic artery thrombosis variable, ranging from silent thrombosis to fulminant failure. In typical cases, the presentation includes iver function studies suggestive of ischemic injury, lood culture positive for gram-negative bacteria. The iliary ducts, which depend entirely on the hepatic or blood supply, usually sustain ischemic injury that sult in bile duct disruption and bile abscess in the renchyma or, if the extrahepatic ducts become ne- n the abdominal cavity. Patients may also present ltiple biliary strictures long after thrombosis occurs. some cases if a thrombosis is promptly detected or d, the arterial reconstruction can be revised and the ved. However, in most cases retransplantation is ulti- required.

Vein Thrombosis. Portal vein thrombosis is much mon than hepatic artery thrombosis after liver trans- on, but many of the same contributing factors apply. al factors include excessive length, poor alignment, ted thrombus in the portal vein confluence or the ric or splenic veins, and disease of the portal vein

al vein thrombosis may present with sudden massive nd variceal hemorrhage or it may be well tolerated. roach to this complication depends on the presenta- he liver remains viable, thrombectomy and revision rtal vein may be possible, or if portal hypertension a problem, a shunt procedure may be of value. If ction is severely compromised by lack of portal inflow ncomitant rejection, retransplantation is indicated.

Biliary Tract Complications (Other than Vascular Related)

Biliary Leak. Technical failure from inappropriate tension on an anastomosis, poor suturing technique, or improper T-tube placement may result in biliary leak. A common site of leak is the exit site of the T-tube from the bile duct. Usually simple suture of such a leak is all that is required. Leak from a duct-to-duct anastomosis is best repaired by conversion to choledochojejunostomy if the duct is viable.

Bile leak is more difficult to detect clinically in patients with a Roux-en-Y choledochojejunostomy, since there may be no external biliary drain. A rising bilirubin level in the absence of rejection, hemolysis, or other sources of sepsis should raise suspicion. Most leaks occur on the anterior surface of the anastomosis. It is best to take down the entire anastomosis and construct a new one.

In the presence of infection or severe inflammation of the duct and contiguous tissues, temporary external drainage and delayed reconstruction of the duct may be necessary.

Biliary Obstruction. Biliary obstruction may present with acute bacterial cholangitis, relapsing febrile episodes with fluctuating liver function studies, or gradual deterioration of graft function with minimal symptoms. Dilated ducts may be seen on noninvasive imaging studies. Localization of the problem requires cholangiography. Angiography may be indicated if a vascular thrombosis is suspected as the cause.

Obstruction may be caused by a T-tube or a retained choledochojejunostomy stent, stone formation, an anastomotic stenosis, or strictures occurring elsewhere in the biliary

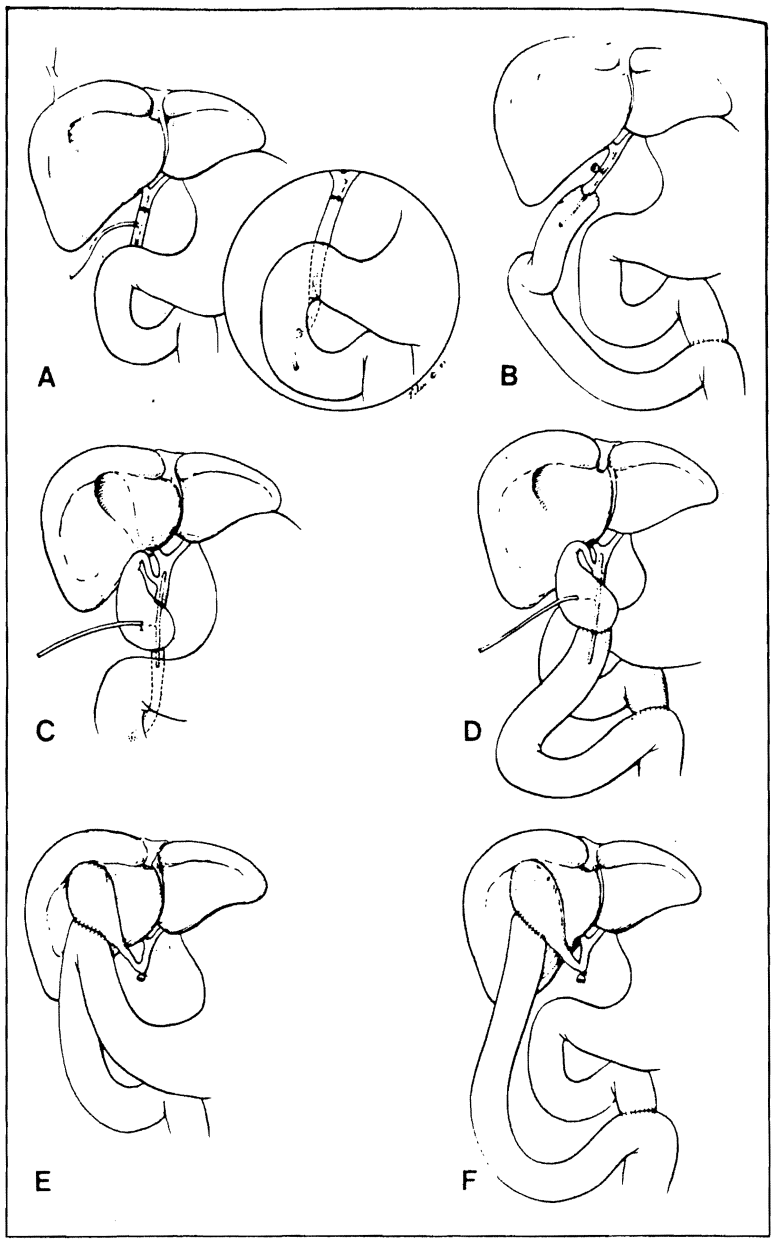

Figure 60–22. Methods of biliary tract reconstruction that have been used with liver transplantation. Method **A**, duct-to-duct reconstruction over a T-tube and method **B**, Roux-en-Y choledochojejunostomy over an internal stent are the preferred methods today. Methods **E** and **F** are so defective that they have been abandoned. Depending on anatomic and clinical circumstances, methods **C** and **D** may be useful in individual cases.

tree from ischemic injury, persistent rejection, and possibly viral infection. The interventional radiologist may be able to push out an obstructing internal stent or dilate and stent some strictures, thereby avoiding or at least delaying the need for surgical correction in some cases.

Infection and Intraabdominal Sepsis

Bacterial and fungal infections are responsible for much of the mortality after liver transplantation. Fever and hyperbilirubinemia in the absence of rejection or biliary obstruction strongly suggest sepsis. Intraabdominal sepsis is usually the result of a technical complication, such as biliary or intestinal leak, or a result of hematogenous seeding or external contamination. Gram-negative enteric organisms, enterococci, and candida are the usual offending organisms. Broad-spectrum antibiotic treatment with a third-generation cephalosporine and ampicillin or one of the newer semisynthetic penicillins in combination with an aminoglycoside are usual first-line drugs. If *Candida* infection is suspected, amphotericin should be added. Intraabdominal collections identified on imaging studies may be sampled for bacterial culture by percutaneous methods, but laparotomy is usually necessary for effective drainage.

Opportunistic infections have been a common and persistent problem in transplant patients. Routine administration of prophylactic Bactrim has nearly eliminated *Pneumocystis carinii* penumonia. *Legionella* pneumonitis has also become rare since routine Bactrim prophylaxis was adopted.

Perhaps the most common and troublesome infection seen presently is CMV, which can and often does affect multiple organ systems, especially the lungs, gastrointestinal tract,

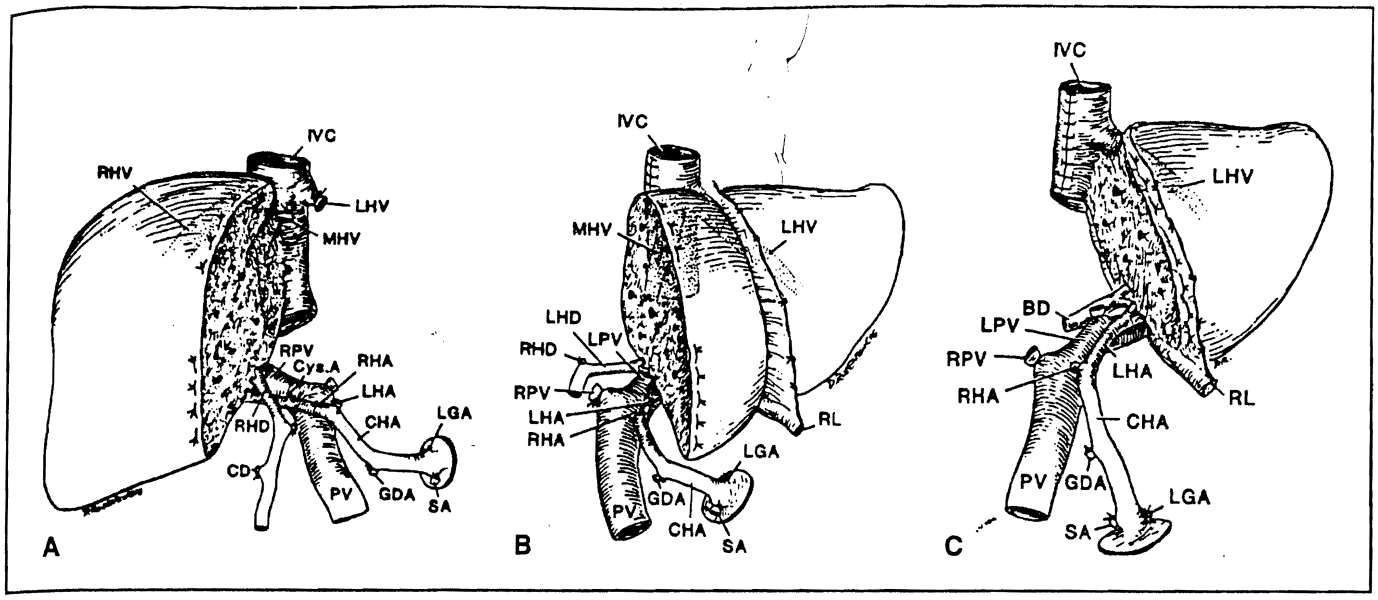

Figure 60–23. Reduced liver grafts. **A,** Right lobe graft. **B,** Left lobe graft. **C,** Left lateral segment graft.

(*Source: Adapted from Broelsch CE, Emond JC, et al: Liver Transplantation, Including the Concept of Reduced-size Liver Transplants in Children, 1988, with permission.*)

and liver. Ganciclovir (DHPG) has shown great promise in clinical trials for the management of systemic CMV infection, but viral resistance has been reported. Herpes infections usually respond to treatment with acyclovir.

The most common fungal infection encountered is caused by *Candida,* but *Apergillus* and *Nocardia* infections are occasionally encountered and are difficult to treat once well established. Mycobacterial infections are infrequently seen. Patients with a prior history of mycobacterial disease should receive prophylactic therapy.

Pancreatitis

Mild pancreatitis with modest elevations of serum amylase is frequently seen after liver transplantation and may result from the manipulation of the gland that is unavoidable during dissection of the hepatic artery or during reconstruction of arterial inflow with an iliac artery graft. Only a small percentage of patients develop significant pancreatic edema, but this may progress to pseudocyst or abscess formation and require drainage.

TABLE 60–4. CLINICAL IMMUNOSUPPRESSIVE DRUG REGIMENS DEVELOPED WITH KIDNEY TRANSPLANTATION

Agents	Year Reported	Place	Deficiencies	Used for Liver Transplantation
Azathioprine	1962	Boston	Ineffective, dangerous	No
Azathioprine and steroids	1963	Denver, Richmond, Boston, Edinburgh	Suboptimal	Yes
Thoracic duct drainage as adjunct	1963	Denver	Nuisance, requires 20–30 d pretreatment	Yes
Thymectomy as adjunct	1963	Denver	Unproven value	No
Splenectomy as adjunct	1963	Denver	No longer necessary	Yes
ALG as adjunct	1966	Denver	Still suboptimal	Yes
Cyclophosphamide substitute for azathioprine	1970	Denver	No advantage except for patients with azathioprine toxicity	Yes
Total lymphoid irradiation	1979	Palo Alto, Minneapolis	Dangerous, extensive preparation, not quickly reversible	No
Cyclosporine alone	1978–1979	Cambridge	Suboptimal	Yes
Cyclosporine and steroids	1980	Denver	Nephrotoxicity, hypertension, lymphoproliferative disorders	Yes
Monoclonal ALG	1983	Boston	Viral infection, development of antibody-mediated resistance	Yes

Splenic Complications

Splenomegaly is present in most of the patients undergoing liver transplantation, and some may develop splenic infarcts. These are usually asymptomatic, but in septic patients in whom no other source can be identified splenectomy may have to be considered.

SUMMARY

Liver transplantation services have expanded dramatically in recent years as indications for liver replacement have broadened, contraindications have diminished, and referrals to transplant centers have increased. Earlier identification of candidates, standardization of surgical techniques, routine use of venovenous bypass, introduction of more effective immunosuppressive agents such as cyclosporine and monoclonal antilymphocyte globulin, and prompt recognition and treatment of complications have contributed to a substantial reduction in morbidity and mortality.

Liver transplantation for most forms of chronic liver disease is associated with a 15 to 30 percent mortality in the first year, but longer term survival is excellent, and disease recurrence is rare. Important exceptions include transplantation for primary liver cancer, in which disease recurrence within 18 to 36 months is common, and for chronic active hepatitis B, in which reinfection is common but the outcome quite variable. Patient survival after liver transplantation for fulminant hepatic failure is excellent if patients are referred early enough and are able to receive the transplant before severe systemic complications such as stage IV coma, renal failure, or metabolic acidosis occur.

Recent advances in organ preservation, especially the new solution developed at the University of Wisconsin by Belzer and associates has significantly extended the preservation time for the liver and will greatly facilitate the retrieval of more and better quality organs.

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