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Chapter 7

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ORTHOTOPIC LIVER TRANSPLANTATION

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The first orthotopic liver transplantation was performed in Denver in 1963.[1] It was an unsuccessful attempt, as were the next seven transplants performed in Denver, Boston, and Paris. The first long-term survival after liver transplantation was in 1967.[2] The late 1960s and 1970s saw very slow progress in this field, with an overall 1-year patient survival of only 35%, as well as frequent and disabling complications.[3]

Several major advances in the early 1980s—the introduction of cyclosporine,[4–6] the progress in donor surgery[7] and organ preservation,[8] and the refinement of the surgical technique[9]—led to greatly improved results.[10] As a consequence, there was an exponential increase in the number of liver transplantations performed—in 1988, a total of 511 were carried out at the University of Pittsburgh alone. Over 40 centers in the United States are currently engaged in liver transplantation, and several of them perform more than 100 per year.

INDICATIONS

The National Institutes of Health Consensus Conference of 1983 established orthotopic liver transplantation as the therapeutic modality of choice for certain end-stage liver diseases,[11] and the indications continue to increase. As more experience has accumulated, the advantages of liver transplantation in terms of survival and quality of life when compared with existing therapeutic modalities have become increasingly evident. There is no accurate estimate of the patients in the U.S. who need liver replacement every year, but their number probably is in excess of 50/1,000,000 inhabitants. Sadly, the need for organ replacement far outstrips both the number of available donors and transplant teams.

Adults

The indications for orthotopic liver transplantation in the adult population, in decreasing order of frequency, are listed

INDICATIONS FOR ORTHOTOPIC LIVER TRANSPLANTATION IN ADULTS

Indication	Relative Result	Recurrence
Chronic active hepatitis (viral)		
C (non-A/non-B)	Good	Low*
B	Fair-to-good	High†
A	Good	Low‡
Primary biliary cirrhosis	Very good	No/
Primary sclerosing cholangitis	Very good	No/
Laënnec's cirrhosis	Good	Low§
Fulminant hepatitis	Fair	Low¶
Neoplasms	Poor	High**
Metabolic disorders	Excellent	No
Autoimmune hepatitis	Good	Low
Budd-Chiari syndrome	Fair-to-good	Medium††
Trauma	Excellent	No

*Clear evidence of recurrence lacking, with the exception of very few cases. †Virtually 100% histologic recurrence; with clinical recurrence, duration to end-stage disease unknown. ‡Very few clearly documented cases of chronic active hepatitis type A. /No evidence of recurrence in our series. Postulated by Caine in one case. §Recurrence rapidly lethal if the patient resumes drinking; most patients do not. ¶Only for hepatitis B; very high seropositivity, but low clinical recurrence. **Apudomas and fibrolamellar hepatomas have lower recurrence, at least in the short term. ††Recurrence virtually the rule, unless the patient is undergoing long-term anticoagulation.

Figure 7.1

LIVER TRANSPLANTATION INDICATIONS IN CHILDREN

Indication	Relative Result	Recurrence
Biliary atresia or hypoplasia	Good	No
Metabolic disorders*	Excellent	No
Neonatal hepatitis	Good to excellent	No
Fulminant hepatitis	Fair to good	Low†
Chronic active hepatitis	Good	Low
Neoplasms	Fair to poor	High
Familial intrahepatic cholestasis	Excellent	No

*(α-1-antitrypsin deficiency, tyrosinemia, glycogen storage disease type IV, familial hypercholesterolemia, etc.). †Same as in adults; toxic hepatitis (especially drug-induced) much more frequent.

Figure 7.2

in Fig. 7.1. Some of the indications have increased in frequency over the last few years (chronic active hepatitis and Laënnec's cirrhosis particularly), while others have decreased, either because less cases are available (primary biliary cirrhosis is the prime example) or because of poor results (tumors). Our group has been particularly aggressive with transplantation for unorthodox or unusual indications, a trend that has been very helpful in breaking new ground in areas heretofore unexplored.

Children

The indications for liver replacement in children (Fig. 7.2) are quite different from those in the adult population. Congenital and/or metabolic disorders form the bulk of the indications.

Disease-Specific Indications

The effect of the timing of liver transplantation on the outcome is not entirely clear. It would be expected that patients in relatively good condition preoperatively would do better than those in poor preoperative condition,[12,13] but this assumption has been questioned.[14] As liver transplantation is a demanding and potentially dangerous procedure, fully active patients may be reluctant to commit themselves even if the natural history of their disease is lethal in the long run. In addition, the priority in most transplant programs is to treat the sickest patients first, forcing patients in better condition to wait until they become ill enough to create pressure on the selection process. Some complications and findings have such serious implications that transplantation should be carried out *before* they develop, whereas other conditions require *earlier* transplantation (Fig. 7.3).

DISEASE-SPECIFIC INDICATIONS

Transplantation Required Before Conditions Develop

Chronic
- Massive variceal bleeding
- Irreversible hepatorenal syndrome
- Catabolic state incompatible with surgical survival
- Severe hepatic osteodystrophy
- Bilirubin 20 mg/dl
- Albumin 1.8 g/dl
- Poorly controlled coagulopathy
- Cardiovascular instability with anasarca, ascites, and pleural effusion

Fulminant
- Grade IV coma
- Cardiovascular instability
- Intractable coagulopathy
- Hepatorenal syndrome
- Septic complications
- Fulminant form of Wilson's disease

Subacute
- Bilirubin 25 mg/dl
- Variceal bleeding
- Hepatic coma
- Hepatorenal syndrome
- Septic complications
- Severe coagulopathy

Early Transplantation Required

- Refractory ascites/hepatorenal syndrome
- Recurrent variceal hemorrhage
- Recurrent spontaneous bacterial peritonitis
- Hepatic osteodystrophy
- Intractable pruritus

Conditions that Delay Transplantation

Infection
- Bacterial
- Viral
- Fungal
- Mycobacterial

Ischemic heart disease
Cardiomyopathy
Acute pulmonary disease

Figure 7.3

CONTRAINDICATIONS

Figure 7.4 lists the absolute and relative contraindications. In addition, it indicates the conditions that require earlier transplantation and those that delay it.

PREOPERATIVE EVALUATION OF THE RECIPIENT

The evaluation of the liver transplant candidate involves relatively straightforward noninvasive and invasive tests intended to define the precise diagnosis, stage of the disease, prognosis, speed of expected progression for the disease, and the result expected from transplantation. The presence of malignancy has to be ruled out. Peptic ulcer disease should be excluded. This workup usually can be performed on an outpatient basis, thus reducing the costs of the initial evaluation.

Any tests that are part of a research protocol are financed by grant money to avoid overcharging the patient or the insurance carrier.

LABORATORY TESTS. These tests, performed 1 to 2 weeks prior to evaluation, comprise complete blood count with differential, platelet count, prothrombin time, partial thromboplastin time, total serum protein/albumin, blood urea nitrogen, creatinine, serum electrolytes, total and direct bilirubin, serum glutamic-oxalacetic transaminase, serum glutamic-pyruvic transaminase, gamma-glutamyl transferase, alkaline phosphatase, lactic dehydrogenase, Mg^{2+}, uric acid, fasting NH_3 level, hepatitis A and B screen, and delta agent screen.

LABORATORY TESTS AT THE TRANSPLANT CENTER. Blood sugar, Ca^{2+}, amylase, serum protein electrophoresis, cholesterol, antiviral titers (cytomegalovirus, Epstein-Barr and herpes simplex virus), panel reactive antibody, and tissue typing tests.

OTHER TESTS. Twelve-lead electrocardiogram, urine analysis and clean catch urine for culture and sensitivity, stool for culture, ova, and parasites (especially *Giardia* and *Strongyloides*), and stool for occult blood x 3.

RADIOGRAPHIC STUDIES. Chest x-ray, abdominal computerized tomography scan with liver volume estimation, and abdominal liver ultrasound with Doppler evaluation

LIVER TRANSPLANTATION CONTRAINDICATIONS

Absolute

Sepsis outside the hepatobiliary system
Metastatic disease from nonhepatic cancer with the exception of apudomas in which resection of the primary tumor in conjunction with transplantation of the liver can be curative
Metastatic hepatobiliary malignancy
Active alcoholic disease or drug abuse
Severe hypoxemia secondary to right to left shunt
Inability of the patient and/or family to understand the implications of and the commitment to liver transplantation and lifelong immunosuppression need
Advanced cardiopulmonary disease
Symptomatic AIDS

Relative

Nonmetastatic hepatobiliary malignancy
Chronic hepatitis B
Extensive portal vein thrombosis
Extensive previous abdominal surgery
Severe alcoholic disease
Asymptomatic HIV-1-positive patients
Severe renal failure
Age over 65 (physiologic age more important than chronologic age)

Figure 7.4

PATIENT CLASSIFICATION

Status	Description
I	At home, fully active
II	At home, disabled
III	In hospital, regular bed
IV	In intensive care unit
UNOS* status	In intensive care unit, using respirator, moribund

*United Network of Organ Sharing.

Figure 7.5

of the patency and flow direction of the hepatic vessels. Optional: celiac and superior mesenteric angiography (to study the portal flow and patency), coronary arteriogram.

PSYCHOLOGIC STUDIES. Complete psychologic profile, evaluation by the social worker.

OPTIONAL STUDIES. *Noninvasive*—electroencephalogram, MUGA (radionuclide calculation of ejection fraction), thallium stress test, pulmonary function tests, peripheral arterial Doppler studies.

Invasive—esophagogastroduodenoscopy with or without biopsy, colonoscopy, angiograms, needle liver biopsy, endoscopic retrograde choledochopancreatography, percutaneous transhepatic cholangiogram with or without biliary duct catheterization and brush biopsies, and exploratory laparotomy (in the cancer cases, to identify the presence and/or extent of extrahepatic spread).

Once all the results are available, the evaluation committee, composed of surgeons, gastroenterologists, anesthesiologists, psychologists, social workers, and transplant nurse coordinators, meets to discuss the patients and decide on their candidacy. If a patient is accepted, he or she is placed on the transplant candidate list. A status (Fig. 7.5) is assigned according to the patient's present condition, expected course of the disease, and urgency.

PREOPERATIVE CARE AND MANAGEMENT

The fundamental goal during the preoperative period, be it a few days or a few years, is to maintain the patient in the best possible condition. This means that the complications of end-stage liver disease have to be avoided carefully and, if they occur, treated early and aggressively.

Nutritional status should be maintained using a diet relatively low in protein to avoid encephalopathy and low in sugar to avoid hyperglycemia. Salt and fluid restriction may be necessary as well. A rather high content of fat in the diet will ensure an adequate caloric intake. Multivitamin preparations and vitamin K_1 also should be administered, particularly to patients with advanced degrees of liver insufficiency.

The patient should exercise as much as the condition allows to maintain good muscular tone. Smoking should be strongly discouraged and alcohol prohibited. All drugs must be taken cautiously, especially narcotics, because their delayed liver metabolism may easily lead to encephalopathy.

Precautions must be taken to prevent infections. If bacterial infections occur, immediate antibiotic therapy must be started, at first with a second- or third-generation cephalosporin and then, once the culture and sensitivity results are available, with a specific agent. Pan-culturing of the patient must be done, including para- and thoracentesis if ascites or effusions are present.

It is also important to try to prevent encephalopathy. Besides diet control, this is achieved by regular administration of lactulose. Periodic measurement of the blood ammonia level may be needed to identify subliminal, unrecognized encephalopathy. If it does occur, vigorous treatment with lactulose and orally administered neomycin is necessary. Sudden onset of encephalopathy in a previously stable patient should raise the possibility of sepsis, because this is a frequent cause of hepatic decompensation, second only to variceal hemorrhage. As a rule, sufficient lactulose is given to produce diarrhea, after which the dose is reduced to the point where the patient has two to four soft bowel movements a day. In the patient with encephalopathy, there should be a low threshold for intubating the patient to protect the airway from aspiration of gastric contents.

Ascites and pleural effusion should be controlled with fluid/sodium restriction and diuretics—loop and potassium-sparing agents are particularly useful for this purpose. However, excessive dehydration should be avoided, because it can lead to renal failure. Massive ascites, which reduces diaphragmatic excursion and causes pulmonary insufficiency, may require multiple paracenteses for alleviation of symptoms. This procedure must be performed with the utmost caution, because it causes loss of proteins and can predispose to renal failure. Besides the obvious discomfort to the patient, massive ascites, particularly if of sudden onset, should alert the physician to the possibility of portal vein thrombosis. This must be immediately investigated with Doppler ultrasound or nuclear magnetic resonance examination and, if the results are inconclusive, even angiography.

Upper gastrointestinal bleeding must be prevented with the use of antacids to reduce gastric irritation. Although of unproven value, propranolol is frequently used for prevention of variceal hemorrhage. Sclerotherapy to treat variceal bleeding may be indicated. Prophylactic sclerotherapy is not warranted in a patient who has not bled and may be associated with lethal complications.

Last, but not least, it is crucial that abdominal operations be avoided at almost all costs in patients known to be transplantation candidates. Even apparently trivial procedures like cholecystectomy or open liver biopsy can cause extensive and highly vascular adhesions, and will enormously complicate the recipient hepatectomy. Other procedures to be avoided include common and/or hepatic duct exploration, gastric and duodenal surgery, liver resection, and even peritoneojugular shunts. Abdominal surgery in the liver transplant candidate can only be justified for lifesaving procedures. Nonoperative intervention (even of the invasive type, like PTC and needle liver biopsy) is the method of choice in this group of patients. Repeated episodes of spontaneous bacterial peritonitis also can cause serious adhesions.

ANESTHESIA IN LIVER TRANSPLANTATION

Anesthesia for liver transplantation is complex and challenging.[15-17] The patient with end-stage liver disease frequently is in a state similar to that found in septic shock, namely, one of high cardiac output and low peripheral vascular resistance.[16] Moreover, the coagulation parameters may be grossly

abnormal (elevated prothrombin time and activated partial thromboplastin time, decreased platelets and fibrinogen, etc.).[19] To complicate the matter, there may be some degree of renal failure, as well as hypoalbuminemia.[18] Preoperative anesthesiology consultation gives the anesthesia team an opportunity to meet the patient and go over any unusual problems.

Blood loss during liver transplantation occasionally can be massive. The anhepatic phase is particularly delicate and used to be a moment of crisis before the introduction of the venovenous bypass. The unclamping and revascularization of the new liver can lead to extreme hyperkalemia.[18] Other products of the intestinal anaerobic metabolism and air previously entrapped in the hepatic microcirculation are major potential dangers. Finally, after reperfusion, there may be a period of fibrinolysis,[18-20] which requires aggressive and sophisticated intervention to achieve reversal and normalization of the clotting parameters. The large amount of administered fluid, particularly during the anhepatic phase, may lead to pulmonary edema and ventilatory difficulty.[15] Involvement of the anesthesia team is constant during the procedure, and difficult situations can demand the participation of several people rotating in groups of two to four.

Positioning

As shown in Fig. 7.6, the patient is placed in the supine position on the operative table, with both arms abducted. A Foley catheter and a rectal temperature probe are placed after induction of anesthesia. The feet are individually wrapped in plastic foam, then wrapped together, and a soft pillow is put under the calves.

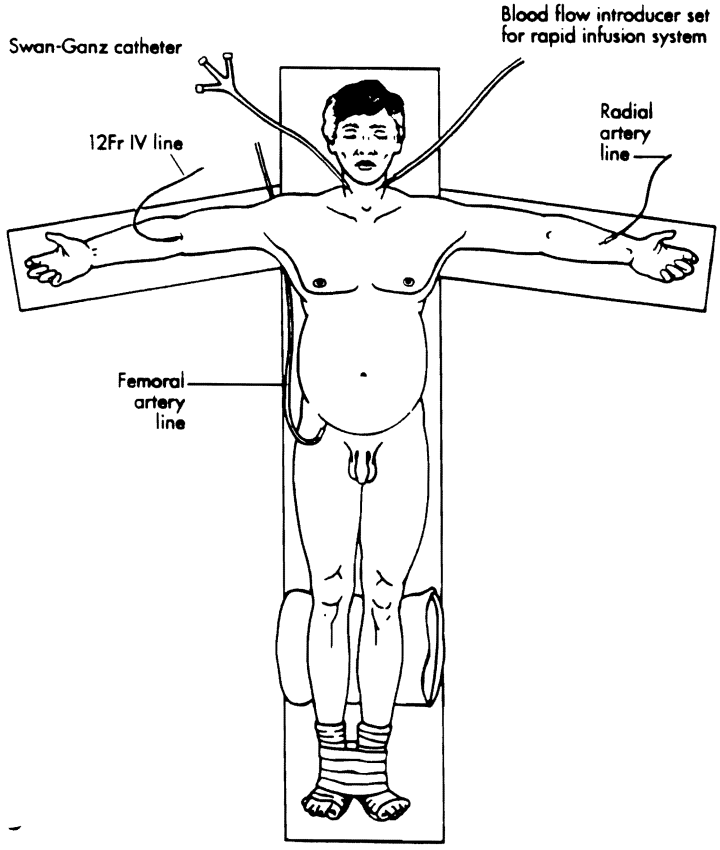

Figure 7.6

Monitoring

Continuous monitoring of many different parameters is used during liver transplantation (Fig. 7.7).

The several lines required (Fig. 7.6) include:

1. Two radial arterial lines (or one radial and one femoral). The Allen test should be performed before these are placed. One line is used for pressure monitoring and the other for blood drawing.
2. One large-bore peripheral intravenous catheter in the antecubital vein of the arm opposite to the side of the bypass.
3. One large-bore external or internal jugular catheter (to serve as access for the rapid infusion system).
4. A Swan-Ganz catheter capable of on-line mixed-venous oximetry. This catheter usually is inserted through the right internal jugular vein.

Preparation

Figure 7.8 shows the equipment necessary during the transplant operation. Figure 7.9 lists the medications available for immediate use.

PARAMETERS FOLLOWED DURING SURGERY

Parameters	Frequency
ECG Radial arterial pressure Central venous pressure Pulmonary arterial pressure On-line mixed-venous oxygen saturation Temperature—esophageal, rectal	Continuous
Urine output Urine specific gravity Arterial blood gas Acid–base status Hemoglobin Hematocrit Serum Na^+, K^+, Ca^{++}, blood sugar Cardiac output (CO)	Hourly or more often if needed
Prothrombin time Activated partial thromboplastin time Platelet count Thrombin time, reptilase time, plasma clot lysis time, levels of factors I, II, and VIII, fibrin split products, ethanol gel test, euglobin lysis time	Every 2 to 4 hours or more often if necessary
Thromboelastogram	Frequently

Figure 7.7

ANESTHESIA EQUIPMENT

Anesthesia gas machine with compressed air supply
Ventilator
Gas humidifier
Vital signs monitor and recorder (multiple channel)
Cardiac output monitor (based on thermodilution technique)
On-line mixed-venous oxygen saturation of hemoglobin
Mass spectrometer (attached to the airway, to measure end-tidal gas tensions)
Thromboelastography (at least two)
Rapid infusion system
Blood pump with warmer
Autotransfusion machine (optional)
Cardiac defibrillator (with external and internal pads)
Warming blanket
Extra supply cart

Figure 7.8

MEDICATIONS AVAILABLE FOR IMMEDIATE USE

Ampicillin	Insulin
Atropine	Ketamine
Cefotaxime	Lidocaine
Cyclosporine	Lorazepam
Dextrose 50%	Methylprednisolone
Dopamine infusion set	Neosporin* ointment
D-tubocurarine	Pancuronium
Ephedrine	Sodium bicarbonate
Epinephrine	Succinylcholine
Fentanyl	Thiopental

*Polymyxin B-Bacitracin-Neomycin.

Figure 7.9

Most patients undergoing liver transplantation today require less than 10 transfusions. However, in difficult cases (and these sometimes are not recognized in advance), the rapid infusion system, capable of delivering 2 to 3 liters/min of warmed blood, may be lifesaving.[21] The warming blanket, multichannel monitor/recorder, and thromboelastograph should be in place routinely. The blood bank must be in a position to supply almost unlimited amounts of blood and clotting products on very short notice. The laboratory must be equipped to provide immediate results any time, day or night.

After positioning, light preanesthesia is administered. This step can be omitted in the encephalopathic patient. The potential pressure points should be well padded and the ECG electrodes secured on the patient's back with tape.

Intraoperative Anesthesia Management

INDUCTION

Most patients in relatively good condition tolerate induction well. Because gastric emptying is delayed in patients with end-stage liver disease, they are all considered to have a full stomach. Consequently, preoxygenation followed by rapid-sequence induction usually are performed.[11] Ketamine or thiopental and succinylcholine or atracurium (in case of hyperkalemia) are commonly used. Ventilation is accomplished with 10 to 15 ml·kg^{-1} to achieve an end-tidal CO_2 at 4 to 4.5% or a Pa_{CO_2} of 35 to 40 mm Hg. The FIO_2 is 50 to 70% and the positive end-expiratory pressure is 5. Nitrous oxide is not used, because it causes intestinal distension and can increase the size of air emboli.[22] Isoflurane is the anesthetic most often used.[23] A narcotic is frequently used as the primary agent or together with an inhalatory primary agent; a sedative such as lorazepam is added. Either pancuronium, metacurine, or atracurium can be used. The fact that they can be "washed out" due to large blood losses is less important for these lipophilic agents.[24]

MAINTENANCE OF A PHYSIOLOGIC STATE

There are three basic stages in the liver transplant operation. Stage I occurs during recipient hepatectomy, stage II is the anhepatic phase, and stage III is the reperfusion stage.

STAGE I (RECIPIENT HEPATECTOMY). *Cardiovascular changes* include high cardiac output. Blood loss may cause hypovolemia, which is treated by volume replacement and administration of $CaCl_2$ and dopamine. *Clotting* usually is poor, although it can be fairly adequate in patients who are less sick or who have cancer. Coagulation products are administered as needed to correct this condition. The *pulmonary function* usually is adequate. *Fluids and electrolytes* often are lost in large amounts, and the *acid base* status experiences considerable shifts. Corrective measures must be taken. The *body temperature* slowly decreases, as a consequence of the open abdomen and possible blood loss. Warmed blood and warming blankets are used.

STAGE II (ANHEPATIC STAGE). *Cardiovascular changes*, if there is no bypass, are characterized by low venous return, high blood loss due to portal hypertension, and low renal function. These changes are treated with volume replacement, although with partial success. If there is bypass, the changes are less pronounced, but adequate blood volume must be ensured. Poor *clotting* may worsen. The treatment is identical to that instituted during stage I, although overcorrection should be avoided to prevent thromboembolism. The *pulmonary function* experiences no major changes. Losses of *fluids and electrolytes*, and *acid base* shifts can be considerable. Replacement is necessary. The K^+ level must be kept as low as practical to prevent postreperfusion hyperkalemia. The *body temperature* changes are identical to those in stage I and should be identically treated.

STAGE III (REPERFUSION). The *cardiovascular changes* frequently include hypotension, bradycardia, and even electromechanical dissociation, all due to release of high K^+ and catabolic product fluid from the liver and bowel. Treatment consists of volume replacement, $CaCl_2$, atropine, epinephrine, etc. There is pulmonary hypertension and low mixed-venous oxygen saturation. The *pulmonary function* may be threatened by edema. The treatment, by way of positive end-expiratory pressure and increase in minute volume, is extremely difficult. If possible, fluid infusion should be decreased. Regarding *fluids, electrolytes* and the *acid base*, hyperkalemia, hypokalemia, acidosis, and fluid losses are common. Early and dynamic treatment is necessary. *Clotting* improves, although initial fibrinolysis may occur. Administration of ε-aminocaproic acid and coagulation products may be necessary. *Body temperature*: hypothermia is very common. Energetic rewarming—including "core" irrigation with very warm fluid—is required.

CONCLUSION OF THE OPERATION

In most cases, if the operation has been successful and the liver is of good quality, the patient's condition continues to improve and stabilize. The lactate level decreases and the coagulation parameters and urine output improve. The pulmonary function, pulmonary artery pressures, central venous pressure, and other parameters normalize. With very brief operations (4 hours or less), the patients can even be extubated on the operative table at the end of the procedure.

Pediatric Anesthesia

This area has been amply described[25] and is essentially similar to adult anesthesia. A notable difference is the high tolerance that children have to venous cross clamping. Because it is very inconvenient or impossible to use venovenous bypass in patients weighing less than 25 or 30 pounds, this is a great advantage. Blood loss must be kept to a minimum, as the pediatric total blood volume is so much smaller. Coagulation products must be avoided as much as possible, because their administration can predispose to hepatic artery thrombosis.[26]

Retransplantation

For patients with primary nonfunction or acute rejection, especially if complicated by multiple organ failure, the management is similar to that used in fulminant hepatic failure. On the other hand, patients retransplanted for chronic rejection or technical problems are much more stable and, except for possible blood loss from extensive adhesions, their management can be relatively simple.

TECHNIQUE OF LIVER TRANSPLANTATION

The donor hepatectomy is technically simpler than the recipient operation, but neither procedure leaves any room for error. Traditionally, a liver transplant surgical trainee goes first through the steps of mastering the donor operation before tackling the complexities of the recipient procedure. Additional details of the donor operation are available in Chapter 3.

THE DONOR

Selection

There are no absolute selection criteria, but some fairly constant guidelines are followed. The HIV-1 and hepatitis screening must be negative. In addition, tissue typing of the donor as well as cytomegalovirus and Epstein-Barr virus titers are routinely checked. Donor age can range from neonatal to over 60 years. Optimally, the donor should be stable, without significant intraabdominal injuries or previous history of liver or biliary tract disease, and require minimal or no vasopressor support. However, none of these criteria are absolutely essential. We accept a significant number of organs rejected by other programs. Our experience demonstrates that the function of organs commonly rated as "substandard" can be as good as that of "blue-ribbon" grafts.[27-29] Sepsis should be absent, although we have occasionally used livers from donors with positive body fluid cultures if the source was obvious and extraabdominal.

Maintenance of the donor is a complex and sophisticated task and should be undertaken, if possible, in an intensive care unit setting, under constant supervision. Poor care of the donor will most likely compromise the quality of the various organs. One useful step, particularly for personnel involved in donor maintenance in a small hospital with minimal or no previous experience, is to enroll the help of the local procurement agency early on. The coordinators working for such agencies have invaluable advice to offer for these particular cases.

The fluid and electrolyte balance must be maintained within normal parameters. Frequently, brain dead patients have diabetes insipidus. Pitressin, especially the oil-vehicle subcutaneous type, should be avoided as much as possible, because it causes a decrease in splanchnic flow and vasoconstriction and can jeopardize the quality of the grafts. Consequently, close monitoring and replacement of free water will be necessary. It is crucial that hypernatremia be avoided, because it seems to considerably increase the incidence of primary nonfunction of the graft. On the other hand, overhydration must be avoided as well, because high central venous pressure will result in swelling of the liver and possible poor function in the recipient later. Attention to pulmonary toilet and maintenance of good urinary output also are important.

The size of the liver must be estimated, because size usually is a crucial limiting factor in matching a donor organ to a specific recipient. While a smaller liver can almost always be put into a large recipient, a liver larger than normal for the recipient may be very difficult or even impossible to transplant. The rule of thumb is that the liver represents approximately 2.5% of the total body weight. The best clues are those obtained by examination of the donor. For example, an obese female donor will have a much smaller liver than expected from her total weight. Because 1 cc of liver tissue weighs roughly 1 g, the hepatic volume can be easily extrapolated from its weight.

Besides hematocrit and electrolytes, the total and direct bilirubin, liver enzymes, prothrombin and partial thromboplastin times, blood urea nitrogen, and creatinine levels are measured. There are no strict upper limits set for acceptability of the liver, but, in the absence of intraabdominal injury and history of previous disease, two to three times normal are acceptable. The indirect bilirubin may be even higher if the patient has had a number of transfusions. On the other hand, initially elevated enzymes (even 10 to 15 times normal) after an initial cardiac or respiratory arrest that subsequently decrease toward normal also are acceptable, particularly if the liver looks normal at the time of the harvest. This generally implies a liver that is soft, pinkish in color, and without obvious injuries, producing normal-looking bile upon opening of the bile duct, and which blanches rapidly and evenly, while staying soft, once the cold perfusion is started.

Surgical Technique–Donor Hepatectomy

There are basically three techniques for the donor hepatectomy: the so-called classic, standard, and rapid perfusion techniques. These will be briefly described here. Additional information is provided in Chapter 3. Special modifications must be used for harvesting of livers from extremely small pediatric donors.

Generally speaking, after initial dissection of the liver and heart and the beginning of cold perfusion, the heart is the first organ to be removed, then the liver, and finally the kidneys. **We strongly emphasize that the kidneys need not be dissected as a preliminary step. This practice, still widespread, is not helpful for the following reasons:**

1. The dissection takes at least 1 hour, frequently 2, is usually quite bloody (contrary to the commonly held opinion of its supporters), and requires extensive manipulation of the intestine, with resulting embarrass-

ment of blood flow to the liver. It is fundamental for the renal procurement team to keep in mind that a compromised liver frequently will need to be replaced in the best of circumstances or, at worst, prove to be lethal.

2. This dissection, taken in the name of "identifying the anatomy," actually tends to increase the risk of renal vascular injury, especially to small lower polar arteries, because the exposure is never perfect. Additionally, the skeletonization of the arteries causes them to go into spasm, consequently decreasing the amount of cold perfusion through the kidneys later. This is exactly contrary to what needs to be achieved.
3. Once the liver is out of the way, the kidneys can be removed safely in about 5 minutes, to be then separated and cleaned leisurely and safely on the back table while kept in a basin filled with crushed ice and preservation solution.

Thus, a better quality of renal graft is possible by deferring unnecessary preliminary dissection. In the final analysis, it gives a false sense of security to the surgeon, while in reality it jeopardizes the organs one is supposed to protect.

CLASSIC AND STANDARD TECHNIQUES

The classic technique requires a rather elaborate dissection of the liver vasculature prior to cross clamping and cold perfusion. In the multiorgan donor, a long incision is made from the jugular notch to the symphysis pubis. Two cannulas are put in place, one into the portal vein (by way of the splenic vein) and one into the lower abdominal aorta, just proximal to the iliac bifurcation (Fig. 7.10). After the placement of the portal cannula, a slow precooling of the liver is begun, which continues until cross clamping. All the vascular structures of the liver are carefully identified and isolated. This is a technique suitable for the surgeon with

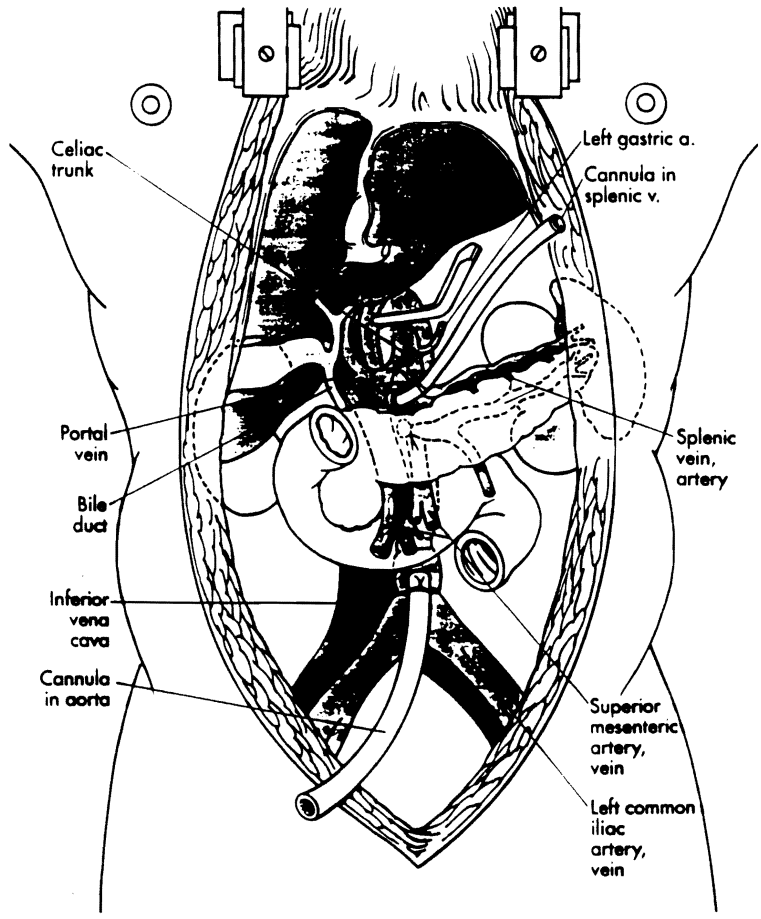

Figure 7.10

somewhat less experience, because it permits the visualization of the various hepatic vessels at leisure. It also permits the manipulation of the fluid balance for a more extended period of time, which may be useful if the fluid level is insufficient or excessive at the beginning. The main disadvantage is the extensive manipulation of the liver and danger of interference with its blood supply.

The standard technique is similar, although the dissection is somewhat less extensive and the precooling phase is eliminated. This facilitates the interface with the heart recovery teams, which frequently have objected to the precooling in the past on the grounds that lowering the temperature could cause arrhythmia. This technique is the one most commonly used.

RAPID PERFUSION TECHNIQUE

The rapid perfusion technique was initially used for liver recovery from extremely unstable donors. It consisted in cannulation of the distal aorta only, without any other vascular dissection. After cross clamping, the liver and kidneys were perfused with cold lactate Ringer's solution. The liver perfusion was still dual, with a direct flush from the celiac axis and an indirect flush by way of the portal vein after passage of the perfusate through the mesenteric circulation from the superior mesenteric artery. The liver was then rapidly excised, without tieing any branches. A fair amount of extra tissue subsequently was removed on the back table. In the present rapid technique, a direct descendant of the method described above, the aorta is cannulated just above the iliac bifurcation, while the portal vein is cannulated via the inferior mesenteric vein (Fig. 7.11), without any preliminary dissection of the hepatic vasculature.[30,31] After cross clamping and cooling, the liver can be rapidly excised by ligating only the major collaterals and only on the hepatic side. The extra tissue removed with the liver can be then excised on the back table. This technique has the following advantages:

1. Preliminary dissection is kept to a minimum, reducing the risk of vascular injury and impairment of hepatic blood flow.

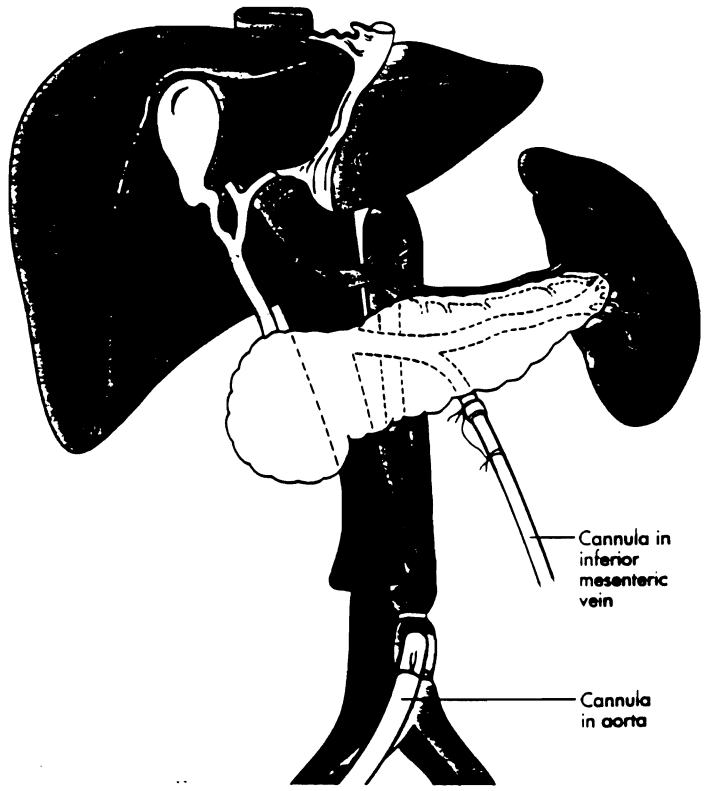

Figure 7.11

2. The collaterals of the hepatic vessels need only to be tied on the liver side, because the dissection is done in a blood-free field after cross clamping.
3. The technique can be employed in stable and unstable donors equally well.
4. The duration of the entire procedure can be reduced to only 45 minutes to 1 hour. Preliminary cannulation can be performed simultaneously with cardiac dissection.

The two major drawbacks of this technique are that the brief time of preliminary work does not allow hemodynamic manipulation of the donor in case the liver is congested, and that it requires more skill and anatomical knowledge because the potential for vascular injury in an unfamiliar bloodless field is increased.

THE RECIPIENT

Surgical Technique

The recipient operation is a *tour de force* of general surgery, with the hepatectomy often being the most difficult step. The recipient operation is an extremely unforgiving procedure, in which seemingly trivial errors can lead to disaster. A typical example is that of the avulsion of a small posterior portal branch leading to either an air embolus (during the venovenous bypass phase) or uncontrollable hemorrhage during futile attempts to place sutures in the face of prominent portal hypertension and friable vessels.

Although the hepatectomy technique has been standardized to a large extent, no two transplants are exactly the same. Thus, a general plan of action must be established as soon as the abdomen is entered. In most cases the hilar dissection should be performed first. In this way, the bypass is started and devascularization of the liver is achieved early, with blood loss significantly reduced. Tedious hemostasis is mandatory and all reasonable attempts should be made to achieve as much of it as possible before implantation of the homograft. On the other hand, it is counterproductive to spend an inordinate amount of time in performing hemostasis during the anhepatic phase, even with venovenous bypass, in unstable patients. In such cases, replacing the liver rapidly with a good homograft and unclamping the venous compartment results in disappearance of the portal hypertension and production of fresh clotting factors by the new liver.

VENOVENOUS BYPASS

We introduced venovenous bypass in 1983.[32-34] Since then we have been using it routinely, and many other liver transplant groups have adopted it. However, its acceptance is not universal. It consists in decompression of the inferior vena cava (via the greater saphenous, femoral, and iliac veins) and portal circulation (by way of a portal cannula) using heparin-bonded Gott shunts, with return flow into the superior vena cava through the axillary vein (Fig. 7.12). Although liver transplants can be performed without the bypass, we believe that its advantages, listed below, make its use almost mandatory.

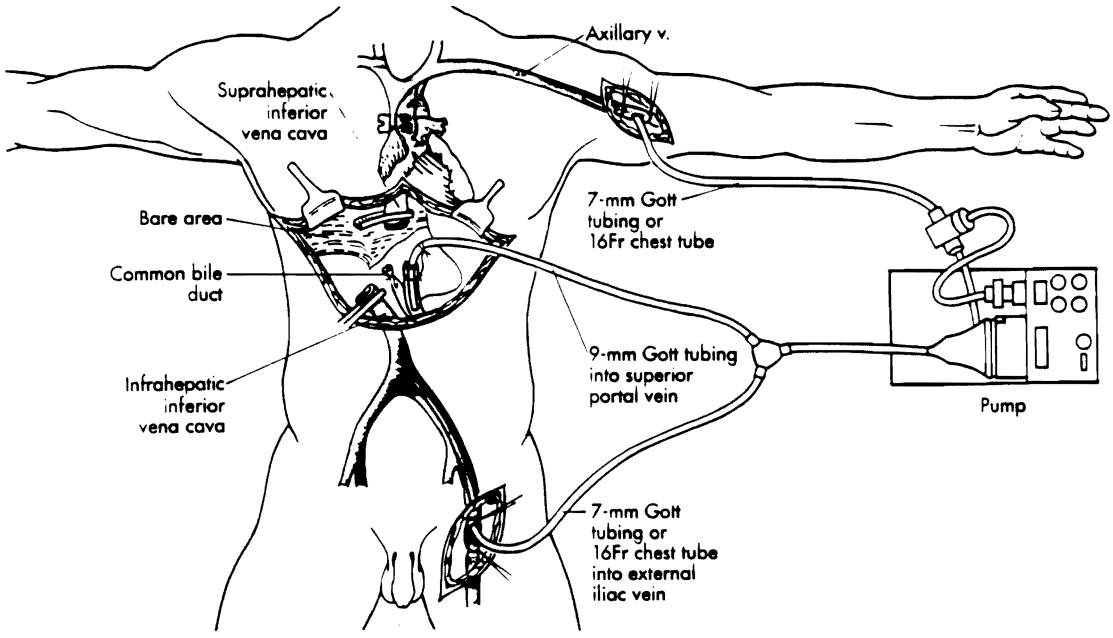

Figure 7.12

1. In patients with acute failure or hepatic tumors not associated with liver cirrhosis, the absence of venous collaterals may lead to cardiovascular collapse during cross clamping due to diminished venous return to the heart.
2. The avoidance of portal clamping prevents mesenteric stasis and subsequent development and release of anaerobic metabolism products into the general circulation after unclamping. Similarly, damage to the kidneys is avoided if the vena cava is effectively decompressed.
3. Early bypass results in decompression of the portal circulation, which decreases blood loss.
4. The lack of portal hypertension and vascular instability during bypass permits a more unhurried operation, allowing a more complete hemostasis as well as the training of new surgeons.
5. Finally, the venovenous bypass can be regarded as a safety net, because if complications arise that require a longer anhepatic phase, these can be dealt with effectively without jeopardizing the patient's life.

BILIARY RECONSTRUCTION

We reconstruct the bile duct either by means of an end-to-end choledochocholedochostomy over a T-tube or an end-to-side choledochojejunostomy with a Roux-en-Y loop over an internal stent. These techniques will be described later. Other methods of biliary reconstruction have been and still are used by other groups.[55]

PRELIMINARY PHASE

The patient is placed on the operative table in a supine position, with both arms abducted (Fig. 7.6). The neck, chest, abdomen, upper thighs, and groin are prepped with organic iodine solution and drapes are placed, leaving an extremely wide field. We start the operation by performing the axillary (Figs. 7.13, 7.14) and greater saphenous vein (Fig. 7.15) dissections through appropriate incisions. These usually are on the left side, although in retransplantations we use the untouched right side. Extreme care is taken so as not to injure the brachial plexus that surrounds the axillary vein. At a later time, once the bypass has been removed, the axil-

Figure 7.13

Figure 7.14

Figure 7.15

lary vein, if single, is repaired with a fine Prolene* running suture; if double, the branch is simply ligated.

RECIPIENT HEPATECTOMY

INCISION. A bilateral subcostal incision with a midline extension to the xiphoid is used, extending more on the right than on the left (Fig. 7.16A). Alternately, a right hockey stick incision can be used (Fig. 7.16B). In pediatric patients, an upper abdominal transverse incision is the norm (Fig. 7.16C). The round ligament, frequently very bulky and containing large collaterals, is divided between ties. Once the upper surface of the liver is free from the diaphragm, a Rochard retractor is placed to retract the costal margins upwards and backwards (Fig. 7.17). The quality of the exposure achieved with the Rochard obviates the need to extend the incision into the chest to expose the suprahepatic vena cava. During the last year, the first author has been using the Iron Intern* (Fig. 7.18), a table-mounted, self-retaining retractor that enables the surgeon to perform the liver transplant procedure with only one assistant, thus reducing manpower requirements by 50%.[35]

EVALUATION. At this point, the situation is evaluated as far as the liver condition and presence of adhesions or other

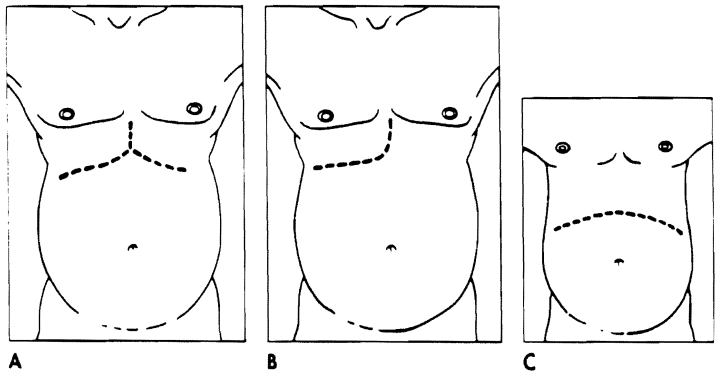

Figure 7.16

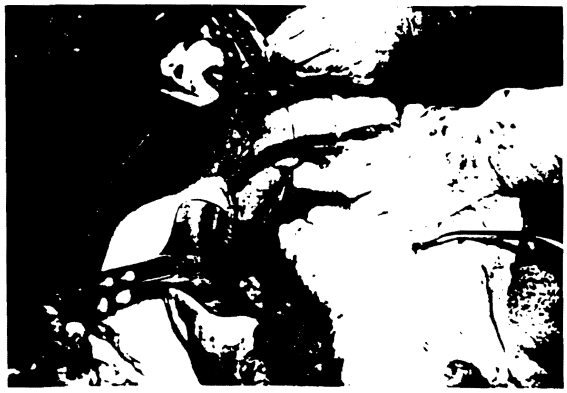

Figure 7.17

Figure 7.18

problems are concerned, and a plan of action is formulated. If no adhesions are present, the left triangular and falciform ligaments are divided with a cautery (Figs. 7.19, 7.20). The gastrohepatic ligament can be divided now as well, usually between ties, especially if an aberrant left branch is present.

HILAR DISSECTION. A detailed inspection and palpation of the hilum must now take place. If possible, a finger should be passed completely around the hilum from behind to palpate the portal vein for thrombosis (in which case it will feel like a hard cord) and from the right posterior margin for an aberrant right branch (Fig. 7.21).

The dissection is then started by first opening the peritoneum covering the hepatoduodenal ligament, either with the cautery or between ties. As opposed to the donor hepatectomy, the recipient dissection takes place high in the hilum to preserve as much length as possible for the various structures that will have to be used later for revascularization.

Figure 7.19

Figure 7.20

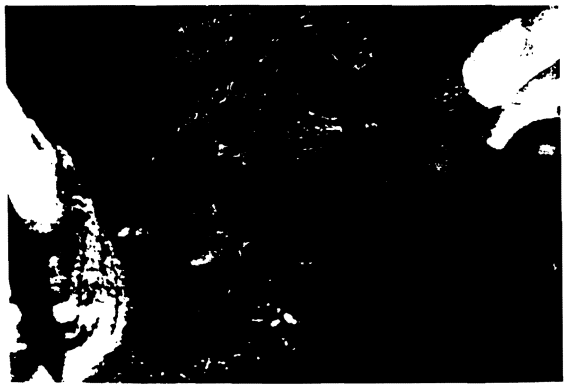

Figure 7.21

Figure 7.22 shows the most important structures that have to be identified during the recipient's hepatectomy. All the structures that need to be divided will be doubly tied. The hepatic artery should be divided first, if possible, because this will reduce the subsequent blood loss (Fig. 7.23). The cystic and common hepatic ducts are then divided between ties (Figs. 7.24, 7.25). The portal vein usually can be identified at this point. All the areolar, lymphatic, and nerve tissues around the portal vein are sectioned between ties so as to completely skeletonize it (Fig. 7.26). Blunt proximal and distal dissection with a Kittner swab (also known as a "peanut") will free the 5 to 6 cm of portal vein necessary for cannulation.

CANNULATION. The axillary and greater saphenous veins are cannulated at this point (Rumel clamps will keep them in place) (Figs. 7.27, 7.28). The portal vein can now be ligated or clamped high in the hilum (if the major branches can be easily dissected, individual ligation should be performed), transected, cannulated end-on with a Gott shunt, and tied in place with heavy silk or umbilical tape (Figs. 7.29, 7.30). The cannulas are flushed with heparinized saline

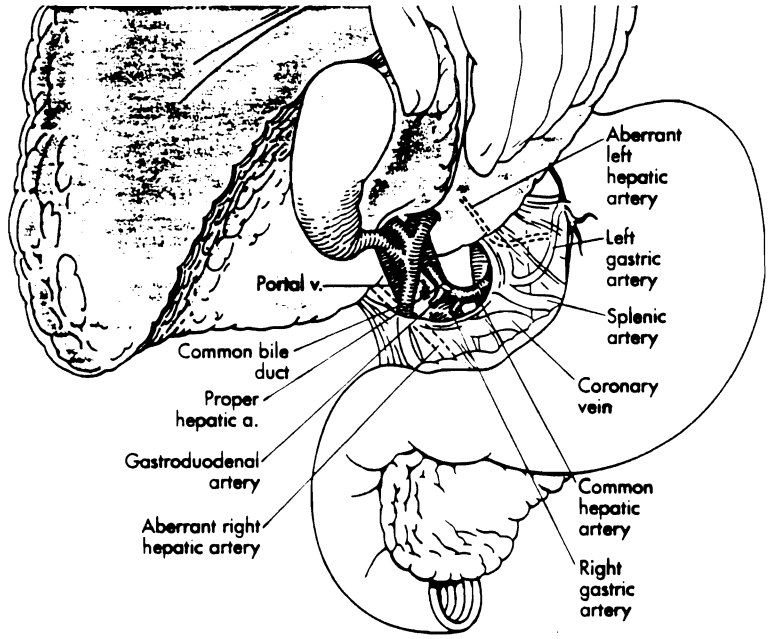

Figure 7.22

Figure 7.23

Figure 7.24

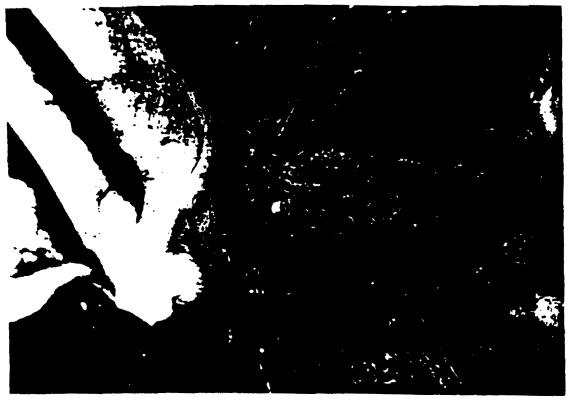

Figure 7.25

Figure 7.26

Figure 7.27

Figure 7.28

Figure 7.29

Figure 7.30

solution (1,000 U/liter) and interconnected. The bypass can then be started. In adults, at least 1,500 cc/min should be obtained. In children, the bypass usually can be used for patients weighing 25 to 30 lbs or more. Flows of 500 cc/min or more are acceptable.

COMPLETION OF HEPATECTOMY. The infrahepatic vena cava can now be encircled and clamped (Fig. 7.31). The remaining part of the falciform ligament, as well as the medial aspect of the right triangular ligament, are divided. The suprahepatic vena cava is encircled and then clamped (Figs. 7.32, 7.33). The liver is now removed. This can best be done by leaving at least the posterior wall of the retrohepatic vena cava in place (Fig. 7.34). In this manner the retroperitoneal structures, especially the right adrenal gland, will not be injured. Also, the adrenal vein can be identified from within the caval lumen and easily tied (Fig. 7.34). The liver also can be excised off the retrohepatic cava, leaving the entire vessel in place (Fig. 7.35). This step is carried out by dissecting from left to right under the caudate lobe, as

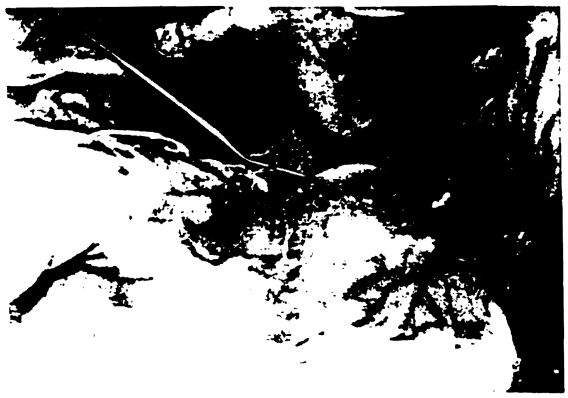

Figure 7.31

Figure 7.32

Figure 7.33

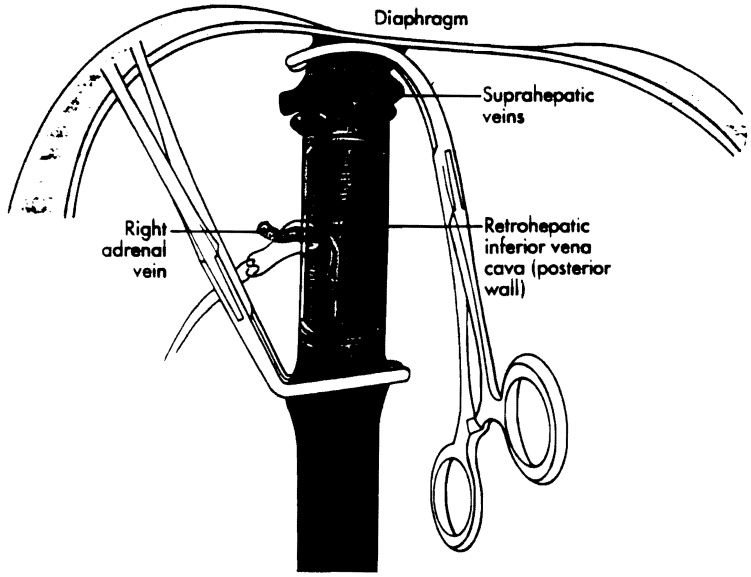

Figure 7.34

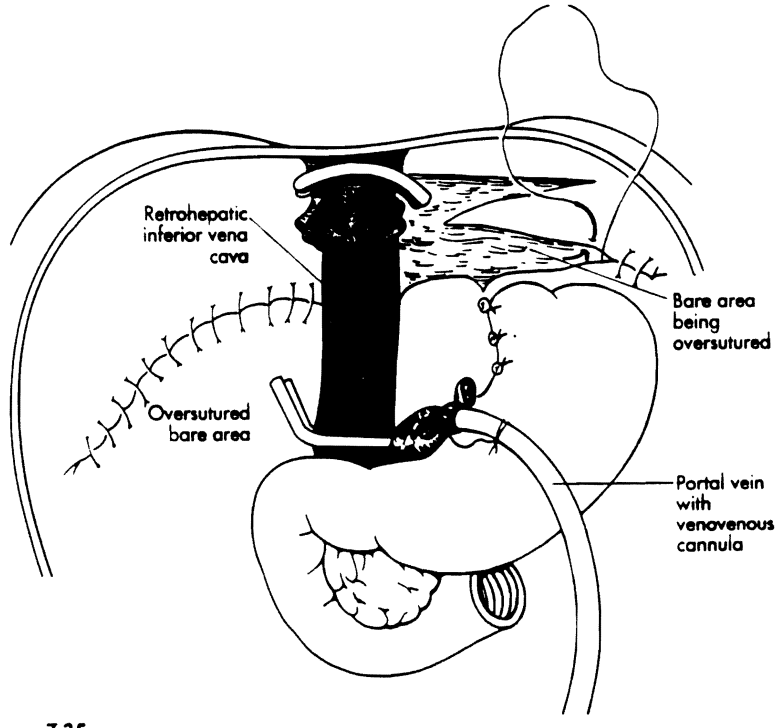

Figure 7.35

shown in Figure 7.36. The advantage of this technique is that it allows the surgeon to fashion adequate caval cuffs under any circumstance.[36]

HEMOSTASIS. Once the liver is removed and the adrenal vein ligated, the "bare area" behind the liver is oversutured with running Prolene sutures (this reperitonealization is excellent for hemostasis) (Fig. 7.35). If the bleeding is not significant, superficial cauterization with electrocautery or an argon beam coagulator is sufficient (Fig. 7.37). Any other major bleeding area can be controlled at this time, when the absence of the liver ensures superb exposure. The recipient hepatic artery also can be dissected free at this time.

FASHIONING THE CUFFS. The lower cuff can be easily fashioned by just trimming the redundant cut vessel. A careful search for severed branches near the proposed anastomosis site is necessary to prevent bleeding after unclamping.

For the upper caval cuff, the openings of the individual major suprahepatic veins are interconnected (dotted lines in Figure 7.38A). An ample common funnel is thus obtained (Fig. 7.38B), which subsequently can be trimmed to the appropriate length. The temptation to leave long cuffs must be resisted, because long vessels can kink and an acute Budd-Chiari syndrome may occur later.

IMPLANTATION (VENOUS ANASTOMOSES)

The liver is brought into the wound for implantation. We usually perform the anastomoses in the following order: suprahepatic vena cava, infrahepatic vena cava, portal vein. After unclamping and revascularization of portal flow, the arterial anastomosis is performed. Occasionally all four vascular anastomoses are completed prior to unclamping.

The same technique is used in all venous anastomoses. One suture is placed at each corner of the vessel to be sutured. Each half of the suture in the left corner of the vessel will

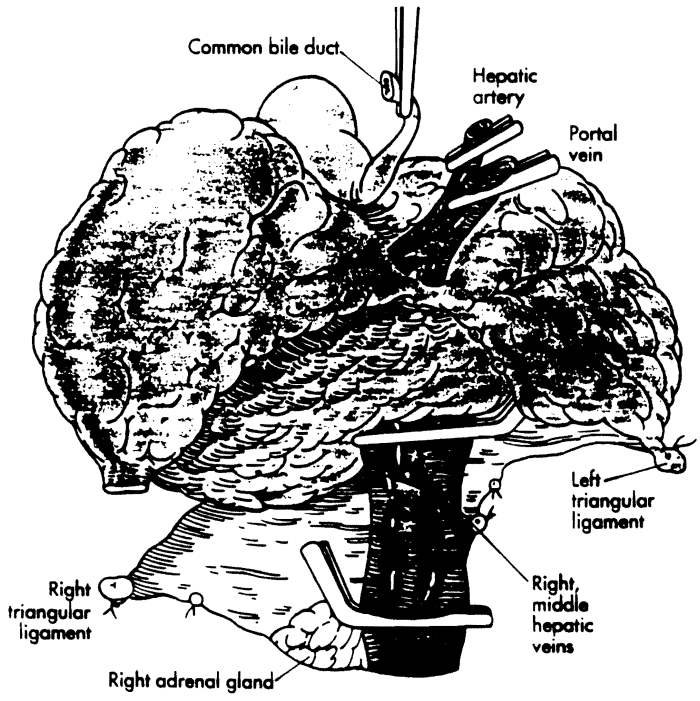

Figure 7.36

be run around half of the circumference of the vessel (Fig. 7.39A). The posterior half will be first brought inside the lumen of the vessel and then the continuous suture will be performed from within the lumen. As shown in Figure 7.39B, a middle suture also was placed, which will elevate two "ridges" of tissue to facilitate the eversion of the posterior anastomosis. The other half of the left suture is then run over-and-over on the anterior wall, completing the anastomosis (Fig. 7.39C). The right corner stay stitch is also tied snugly. For vessels of medium or small caliber we use a "growth factor,"[37] that is, the suture used for anastomoses is tied some distance away from the wall of the vessel (one half to one diameter) while

Figure 7.37

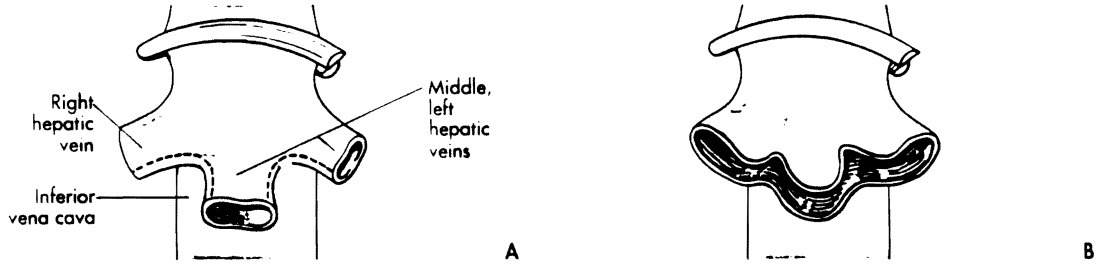

Figure 7.38

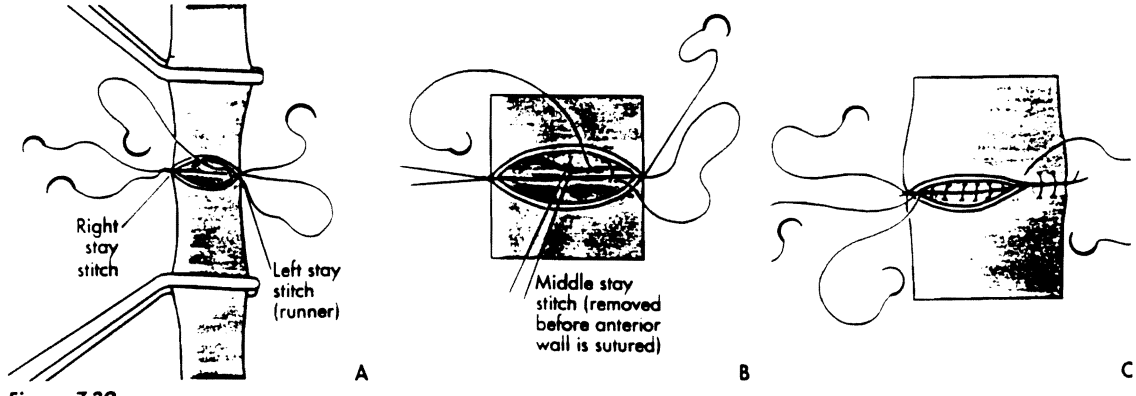

Figure 7.39

the stay suture is tied down snugly (Fig. 7.40A,B). In this manner, the redundant runner can distribute itself along the perimeter of the vessel, once it distends with blood after unclamping. The suture placed in the right corner of the vessel prevents the right angle from opening. This small artifice prevents an hourglass stricture at the anastomosis. Although particularly indicated for venous anastomoses, the growth factor also is frequently used in end-to-end arterial anastomoses.

The suprahepatic vena cava is sutured with 3–0 Prolene (Figs. 7.41–7.43), and the infrahepatic cava is sutured with 4–0 Prolene (Figs. 7.44, 7.45). Before the infrahepatic caval anastomosis is completed, the liver is flushed through the portal cannula with 100 to 500 cc of cold lactate Ringer's solution, depending on its size. This serves to flush out of the liver any previously entrapped air, as well as the preservation solution, which has a high potassium content. The portal cannula is then clamped and removed. The portal veins on both the donor and recipient sides are then trimmed for anastomosis. It is better to trim as little as possible on the recipient side, in case the patient has to undergo retransplantation at a later time. In any case, the veins have to be just snug after one or more laparotomy pads are placed behind the liver. The tendency is to leave the veins too long, but later, when the viscera now retracted inferiorly are released and returned to a normal position, the resulting vein can be too long and kink. In fact, the veins must look almost too short to ensure that the ultimate length is correct. Once the two veins have been trimmed, they are anastomosed in an end-to-end fashion with 6–0 Prolene, leaving a one-diameter growth factor (Figs. 7.46, 7.47). The clamps are removed and the liver is revascularized. It should reperfuse evenly and remain soft (Fig. 7.48). Rapid inspection of the anastomoses is then performed and hemostasis of major bleeding points achieved.

IMPLANTATION (ARTERIAL ANASTOMOSIS)

If not already done, the recipient hepatic artery is now mobilized to a level at least 2 to 3 cm proximal to the gastroduodenal artery bifurcation. The anastomosis site on the

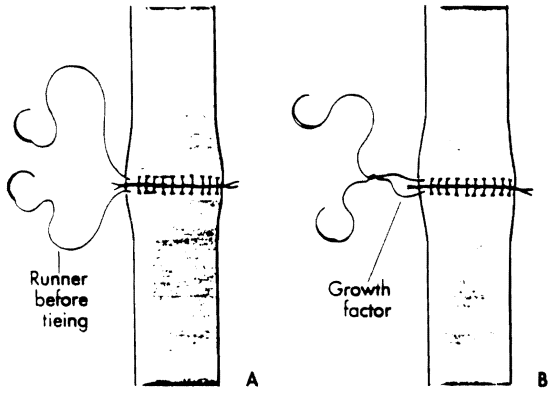

Figure 7.40

Figure 7.41

Figure 7.42

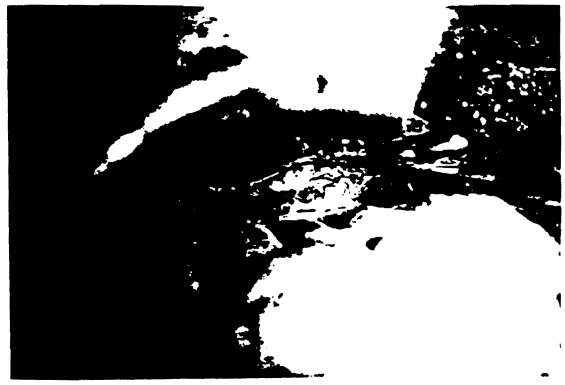

Figure 7.43

Figure 7.44

Figure 7.45

Figure 7.46

Figure 7.47

Figure 7.48

recipient side depends on the length and caliber of the donor vessel. Figure 7.49A–D shows the various anastomoses of the hepatic artery possible in the recipient: at the proper hepatic artery level (A), at or near the gastroduodenal artery takeoff level (B), at the common hepatic artery level (C), or encompassing the bifurcation of the celiac axis into the splenic and common hepatic artery (D).

A Carrell patch is always removed around the celiac and/or superior mesenteric artery from the aortic wall to facilitate the anastomosis to the recipient vessel. On the recipient side, the openings of two branches can be interconnected, resulting in a "branch patch" (Fig. 7.50). The anastomosis is done with 6–0 or 7–0 Prolene, with or without a growth factor, which is usually omitted if patches (Carrel or branch) are used. The liver is then rearterialized.

HEMOSTASIS. The remaining hemostasis is done at this point. In a simple case, little or no hemostasis is necessary

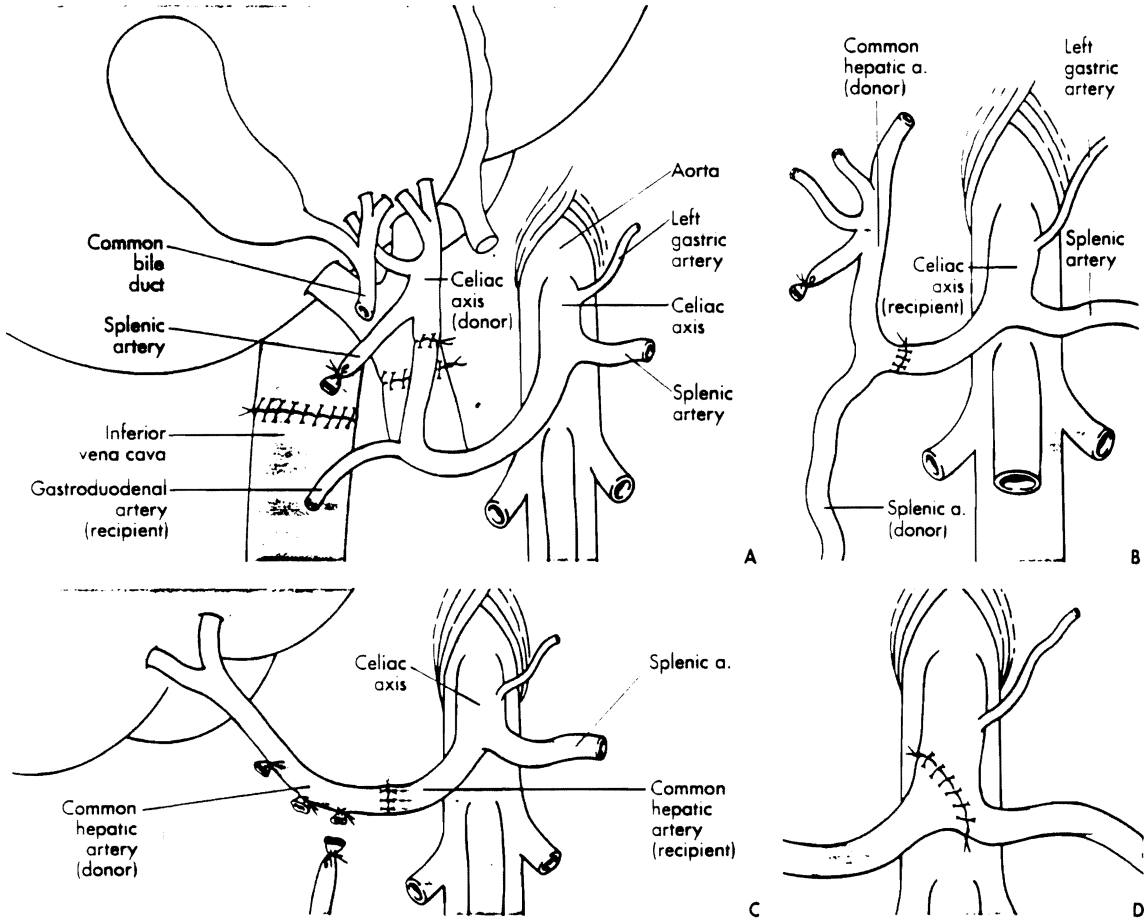

Figure 7.49

now. In difficult cases, with portal vein thrombosis or extensive adhesions, many hours of tedious work are necessary. Sutures, cautery, infrared sapphire coagulator, argon beam, and hemostatic agents are used singly or in combination to achieve hemostasis.

BILIARY ANASTOMOSIS (CHOLEDOCHOCHOLEDOCHOSTOMY—DUCT-TO-DUCT)

This is the type of biliary reconstruction that we favor. It is simple technically, rapid, physiologic, and allows access to the bile duct for monitoring of the bile and cholangiographic exams. Absorbable material is used for the anastomosis, either of the braided (Vicryl® or Dexon®) or monofilament (PDS® or Maxon®) type.

The donor and recipient bile ducts are first trimmed to the appropriate length; care is taken to ensure that the margins are viable. Fine silk stay sutures are placed on the two cut ends (Fig. 7.51A). A metal probe is then introduced into the recipient duct for 2 to 3 cm and pushed through a small stab wound. Electrocoagulation should never be used for this purpose.

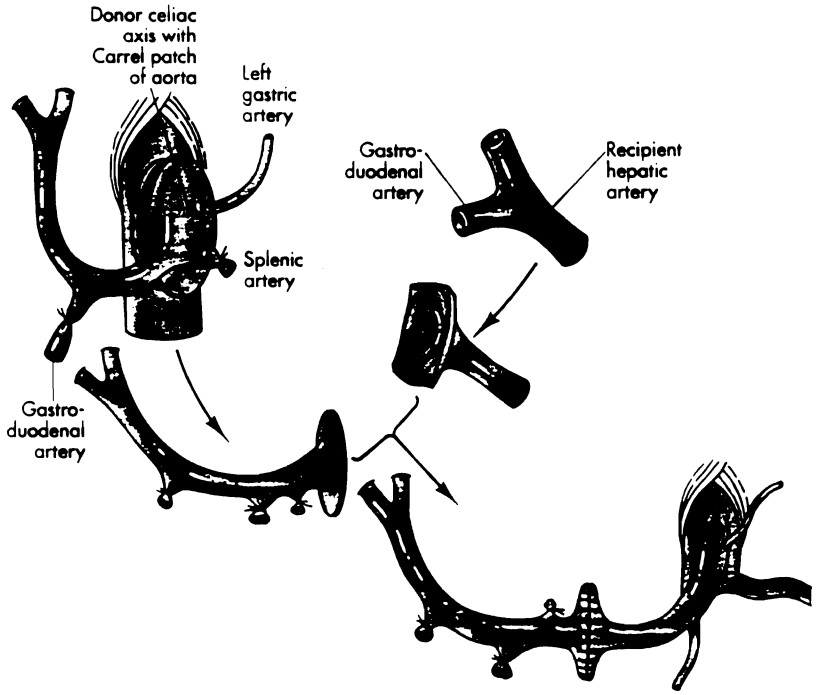

Figure 7.50

because tissue destroyed by heat may cause a biliary leak during the postoperative course. After the probe has been pushed through, a 2–0 silk tie is knotted to its end (Fig. 7.51B) and the probe is pulled through the duct wall and out the cut end. A French-eye needle is loaded on the silk tie and passed through the end of the long limb of an 8 or 10 French T-tube (Fig. 7.51C), which can then be pulled through the same stab wound (Fig. 7.51D). At least a V-cut should be made in the short limb opposite the long limb to facilitate its later removal (Fig. 7.52A). Alternatively, the short limb can be sectioned longitudinally to form a gutter (Fig. 7.52B). The T-tube is then pulled inside the recipient duct and out through the side hole, until the short limb lies inside the duct. Its superior end protrudes out of the cut end of the recipient bile duct and will cross the anastomosis into the donor duct.

The anastomosis can now be performed either with running or interrupted sutures. If the running method is selected, the same technique as in a venous anastomosis is used. Two sutures are placed at the corners of the suture line and then two halves of the left suture are run around both the posterior and anterior walls (Fig. 7.53A). The two ends are then tied at the right corner (Fig. 7.53B). If interrupted sutures are used, we start with one posterior suture (Fig. 7.54A), following which serial interrupted stitches are placed in succession, moving on both sides toward the anterior wall (Fig. 7.54B). All the sutures can be put in, tagged, and tied at the end, or they can be tied and cut as the surgeon proceeds (Fig. 7.54C). The superior end of the short T-tube limb is introduced into the donor duct just before starting on the anterior wall of the anastomosis.

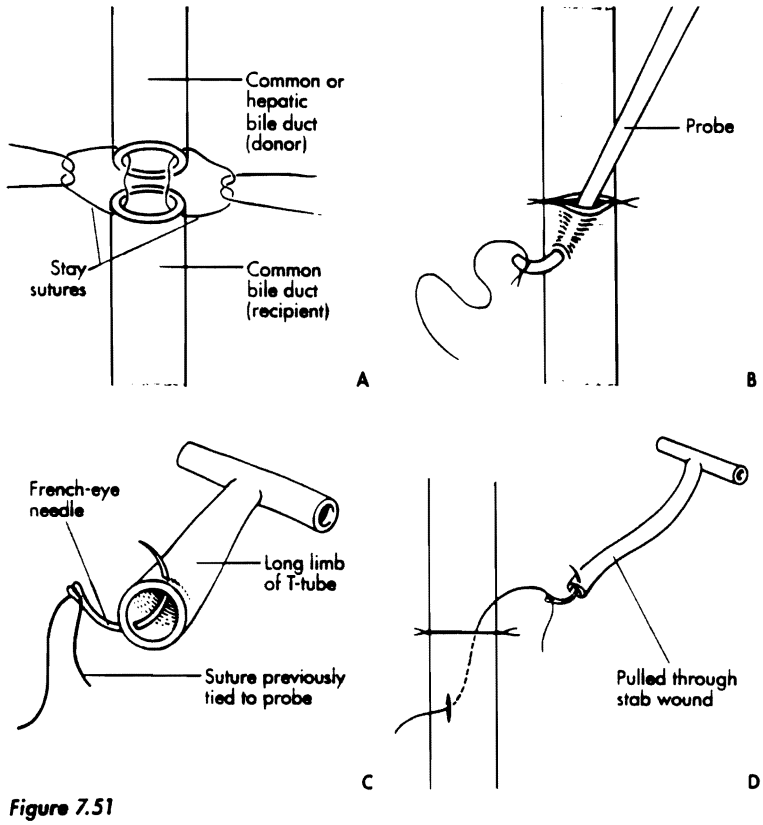

Figure 7.51

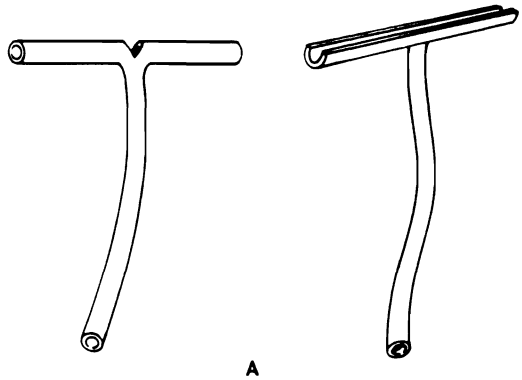

Figure 7.52

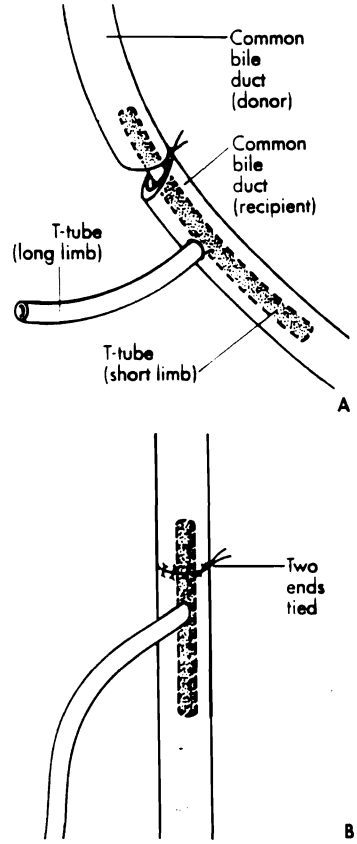

Figure 7.53

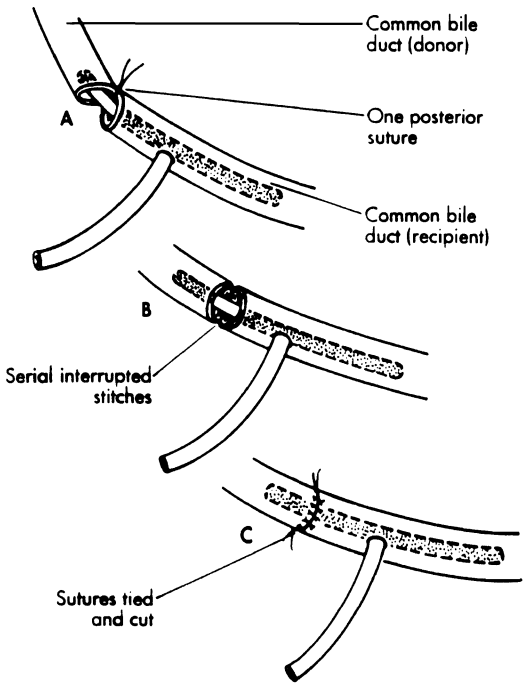

Figure 7.54

When the anastomosis has been completed, it is checked for leaks. This is done by first flooding the area with saline solution, then injecting air through the T-tube, and finally by performing a T-tube cholangiogram (Fig. 7.55). For small leaks, individual fine absorbable sutures are sufficient; for large leaks, a complete revision of the anastomosis is necessary.

The complications of the choledochocholedochostomy are the following:

1. Dysfunction of the sphincter of Oddi, leading to a diffuse dilation of both the recipient and donor ducts[38] (Fig. 7.56). This is corrected by conversion to a choledochojejunostomy with a Roux-en-Y loop.

Figure 7.55

Figure 7.56

Figure 7.57

Figure 7.58

Figure 7.59

Figure 7.60

2. Bile extravasation, either from the suture line (Fig. 7.57) or the T-tube exit site (Fig. 7.58). It can be corrected either by primary repair or conversion to a Roux-en-Y choledochojejunostomy, depending on the size of the leak and degree of contamination.
3. Stricture. Single strictures usually occur at the anastomosis (Fig. 7.59). Multiple intrahepatic strictures usually are the result of arterial thrombosis. Balloon dilatation can be attempted for single strictures (Fig. 7.60), although most patients will eventually require a conversion to choledochojejunostomy.

The overall incidence of complications after choledocho-choledochostomy is approximately 18%, which is consistent with that found in the series from other centers, using this or different reconstruction methods. The advantage is that these complications usually can be dealt with rather easily and definitively by a conversion to a choledochojejunostomy.

BILIARY ANASTOMOSIS (CHOLEDOCHOJEJUNOSTOMY)

This procedure is used in the great majority of pediatric patients, who have absent or small caliber ducts, and adult patients with either primary diseases involving the biliary tree (primary sclerosing cholangitis, Caroli's disease), cancer, or a major discrepancy between the donor and recipient ducts.

First the donor duct is trimmed to viable tissue and hemostasis of the margins is achieved. Then a 40-cm-long Roux-en-Y loop of jejunum is fashioned. Either hand-placed sutures or staples can be used, depending on the surgeon's preference. Figure 7.61 shows a Roux-en-Y loop performed with stapling devices. A small incision has been made in the

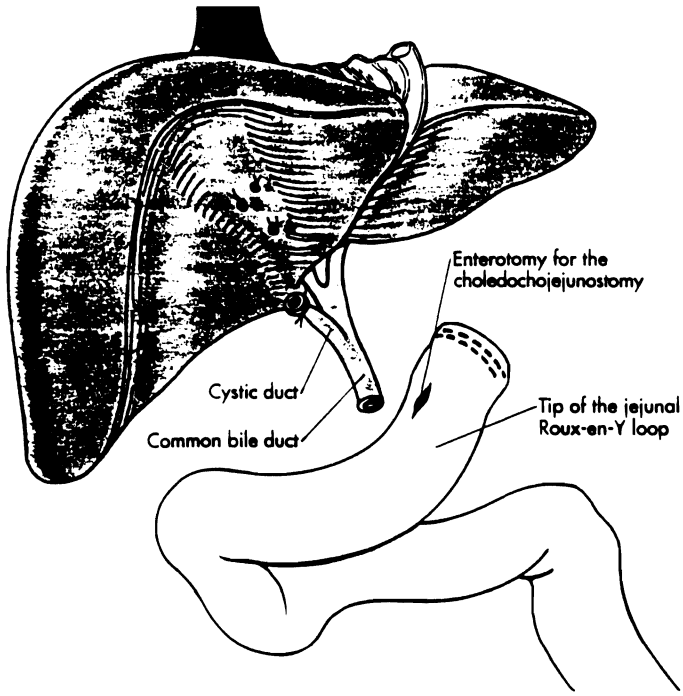

Figure 7.61

antimesenteric border of the Roux-en-Y, which will be anastomosed to the donor's bile duct.

The biliary anastomosis is then performed using either running or interrupted sutures just as for the choledochocholedochostomy (Fig. 7.62). A small stent is made out of 8 or 10 French Silastic® tubing with additional side holes and placed across the anastomosis. The stent is kept in place by a single 5-0 chromic suture tied loosely to allow it some movement during the performance of the anterior anastomosis. Testing of the anastomosis by air injection and chol-

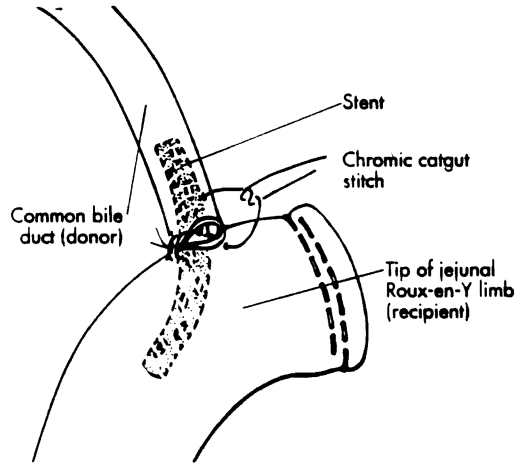

Figure 7.62

Figure 7.63

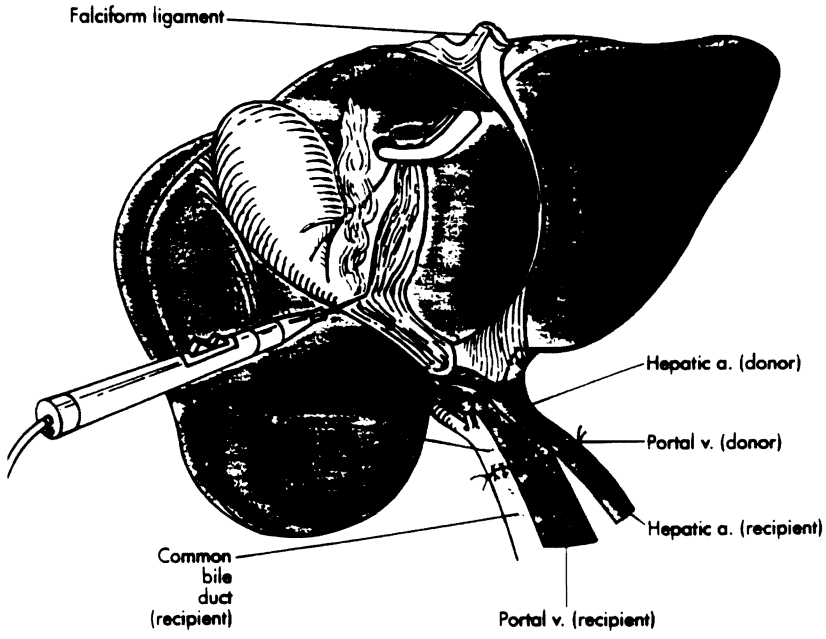

Figure 7.64

angiogram can be done using a cholangiography catheter placed inside the cystic duct (Fig. 7.63) if the latter joins the hepatic duct above the level of the anastomosis.

The complications of this reconstructive method are as follows:

1. Bile leaks, which are usually anterior. Revision of the anastomosis is necessary, although in the presence of extensive contamination temporary external drainage may be the only viable solution.
2. Strictures. If they occur at the anastomosis, strictures can be readily managed with percutaneous balloon dilation.
3. Retention of the stent can cause biliary obstruction. This is treated by percutaneously pushing the stent into the bowel or by extracting it operatively.
4. Ascending cholangitis, although rare with a defunctionalized limb, can occur. It will require antibiotic treatment. Repeated recurrences may require a revision of the Roux-en-Y loop.
5. A "blind loop syndrome" may sometimes be diagnosed posttransplantation. Long-term oral administration of tetracyclines is curative.

CONCLUSION OF THE OPERATION

At the end of the biliary anastomosis, the gallbladder is rapidly removed with the electrocautery, proceeding from the fundus toward the neck (Fig. 7.64). The cystic artery and duct are ligated with silk. The hemostasis is checked one more time; then closed suction drains are placed around and behind the liver (Fig. 7.65). The abdomen is closed in

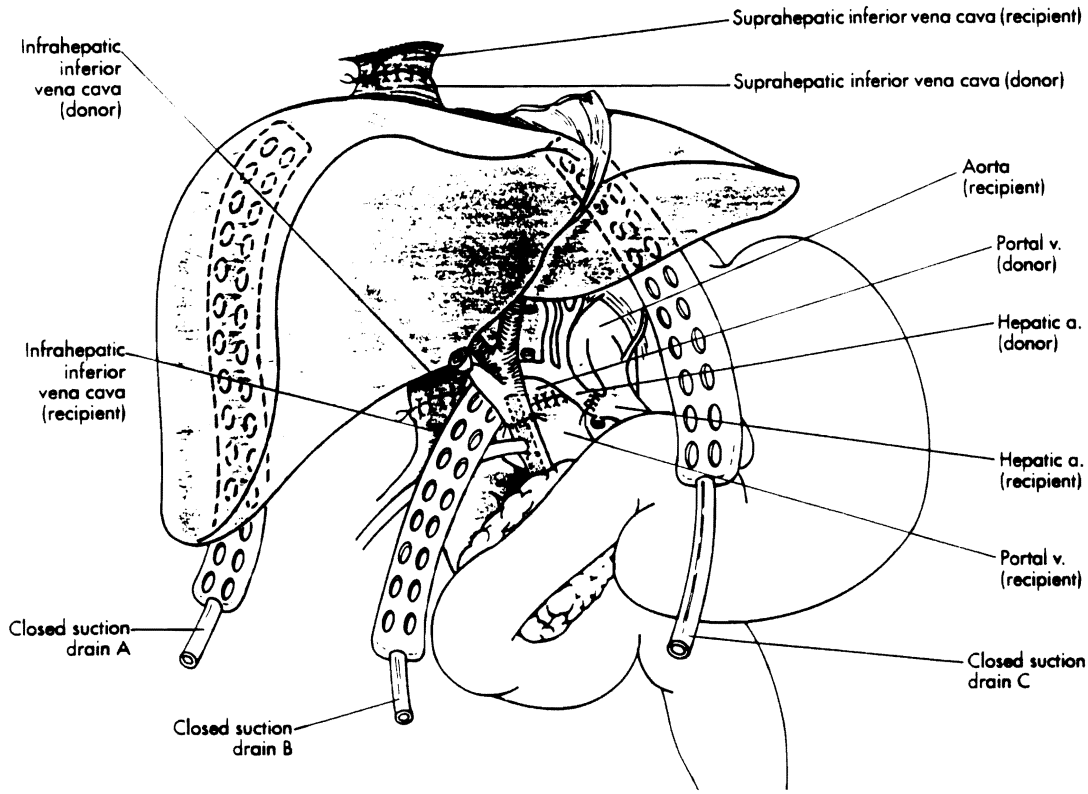

Figure 7.65

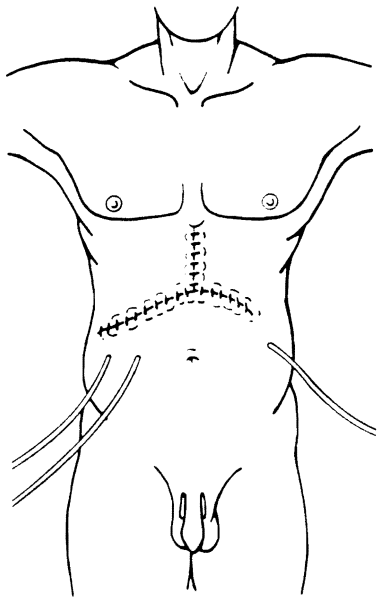

Figure 7.66

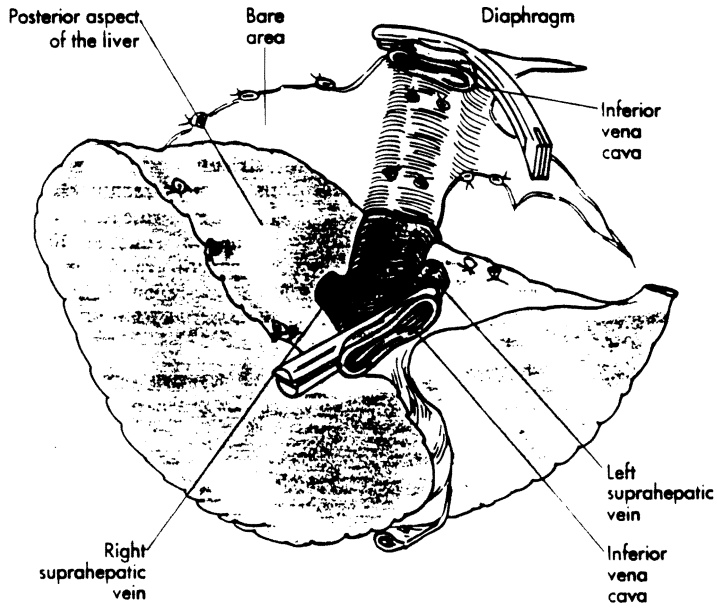

Figure 7.67

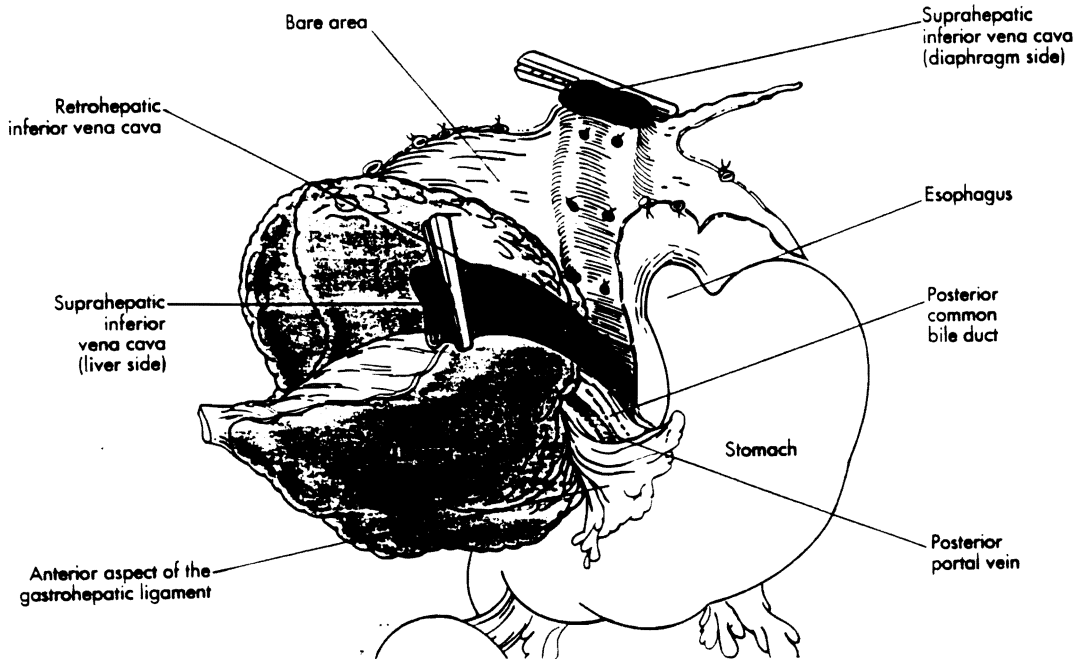

Figure 7.68

layers and the skin margins are approximated with staples, as demonstrated in Figure 7.66.

Modifications of the Basic Procedure

Various modifications of the basic technique have to be used under certain circumstances. These techniques will be described in the same order: hepatectomy, venous anastomoses, arterial anastomoses, and biliary anastomosis.

MODIFIED HEPATECTOMY

The hepatectomy can be extremely difficult in the presence of adhesions from previous surgery. Sometimes the hilum simply cannot be approached anteriorly, so the upper vena cava must be defined first, clamped on the two sides and divided, with the liver then being mobilized posteriorly (Fig. 7.67). Because this mobilization proceeds from cephalad to caudad, the hilum can be approached from the posterior aspect, which is relatively free of adhesions (Fig. 7.68).

Another situation is that of extremely tenacious adhesions present around the suprahepatic vena cava. In this instance, the infrahepatic vena cava can be divided between clamps and the dissection done posteriorly, proceeding from a caudad to a cephalad direction (Fig. 7.69).

In the presence of scar tissue around the infrahepatic cava, or when a patent end-to-side portocaval or mesocaval shunt is present, the liver can be completely dissected off the retrohepatic vena cava. All the secondary hepatic veins are ligated

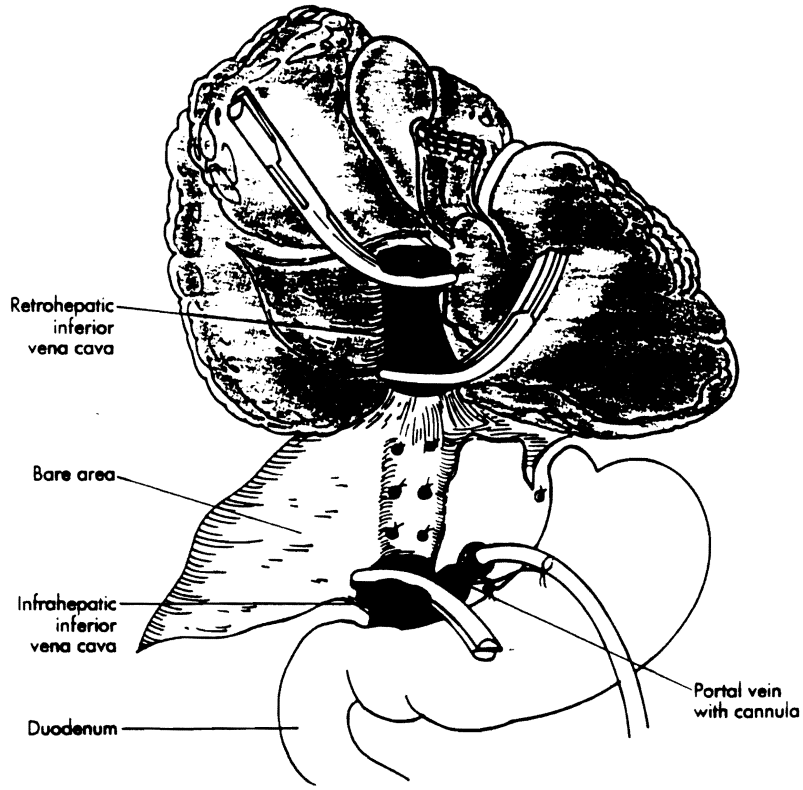

Figure 7.69

and then a clamp is placed across the main suprahepatic veins—the opening of which will be interconnected in order to fashion a common funnel (Fig. 7.70). The vena cava is thus never interrupted. The openings of the suprahepatic veins are then interconnected, so that the donor liver can be anastomosed to this common funnel in a piggyback fashion. The donor infrahepatic cava can be simply ligated.

MODIFIED VENOUS ANASTOMOSIS

When the portal vein is thrombosed, extremely friable, or considerably smaller in size than the donor's vessel, the dissection in the recipient must proceed until the confluence of the splenic and superior mesenteric veins is visible, with enough room to spare for placement of a vascular clamp (the so-called "classic approach"). Depending on the specific situ-

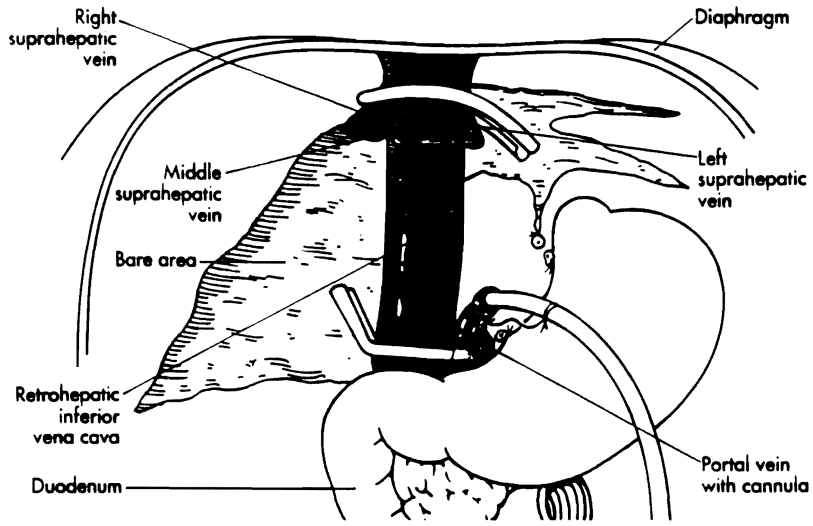

Figure 7.70

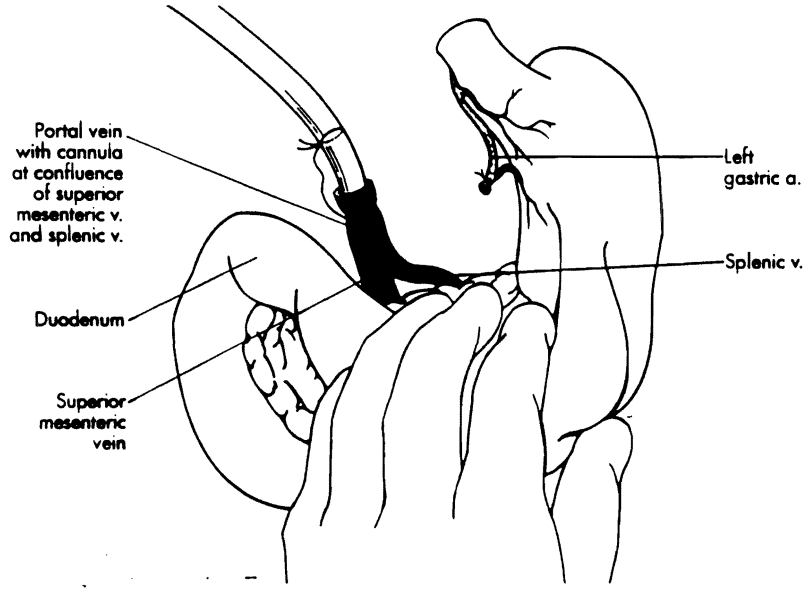

Figure 7.71

ation, the superior mesenteric vein may or may not be cannulated for bypass (Fig. 7.71). Even in cases of thrombosis of the main trunk, the portal vein is usually patent at this level. The venous anastomosis can then be done directly if the donor vein is long enough; if not, a free interposition graft (from iliac vein harvested from the donor) is necessary to bridge the gap[39] (Fig. 7.72). The recipient portal vein–graft anastomosis is done during the preliminary dissection phase; the vessel is then flushed with heparinized solution and clamped distally. The graft–donor portal vein can then be performed at the appropriate time, before unclamping. Occasionally, the only patent vessel is the superior mesenteric vein, in which case a free graft will have to be either tunneled under the pancreas (after infrahepatic anastomosis) or anteriorly over the duodenum. Although they may seem rather straightforward, these situations are exceptionally complex and difficult because of the extensive dissection required in the presence of unusually high portal hypertension and large collaterals. In some instances, we have been forced to divide the pancreas transversely to have sufficient exposure and control of the superior mesenteric vein.

More recently, a much easier way of bypassing the thrombosed portal vein has been devised.[40] The superior mesenteric vein is identified under the transverse mesocolon (just to the right of the superior mesenteric artery, which can be palpated with ease) and freed from the last branch confluence to the inferior border of the pancreatic neck. A tunnel can then be made bluntly in the avascular plane found between the anterior surface of the pancreas and the posterior wall of the pylorus. A free iliac vein graft is then anastomosed in an end-to-side fashion to the superior mesenteric vein. The graft is threaded through the tunnel and anasto-

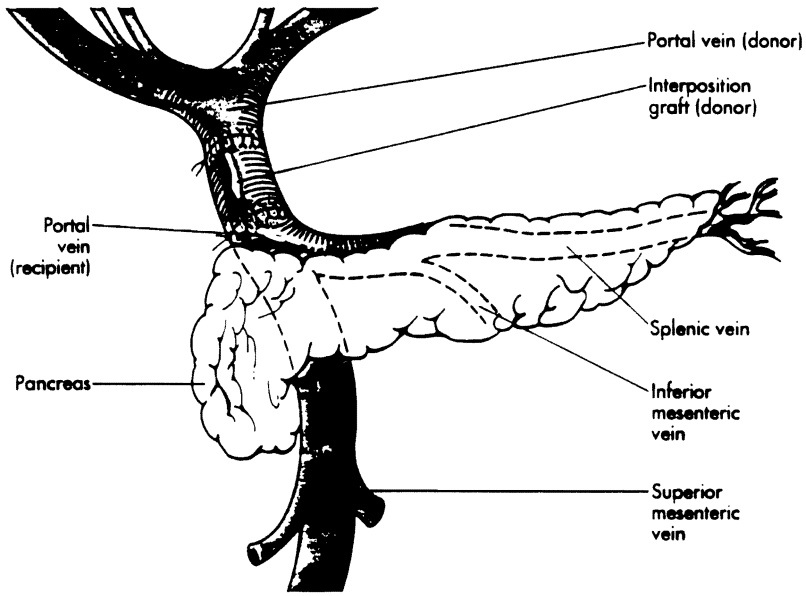

Figure 7.72

mosed end-to-end to the donor portal vein (Fig. 7.73). This method is very simple and rapid, and presents a low degree of technical risk. In fact, this approach has virtually eliminated portal vein thrombosis as a contraindication to transplantation, be it absolute or relative. Naturally, with either method the portal component of the venovenous bypass is omitted, and only a femoroaxillary bypass is used.

MODIFIED ARTERIAL ANASTOMOSIS

The previously described technique applies in the straightforward cases. However, there is enormous potential variability with regard to the hepatic artery, and the surgeon should be aware of the need to modify the standard approach.

In general, is it preferable to use Carrel or branch patches for arterial anastomoses; these will allow wide openings, without the danger of stenosis and thrombosis. On the donor side, the aortic Carrel patch, the celiac axis, or the splenic/common hepatic bifurcation are the most frequently selected sites. When a bifurcation is used, the two branches are severed a few millimeters downstream and the openings are then interconnected by cutting the septum in between. The branch patch thus obtained can be trimmed to the appropriate size and shape. On the recipient side, the same technique is used for the bifurcation of the proper hepatic artery into the right and left hepatic branches, the bifurcation of the common hepatic and gastroduodenal arteries, or the bifurcation of the celiac axis and splenic artery. In the latter case, the splenic artery can be completely divided between ties or the section can pass tangentially over the celiac and splenic openings, the resulting oblique opening having a large diameter. In general, a right branch originating from the superior mesenteric artery is not used for rearterialization of the liver unless it is the dominant vessel.

When for whatever reason the inflow is unsatisfactory, an interposition graft can be used.[41] This can be a small straight segment placed between the recipient celiac axis just distal

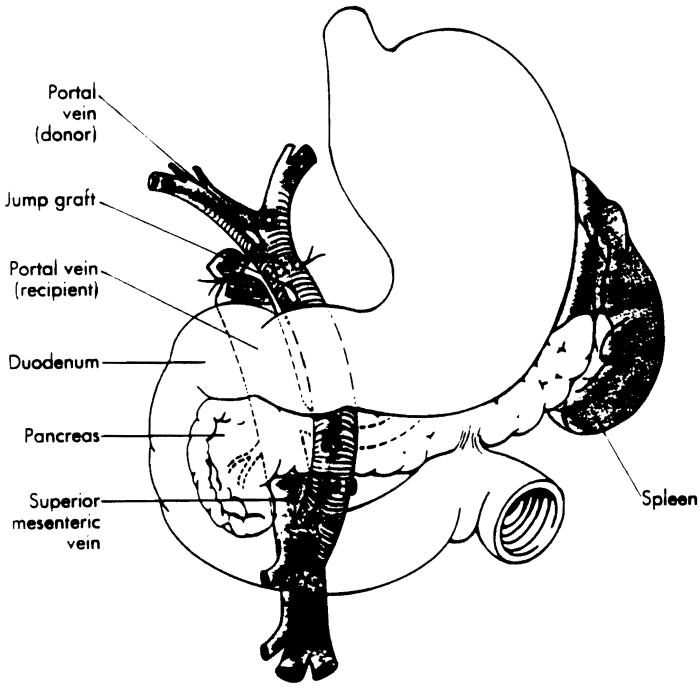

Figure 7.73

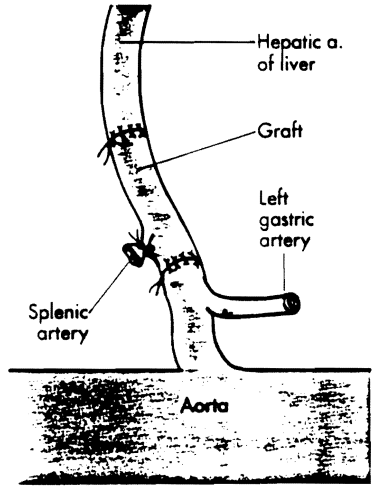

Figure 7.74

to the takeoff of the left gastric artery and the common hepatic artery of the donor, in cases when the two vessels cannot be approximated directly without undue tension (Fig. 7.74), or it may be a long segment placed between the recipient's infrarenal aorta and the donor's vessel. In this latter case, the graft is tunneled under the pancreas and the root of the mesentery to reach the hepatic hilum. The formation of the tunnel can be seen from an anterior view (Fig. 7.75A) and from a left sagittal view (Fig. 7.75B). Several routes have been employed, either to the right or left of the superior

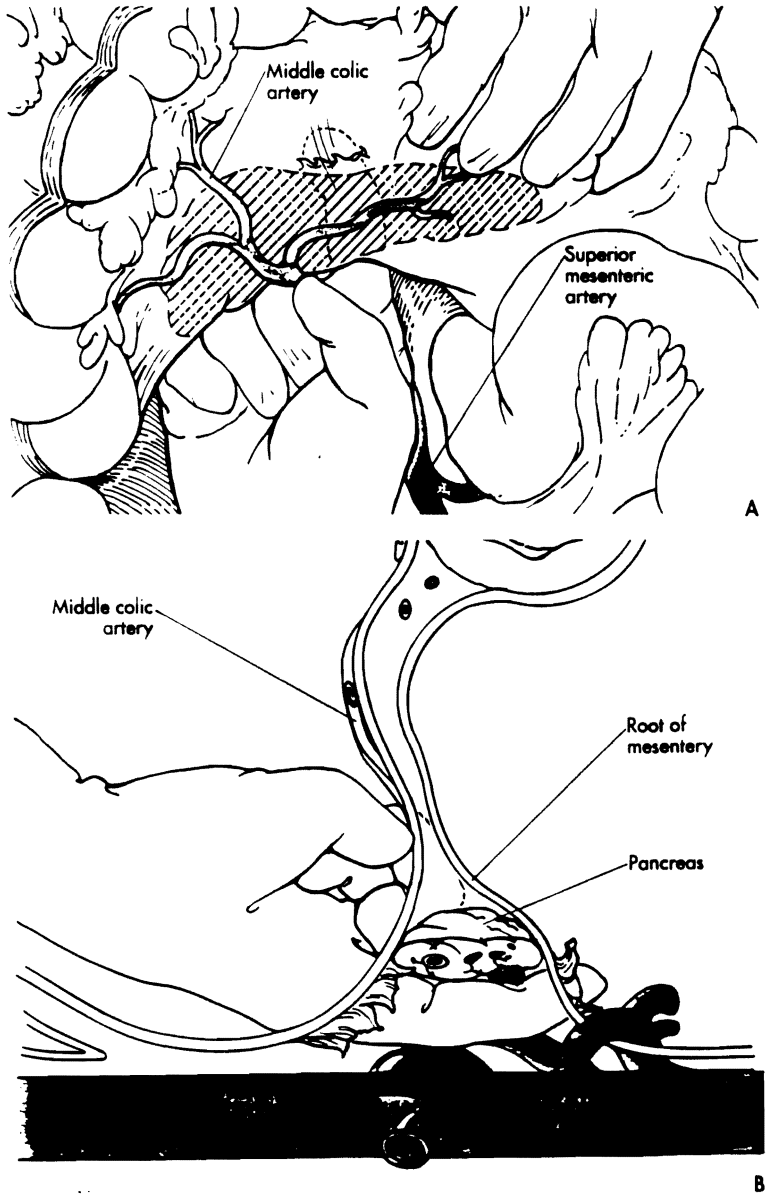

Figure 7.75

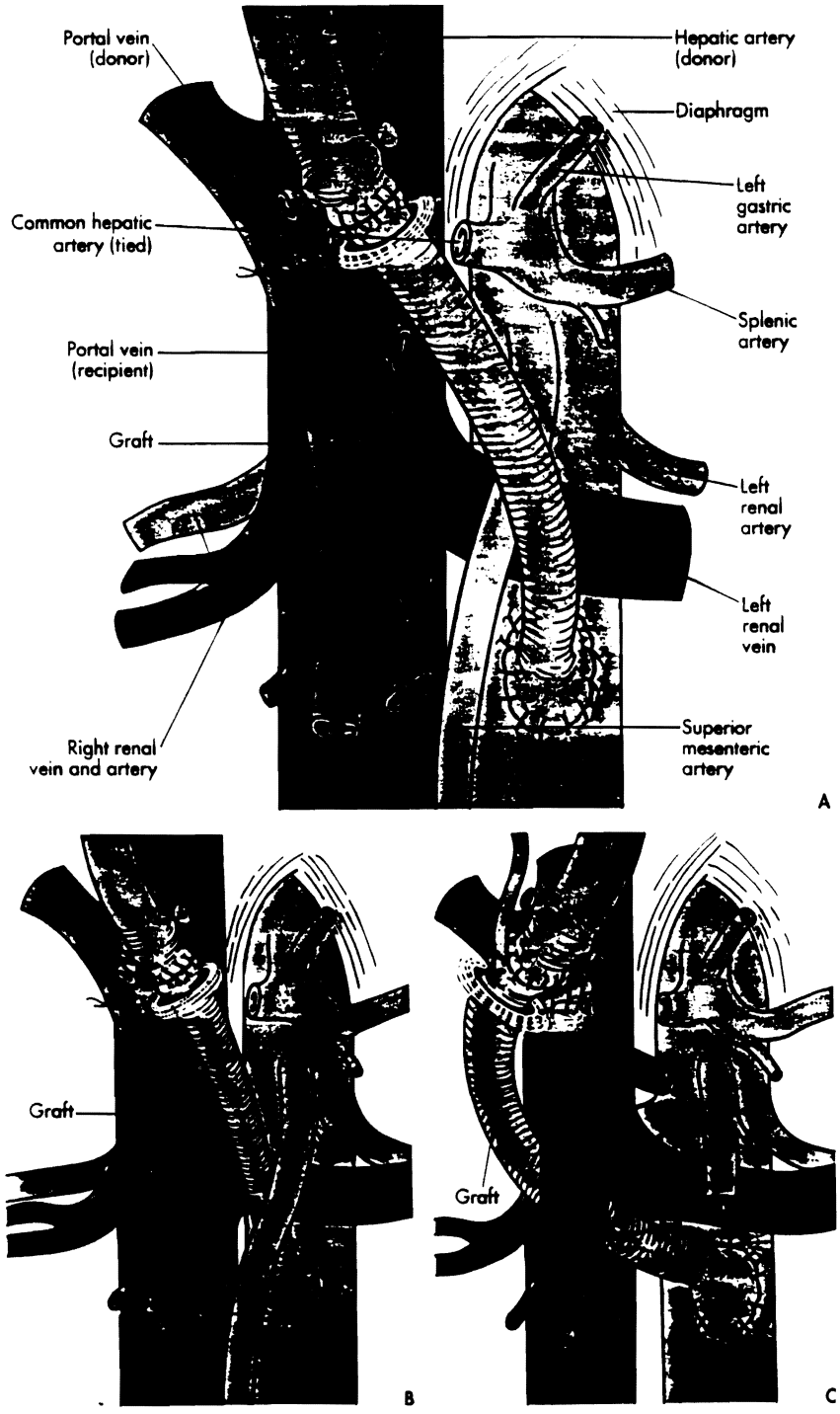
Portal vein (donor)
Hepatic artery (donor)
Diaphragm
Left gastric artery
Common hepatic artery (tied)
Splenic artery
Portal vein (recipient)
Graft
Left renal artery
Left renal vein
Right renal vein and artery
Superior mesenteric artery
A
Graft
B
Graft
C

Figure 7.76

mesenteric artery. Figure 7.76 shows the long route (A), the short route (B), and the very long route (C). The short route, going in a straight line to the hilum, is riskier because it may injure the more numerous collaterals behind the head of the pancreas. The route involving the least risk probably is to the right of the superior mesenteric artery, passing on top of the vena cava. However, this route may prove to be too long for the available graft, and positioning the donor artery without kinking can become more difficult because the artery is to the right of the portal vein. The preferred route is to make a tunnel anterior to the pancreas and behind the stomach, passing through an avascular and consequently danger-free area[42] (Fig. 7.77).

Another technique is the direct anastomosis of the donor aortic Carrel patch to the recipient supraceliac aorta (Fig. 7.78). The aorta is dissected during the anhepatic phase and then a Satinsky clamp is used for the anastomosis. The exposure for this type of anastomosis is suboptimal, but it may be the only viable alternative in the case of a calcified infrarenal aorta. Longer grafts have been used occasionally, but without long-term success.

The grafts used are iliac arteries harvested from the donor. If the specific donor could not provide adequate grafts (either because of the presence of lower polar renal arteries with iliac takeoff or because of catheter thrombosis), arterial grafts of the same blood type but from a different donor can be employed. Synthetic grafts are avoided, given the very high risk of infection in immunosuppressed patients.

MODIFIED BILIARY ANASTOMOSIS

The so-called Waddel-Calne gallbladder conduit[43] also can be used. The gallbladder is mobilized, but the cystic artery and duct are left untouched. The neck of the gallbladder is anastomosed to the donor common bile duct, then the fundus of

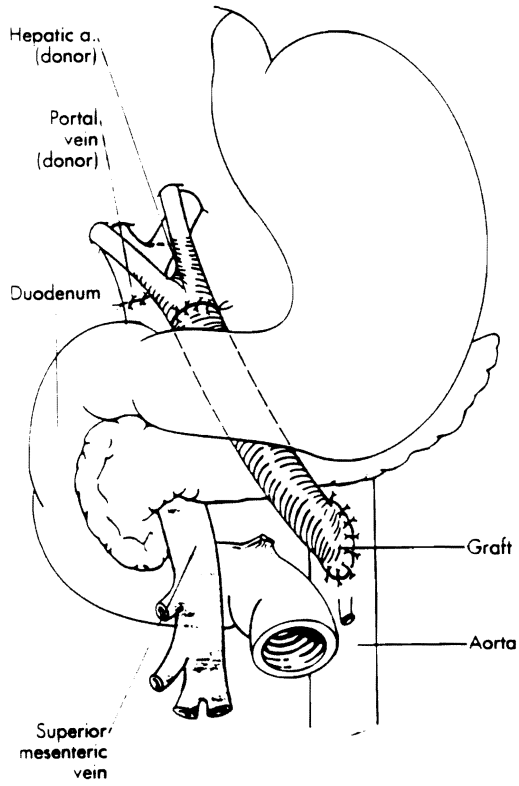

Figure 7.77

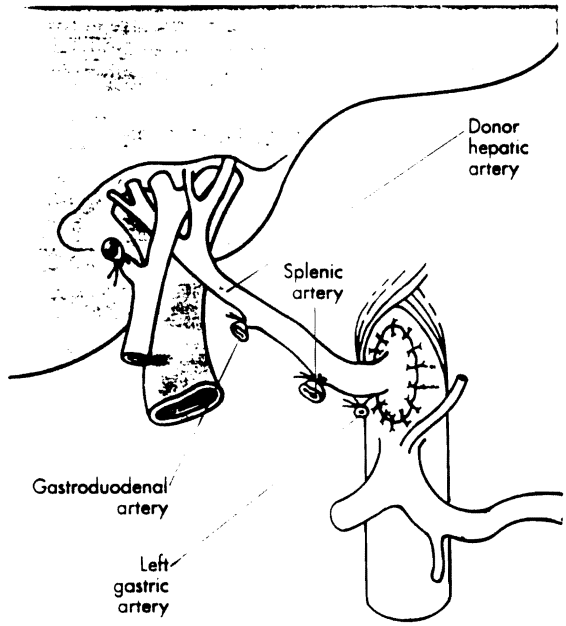

Figure 7.78

the gallbladder can be anastomosed to the donor's common bile duct or intestine (Fig. 7.79). This reconstruction permits a larger stoma between the donor and the recipient, but it involves two anastomoses and a large saccular structure in the middle of the biliary tract reconstruction. Although the favorite of the Cambridge group, this method has been rarely used by us.

LIVER TRANSPLANTATION IN THE SMALL PEDIATRIC PATIENT

Liver transplantation in the relatively large pediatric patient (35 lbs or more) is essentially the same from the technical point of view. Naturally, in dealing with smaller and more delicate structures, maximal care must be exercised during the operation. Bypass can be used, usually with a pediatric-size pump. Blood loss must be kept to a minimum, given the small total blood volume of the child. A choledochojejunostomy is almost always used in the biliary reconstruction, because a good percentage of pediatric patients are transplanted for biliary atresia and because the size of the bile duct is too small for a safe duct-to-duct anastomosis.

On the other hand, the very small pediatric patient presents some special problems.[44,45] Venovenous bypass cannot be used, because the extremely low flow would predispose to almost certain formation of emboli. Fortunately, such patients tend to tolerate cross clamping of the venous flow quite well. There are frequently extensive adhesions from multiple previous portoenterostomies as well as external stomas. The baby is often malnourished and infected from cholangitis. The arterial anastomosis is a major challenge because of its small diameter. Creative use of grafts (either iliac, as previously described, or carotid and aortic conduits —Fig. 7.80) must be employed. Because a liver of appropriate size cannot always be found, a larger liver must sometimes be trimmed down by means of a partial hepatectomy to be able to fit the organ in the small abdominal cavity.[46] (Figure 7.81 shows a left lateral segment being used for implantation.) The use of coagulation products during the operation is avoided, because it would predispose to arterial thrombosis. Thus, the hepatectomy must be done almost bloodlessly to avoid subsequent diffuse bleeding after reper-

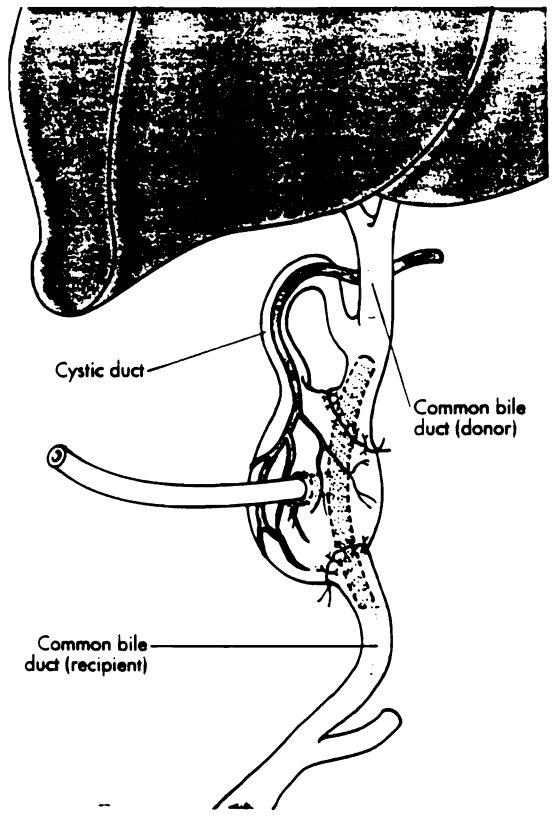

Figure 7.79

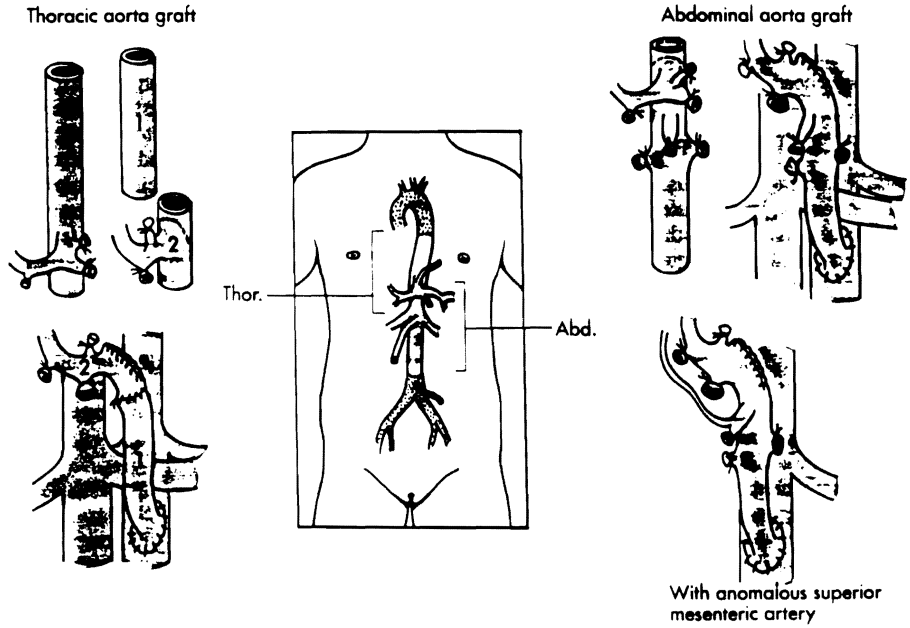

Figure 7.80

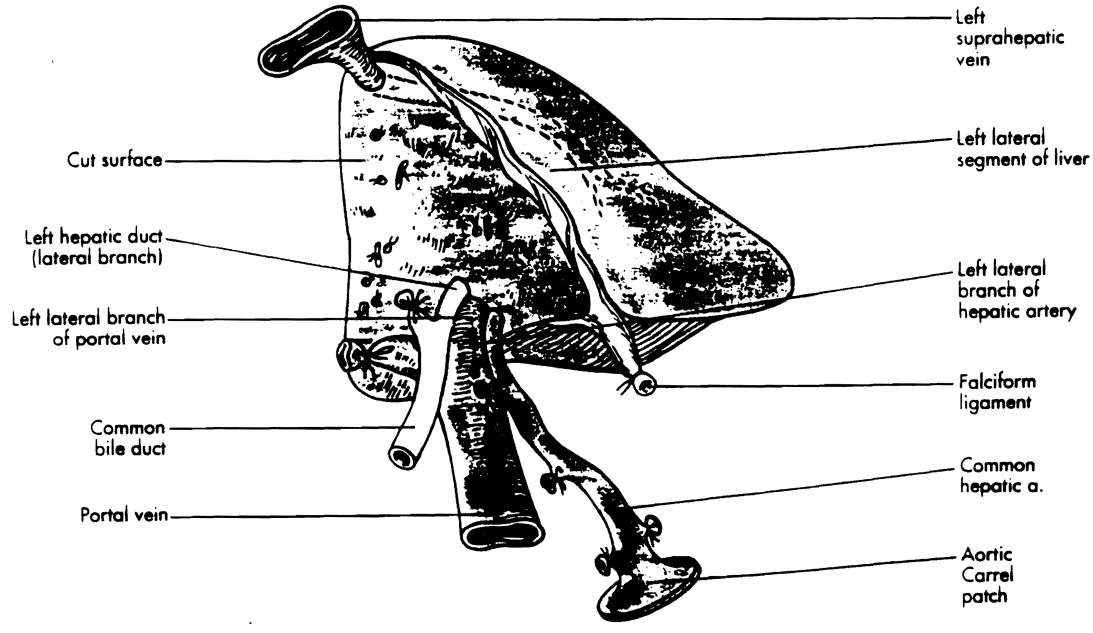

Figure 7.81

fusion. Postoperatively, the patients receive low molecular weight dextran and low doses of heparin or aspirin in an effort to avoid thrombosis. This has been particularly effective in our experience.[47]

POSTOPERATIVE MANAGEMENT

Early Period

After surgery, the patient is transferred to the intensive care unit, where he or she will spend the next 24 to 72 hours (for uncomplicated cases). Depending on the preoperative condition, the magnitude and duration of the procedure, blood loss, and other factors, the patient will need mechanical respiratory support for a variable length of time, but rarely less than 18 to 24 hours. As might be expected, the monitoring of these patients is intense and complex (Fig. 7.82).

Sedatives and narcotics are avoided as much as possible so as not to cloud the sensorium. Interestingly, the overwhelming majority of orthotopic liver transplantation patients do not experience significant postoperative pain.

Because of intraoperative fluid overloading and cyclosporine administration, most patients tend to become hypertensive. Aggressive and early treatment is mandatory, because the still-abnormal coagulation predisposes to intracerebral bleeding, which is frequently lethal. The diuresis must be maintained at adequate levels. Diuretics and intravenous colloids (crystalloids are usually lost in the "third space" in liver patients) must be used generously, alone or in combination.

The pulmonary toilet is extremely important, especially after long, difficult transplants. Chest physiotherapy and endotracheal suctioning must be employed aggressively.

Broad spectrum antibiotics (usually third generation cephalosporines) are administered for 2 to 5 days. "Stress" ulcers are prevented by administration of antacids as often as necessary to keep the gastric pH higher than 5. Sucralfate is also given routinely. In addition, nystatin (Mycostatin) is administered orally (and in females also vaginally) to prevent secondary fungal infections.

The basic immunosuppression is listed in Figure 7.83.

If rejection occurs, one or two additional boluses of methylprednisolone (1 g IV) are administered. If a partial response is obtained, a "recycle" (repetition of the primary steroid tapering scale) is given. Repeated episodes of acute rejection or steroid-resistant rejection are treated with the monoclonal anti-T-cell antibody preparation (OKT3) (Orthoclone). Mild recurrent rejection or higher than anticipated cyclosporine toxicity can be treated with the addition of azathioprine (Imuran), 0.5 to 1.5 mg/kg/day in a single dose, with or without concomitant reduction of the cyclosporine dose. If necessary, OKT3 can be repeated if no antimurine antibodies can be detected in the patient's serum.

FK 506

FK 506 is a new immunosuppressive agent that has been extensively studied at the University of Pittsburgh since 1987. It has demonstrated enormous potential in experimental and clinical liver, heart, and kidney transplantation.[48-52] The mechanisms of action of this agent are not yet entirely known, but appear to involve interleukin 2.[53,54] While not entirely without side effects,[55,56] FK 506 seems to have less toxicity than cyclosporine;[57,58] it also is about 100 times more potent. At the present time, a randomized clinical trial is being conducted at the University of Pittsburgh to compare FK 506 with cyclosporine, and two multicenter trials are already underway in this country and in Europe. From the data accumulated so far, it appears that FK 506 will replace cyclosporine as the cornerstone of immunosuppressive therapy.

POSTOPERATIVE MONITORING

Tests and Parameters	Frequency
ECG, systemic arterial tracing, central venous tracing, pulmonary artery and/or wedge tracing, pulse oximeter	Continuous
Urinary output	Every 2 hours
Mental status	Frequently
Complete blood count, serum electrolytes, coagulation, blood sugar, Mg^{++}, Ca^{++}, $H_2PO_4^-$, blood urea nitrogen, Cr	Every 6 hours for the first 24 hours, then every afternoon; more frequently if necessary
Liver function tests (bilirubin—total/direct—SGOT, SGPT, alkaline phosphatase, gamma-glutamyl transpeptidase), cyclosporine level, chest x-ray	Every morning; more often if necessary

Figure 7.82

Late In-Hospital Period

When stable, the patient is moved to the regular ward. Rapid ambulation follows: oral intake is started and rapidly advanced. No isolation precautions are undertaken unless specific circumstances dictate it. In fact, as soon as the patients are sufficiently active, they are even allowed to leave the hospital for a few hours a day. The complete blood count, serum electrolytes, renal function, blood sugar, coagulation, liver function tests, and cyclosporine level are measured daily. Total serum protein, albumin, Ca^{++}, Mg^{++}, $H_2PO_4^-$, amylase, and uric acid are measured twice weekly. The immunosuppression is regulated according to the clinical picture and cyclosporine blood levels. If a T-tube has been placed, a T-tube cholangiogram is performed as soon as the bilirubin is 2 mg/dl or less (usually after 7 to 10 days) and, if the study results are normal, the tube is clamped (Fig. 7.84). This allows improved absorption of the oral cyclosporine; the intravenous drug usually can be discontinued at this time. When the patient's condition is stable and the immunosuppressive regimen regulated (3 to 4 weeks in the uncomplicated case), the patient can be discharged and be followed in the outpatient department.

Low-dose trimethoprim/sulfamethoxazole and high-dose acyclovir are given for at least 1 year as prophylaxis for Pneumocystis carinii, herpesvirus, and cytomegalovirus infections.

Outpatient Period

Initially, the patient is seen in the outpatient department twice a week. In addition to clinical evaluation, serum electrolytes, blood sugar, blood urea nitrogen, creatinine, prothrombin and partial thromboplastin times, complete blood count, liver function tests, and uric acid are measured. The cyclosporine level is checked as well. The immunosuppression is fine-tuned during this period and, frequently, the steroids can already be lowered to 15 mg/day. If stable after the first 2 to 3 weeks, the patient is seen in the outpatient department once a week for another 1 to 3 weeks and then discharged home, in the care of the family physician. The coordinator assigned to the case will keep in contact with the patient. Laboratory exams are continued weekly for 1 to 2 months, then at increasingly longer intervals. Eventually, the patient needs to be checked by the local physician only

BASIC IMMUNOSUPPRESSION

Agent	Dose and Frequency
Cyclosporine	6 mg/kg/day IV in two divided doses: as soon as the gastrointestinal transit is established, 20 mg/kg/day of oral cyclosporine is added in two divided doses. After overlapping for a few days, the IV cyclosporine is gradually tapered, while the absorption of the oral drug improves. The cyclosporine level will help guide and individualize the therapy
Steroids	1 g of IV methylprednisolone is given intraoperatively, immediately after reperfusion; a tapering regimen is then administered: 50 mg IV q.6h x 4, then 40 mg IV q.6h x 4, then 30 mg IV q.6h x 4, then 20 mg IV q.6h x 4, then 20 mg IV q.12h x 2, then 20 mg IV q.d. Prednisone is substituted for methylprednisolone once intestinal transit is reestablished

Figure 7.83

Figure 7.84

two to four times a year. The only other required visit to our outpatient department is at 1 year after transplantation, when an abdominal ultrasonographic exam is performed along with the routine laboratory tests and a thorough clinical checkup.

COMPLICATIONS

Primary Nonfunction of the Homograft Liver

This complication occurs in 6.9 to 10% of our cases,[60,61] and it is experienced immediately after transplantation. Primary nonfunction can result from an unstable donor, preexisting disease in the donor, inadequate or overly long preservation, an imperfect recipient operation, or a perioperative immunologic reaction. These factors can occur separately or in combination.

In a majority of the cases of primary liver nonfunction, the liver produces little or no bile after reperfusion; the preexisting coagulopathy worsens (or occurs *de novo*), and the lactate level fails to decrease or even increases. Occasionally, the liver function is good or fair during the first 24 hours or so, only to deteriorate rapidly after. Postoperatively, the patient is either comatose or extremely agitated, and the bile output is minimal (if a T-tube is present), with mucous, greenish bile. The urine output usually decreases, with a concomitant increase in the blood urea nitrogen and creatinine. The coagulation parameters are abnormal; the liver enzymes are very high, and the bilirubin increases rapidly. If the situation does not improve within 24 to 36 hours, the patient's only chance for survival lies with emergency retransplantation. Recently, repeated sessions of plasmapheresis have been used by us with notable success in buying time to allow the liver function to return to normal (unpublished material).

The morbidity and mortality of this complication are high.[62] Survival following retransplantation for primary nonfunction is only half of that seen in the general liver transplant population. Overall, it is the most lethal of all possible complications of liver transplantation. Attentive selection of the donor, careful management, perfect harvesting technique, optimal preservation, and uncomplicated recipient operation are each an essential factor in the struggle to minimize the incidence of primary nonfunction.

Rejection

The existence of hyperacute rejection in liver transplantation (even when the transplant is done across blood group lines) is a controversial subject, and the evidence supporting or refuting it is incomplete at best.[63-68] There is no good, reliable evidence for it, and the diagnosis is usually one of exclusion when there is no reason to believe that the graft is of poor quality—especially when two or three livers transplanted in rapid succession do not function. We call these patients informally "liver eaters" and believe that a humoral immunologic (or possibly nonimmunologic) mechanism can explain the livers' repeated failure to function.

On the other hand, acute cellular rejection occurs in at least 90% of the patients at one point or another during the postoperative course, usually 7 to 10 days after orthotopic liver transplantation. There is a mild to moderate elevation of the liver function test results (frequently the bilirubin and the "secretory" enzymes—alkaline phosphatase and gamma-glutamyl transpeptidase—are affected in a greater measure). If a T-tube is present, it will be noted that the bile is lighter in color and consistency. Although the diagnosis can be made on clinical grounds alone, a liver biopsy will give a definitive answer.[69] The differential diagnosis includes ischemic injury, hepatitis (A, B, or non-A/non-B, cytomegalovirus, herpes simplex, adenovirus), sepsis, biliary tract complications.[70] The treatment guidelines for liver rejection are listed in Figure 7.85.

Sepsis

Sepsis is common in transplant patients in general because of immunosuppression. It may be related to technical complications (biliary leak, arterial thrombosis, intestinal leaks), catheters (central venous, urinary), or overimmunosuppression (bacterial, viral—especially cytomegalovirus and herpes simplex virus—fungal, protozoal). The diagnosis is based on appropriate cultures, and treatment is directed against

the infectious agent(s) based on specific sensitivities. Early and aggressive diagnosis and treatment are mandatory, as the immune system is depressed. A host of noninvasive and invasive procedures can be used for diagnosis, including ultrasonography, computerized tomography, abdominal paracentesis, thoracentesis, gastrointestinal endoscopy, bronchoscopy with bronchoalveolar lavage, lumbar puncture, percutaneous drainage of collections, and exploratory laparotomy.

Technical Complications

ARTERIAL THROMBOSIS

Arterial thrombosis is a very serious complication in liver transplantation. This is easy to understand, considering that the new liver has no collateral circulation and that the hepatic arterial flow is the only blood supply to the donor biliary tree. Early thrombosis is almost invariably a disastrous event (see Fig. 7.86 for clinical descriptions and treatments).[71]

LIVER REJECTION TREATMENT

Type of Rejection	Therapy
Mild, mild-to-moderate	Steroid bolus (1 g methylprednisolone)
Moderate	Steroid bolus and recycle (tapering scale repetition)
Severe	OKT3 (includes 1 g hydrocortisone on the first day and 0.5 g hydrocortisone on the second day, prior to infusion)
Recurrent mild	Repetition of the steroid bolus with or without a recycle
Recurrent mild, severe, or steroid-resistant	OKT3
Persistent mild	Azathioprine, 0.5–1.5 mg/kg/day

Figure 7.85

ARTERIAL THROMBOSIS

Clinical Description	Treatment
Massive necrosis (rare, but extremely lethal*)	Urgent retransplantation
Biliary leak (due to necrosis and sloughing of anastomosis)	Drainage and semiurgent retransplantation
Central hepatic biloma (due to central necrosis of the biliary tree, without bile extravasation)	Percutaneous drainage and delayed retransplantation
Recurrent bacteremia, without necrosis	Long-term antibiotic treatment; late retransplantation?

*See Fig. 7.87.

Figure 7.86

Figure 7.87 shows gangrene of the liver caused by Clostridium species after thrombosis of the hepatic artery. Late thrombosis caused by either anastomotic stricture or intimal hyperplasia may be more forgiving, due to the development of collateral circulation via adhesions. Figure 7.88 shows a pediatric patient with hepatic artery thrombosis and re-arterialization of the liver by collaterals from the superior mesenteric artery.

The diagnosis must be entertained each time there is a sudden deterioration of liver function or a significant and otherwise unexplained elevation of liver function test results. Sonography with Doppler tracing usually is diagnostic: if the arterial pulse is present, thrombosis can be ruled out. On the other hand, if the pulse is absent, angiographic confirmation is mandatory before undertaking retransplantation.[72] Because none of the frames of the liver ultrasonogram with

Figure 7.87

Figure 7.88

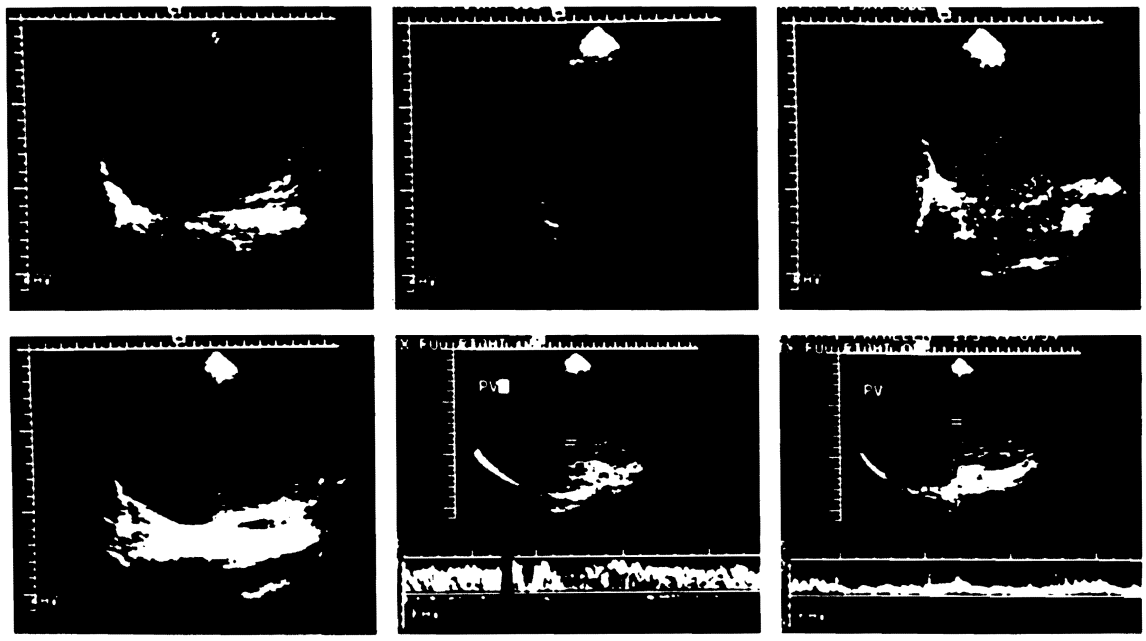

Figure 7.89

Doppler study shown in Figure 7.89 reveals the characteristic arterial tracing, the study is consistent with thrombosis of the hepatic artery. A confirmatory angiogram (Fig. 7.90) demonstrates the absence of the hepatic artery. While awaiting retransplantation, antibiotics (intravenous or oral) must be administered.

BILIARY LEAK

Bile extravasation can be seen independently, apart from its association with arterial thrombosis. In duct-to-duct anastomoses, the extravasation can occur at the anastomosis or, more often, at the T-tube exit site (Figs. 7.57, 7.58).[73] It is heralded by fever, elevation of liver function test results, and bile-stained drainage. The diagnosis is easily made with a T-tube cholangiogram. With the exception of very small, asymptomatic, incidental leaks from the exit site, which can be managed nonsurgically, all other leaks necessitate urgent exploratory laparotomy. Depending on the type and site of extravasation, as well as the degree of contamination, the problem can be corrected with simple suturing of the defect, revision of the choledochocholedochostomy, conversion to a Roux-en-Y choledochojejunostomy, or temporary external drainage.

In cases of choledochojejunostomy, the leak originates from the anastomosis and almost invariably occurs on the anterior wall. The symptoms are the same as previously described. The diagnosis is made with percutaneous transhepatic cholangiography.[74] Although the leak rarely can be controlled by placing a few simple sutures, repair usually requires complete revision of the anastomosis or temporary external drainage.

HOLLOW VISCUS PERFORATION

Occasionally, leaks from the jejunojejunostomy are encountered in liver transplant patients. Also, on occasion, perforated peptic ulcers have been described. Treatment is directed toward correction of the leak and possible underlying cause. In this respect, management does not differ from that used in normal general surgery patients. The only difference consists in the need for aggressive use of broad-spectrum antibiotics (including amphotericin B, because candidiasis always occurs with intestinal leaks) and possible temporary reduction of the immunosuppression.

BLEEDING

Bleeding can occur early, secondary to inadequate hemostasis.[75] Reoperation is usually required. Peptic or stress ulcers also can be the source of massive bleeding, as can be bleeding from the jejunojejunostomy. Ulcer disease is controlled with nonsurgical measures, unless the situation is desperate. Bleeding from the jejunojejunostomy can be watched, but if more than 5 U of blood are needed within 48 to 72 hours, reoperation is indicated.

Other sources for bleeding are cytomegalovirus involvement of the gastrointestinal tract and ruptured false aneurysms of the various vascular anastomoses. When an aortograft anastomosis is involved, the patient usually dies of exsanguination before operative intervention can be undertaken.

Nontechnical Complications

CYCLOSPORINE TOXICITY

NEPHROTOXICITY. The nephrotoxicity of cyclosporine was established soon after the introduction of the drug in humans.[76] Although generally dose-dependent (or rather blood level-dependent), this toxicity may manifest itself at lower than predicted dosages in certain individuals. Acute toxicity is reversible after cyclosporine dosage reduction, but chronic toxicity causes permanent damage. Interstitial fibrosis is the most prominent of the side effects.[77–79] In general, the smallest effective dose should be given, to avoid renal

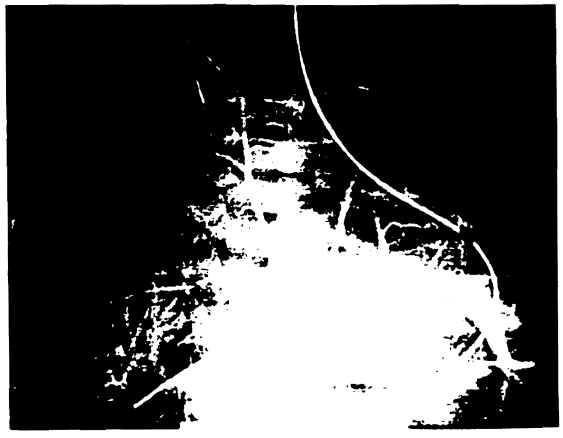

Figure 7.90

toxicity. In some patients, azathioprine must be added to the immunosuppressive regimen to allow safe reduction of the cyclosporine dosage.

Severe, acute nephrotoxicity can be seen in susceptible patients as a result of hepatorenal syndrome, shock, sepsis, primary nonfunction, and concomitant administration of other nephrotoxic drugs. The intravenous form of cyclosporine is the most damaging. Dosage reduction, or even temporary suspension is necessary to counteract the toxicity. High dosages of azathioprine or OKT3 can be given in the interim to prevent rejection. Hemodialysis also may be necessary until renal function returns to acceptable levels.

HEPATOTOXICITY. The liver toxicity of cyclosporine also was described early in the course of human trials.[80] Occurring much less frequently than nephrotoxicity, the hepatotoxicity can be quite severe, although it is usually relatively mild. It is diagnosed after ruling out other causes of liver enzyme elevation, as well as by monitoring for drug toxicity signs on the biopsy. A slight dosage reduction usually is sufficient to reverse the changes.

NEUROTOXICITY. This can affect either the central[81] or the peripheral nervous system,[82] and frequently both. Restlessness, slurred speech, seizures, paresthesias (especially perioral and lower extremity), change in taste, and dysphagia have all been described alone or in combination. The central nervous system toxicity at times can be so disabling (particularly in the elderly) as to require complete though temporary cessation of the drug. It can be restarted, in small oral doses, after resolution of the neurologic symptoms.

One of the most frequent aspects of neurotoxicity, observed both early and late during the postoperative course, is represented by tremors. These are rather fine, but extremely disabling at times, not allowing the patient to perform fine or moderately fine tasks such as writing or using a spoon for feeding. Tremors frequently are the first subjective sign of cyclosporine toxicity. A reduction in the drug dosage is normally sufficient to resolve the symptom.

HYPERTENSION. This affects more than 50% of the transplant patients who had never experienced it before.[83,84] The mechanism of hypertension in these patients remains largely unclear. It is dose-dependent to a large extent; a cyclosporine dosage reduction frequently is very helpful. The degree of hypertension can be very significant, and aggressive therapy is needed to control it. The angiotensin-converting enzyme inhibiting drugs captopril or enalapril, combined with a diuretic, are the most effective, although many other agents are used.

HYPERKALEMIA. As with hypertension, the mechanism is unclear.[85] Very severe hyperkalemia may occur in some patients. Potassium levels of 6.5 to 7 mEq/liter are not uncommon. A strict low-potassium diet is mandatory, along with high dosages of sodium-potassium-exchanging resin preparations. Hemodialysis must be used occasionally for rapid reduction of the potassium. A cyclosporine dosage reduction also is ultimately necessary for control of the hyperkalemia.

HIRSUTISM. This can be particularly bothersome in female patients. It is largely dose-dependent[86] and usually less of a problem as time passes and the cyclosporine dosage is reduced. When severe, it requires an early dosage reduction. Otherwise, a depilatory cream is used until the condition becomes less acute.

GINGIVAL HYPERPLASIA. Similar to that observed in patients taking phenytoin,[87] it is generally dose-dependent and can be controlled by reducing the cyclosporine dosage. Occasionally, susceptible patients will exhibit a high degree of gingival hyperplasia on minimal dosages. Careful dental hygiene is mandatory in all patients taking cyclosporine, to prevent some of the problems related to this complication.

RENAL FAILURE

As mentioned earlier, this complication may be the result of cyclosporine toxicity. On the other hand, it is frequently seen as a result of shock or, in general, large blood losses during orthotopic liver transplantation, as a worsening of preexisting hepatorenal syndrome, or as a result of the use of nephrotoxic drugs, particularly antibiotics. It is also seen in primary nonfunction, where it resembles the hepatorenal syndrome of fulminant hepatic failure.[88] Dialysis must be employed to control these patients. Although usually a temporary phenomenon, renal failure can be permanent at times, requiring kidney transplantation at a later date.

DIABETES MELLITUS

This occurs as a worsening of a preexisting condition or a *de novo* result of steroid administration.[89-91] Diabetes mellitus is noted early in a great number of patients during the period of high-dose steroid administration, and it usually corrects itself when the dosages are decreased. Occasionally, a patient who had not been diabetic before orthotopic liver transplantation will require permanent treatment after the operation. Also, patients who previously had been treated with only oral hypoglycemic agents will require insulin after transplantation. A reduction in the steroid dosage is usually helpful, at least in part, in controlling the hyperglycemia. Occasionally, we have also stopped the steroid therapy altogether, treating the patient with cyclosporine only.

CUSHING'S SYNDROME

A large percentage of patients will acquire some of the features of steroid-induced Cushing's syndrome. These symptoms tend to improve with time, as the steroid dosages are lowered, but occasionally they can be seen even with extremely small amounts of the drug.

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS

These lymphoma-like disorders are seen in 1.5 to 2% of liver transplant patients. They are related to the Epstein-Barr

virus, and occur as either new infections or reactivations of previous infection.[32] Posttransplant lymphoproliferative disorders present with fever and lymphadenopathy, deteriorating liver function, intestinal symptoms, or any combination thereof. A relatively high index of suspicion is necessary to make an early diagnosis. Because every one of these disorders is a disease of overimmunosuppression, patients at risk are those heavily treated for repeated episodes of rejection. Uric acid level, immunoglobulin electrophoresis, CT scan, and lymph node and/or liver biopsy are the usual means to establish the diagnosis. Histologically, the disorder can be mono- or polyclonal. The polyclonal type tends to have a more benign course.

Treatment consists in temporary reduction or suspension of immunosuppression and administration of acyclovir. The response to therapy usually can be seen within a few days. In the case of gastrointestinal involvement, there is an unusually high incidence of small bowel perforation during the early remission period, probably due to lysis of tumoral masses in the intestinal wall. Incidental small bowel posttransplant lymphoproliferative disorders can be resected. Immunosuppression can be reinstituted or increased again once the disorder is in remission.

OSTEODYSTROPHY

This may be due to preexisting disease (e.g., primary biliary cirrhosis[33]) and/or steroid administration. Pathologic fractures, particularly of the vertebrae, can be seen. High doses of calcium and vitamin D_3 can be administered, although their effectiveness is debatable.

OBESITY

This is due to increased caloric intake, secondary to steroid administration and general improvement in quality of life. Attentive diet control is frequently necessary to prevent the side effects of obesity.

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