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## Chapter 176

# Transplantation and Other Aspects of Surgery of the Liver

Thomas E. Starzl • Shunzaburo Iwatsuki •  
Byers W. Shaw • David H. Van Thiel

### Liver Transplantation

*Experimental Beginnings*  
*Clinical Trials of Orthotopic Transplantation*  
*Indications for Orthotopic Transplantation*  
*Tissue Matching*  
*The Donor Operation*  
*The Recipient Operation*  
*Postoperative Care*  
*Immunosuppression*  
*Rejection Under Immunosuppression*  
*Survival After Liver Replacement*  
*Causes of Mortality*  
*Steps to Reduce Mortality*  
*Option of Auxillary Liver Transplantation*  
*Potential Role of Liver Transplantation*

### Partial Hepatectomy

*Work-up of Localized Hepatic Lesions*  
*Kinds of Hepatic Resections*  
*Drainage and Other Care*  
*Indications for Hepatic Resection*  
*Results of Hepatic Resection*  
*Portal-Systemic Diversion*  
*Hepatotropic Physiology Before 1973*  
*Hormonal Nature of Hepatotrophic Substances*  
*Function of the Portoprival Liver*  
*Relevance of Animal Studies to Man*  
*Complete Portal Diversion for Metabolic Dysfunction*  
*Portal-Systemic Shunt for Complications of Portal Hypertension*

The decades between 1960 and 1980 witnessed a major change in attitudes about hepatic surgery. The era began with the realization by a small group of investigators that hepatic transplantation might become a realistic option for patients with otherwise untreatable liver diseases. A ripple effect of research directed toward this objective was a better understanding of the role of portal blood in maintaining hepatic homeostasis as well as a more complete appreciation of the physiologic consequences of portal-systemic diversion procedures. The increased knowledge and boldness engendered by this experience with the liver were factors in the standardization and extension of techniques of partial hepatectomy, which previously had too high a mortality for general use. Finally, the techniques of biliary tract reconstruction that were refined or developed as part of liver transplantation have made their way into more general use.

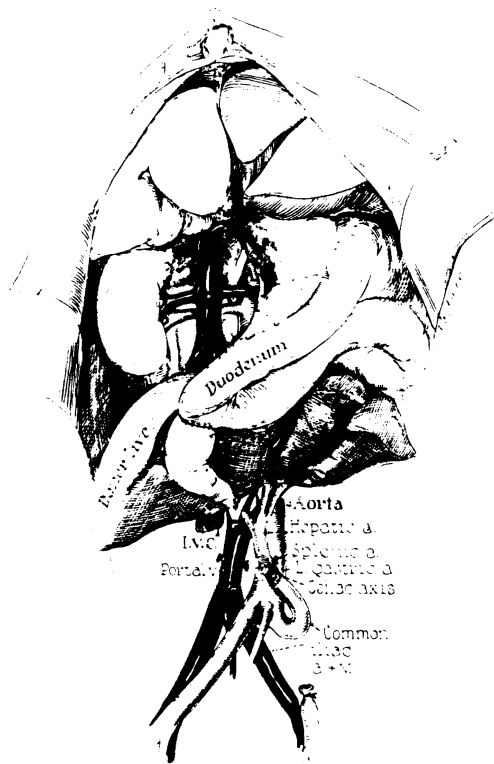
This chapter describes these advances under the headings of: (1) liver transplantation,

(2) partial hepatectomy, and (3) portal-systemic diversion. Techniques of biliary tract reconstruction that are applicable in a variety of non-transplant circumstances are covered under liver transplantation.

### Liver Transplantation

**Experimental Beginnings.** There are 2 general approaches to transplantation of the liver: (1) insertion of an extra liver (*auxiliary homotransplantation*) at an ectopic site, and (2) removal of the host liver and replacement with a homograft (*orthotopic homotransplantation*).

**Auxiliary Transplantation.** The first experiments with whole organ liver grafting were carried out with the auxiliary operation in dogs by Welch et al.<sup>1,2</sup> The operation, as originally described or slightly modified by later authors (Fig. 176-1), involved the transplantation of an extra canine liver in the right paravertebral gutter or pelvis of a non-related mongrel recipient. The hepatic arterial sup-



**Figure 176-1.** Auxiliary liver transplantation in dogs by a modification of Welch's original technique. Note that the reconstituted portal blood supply is from the distal inferior vena cava. Cholecystoduodenostomy is performed. (From Starzl TE et al. *Ann Surg* 1964; 160:411-39. Reproduced with permission.)

ply was derived from the aorta or iliac artery. Venous inflow was provided by anastomosing the distal iliac vein or inferior vena cava to the homograft portal vein. Outflow was into the proximal iliac vein or inferior vena cava.

Welch<sup>1</sup> and those who followed<sup>2-5</sup> proved that such livers produced bile for several days after transplantation but then ceased to function. On examination, the transplanted organs had histopathologic evidence of rejection. This was to be expected, as immunosuppressive therapy was not given. Almost 10 years elapsed after Welch's first publication before his operation was attempted in immunosuppressed canine recipients.<sup>6,7</sup> Auxiliary homografts inserted by a modification of Welch's techniques into dogs being treated with azathioprine were much more severely damaged than orthotopically placed livers that had been provided with a normal portal inflow. A search for the explanation of this discrepancy was the beginning of hepato-

trophic physiology, the subject of the third section of this chapter.

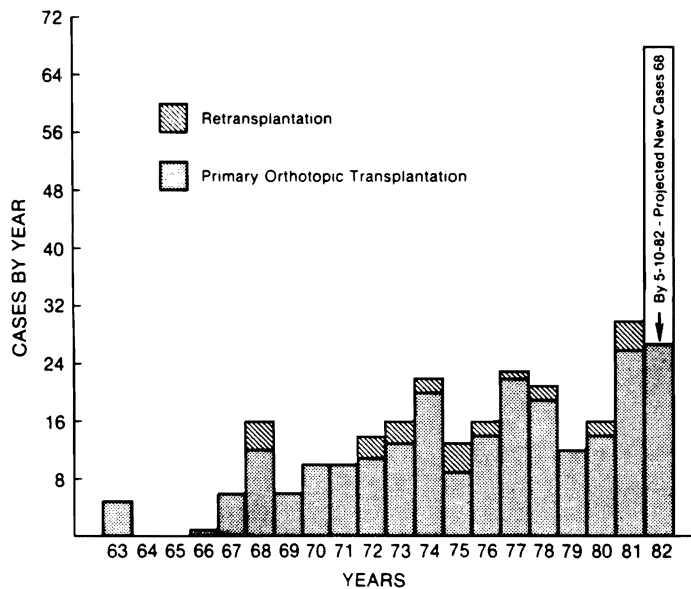
**Orthotopic Transplantation.** The first known efforts at experimental orthotopic transplantation of the liver (liver replacement) were made by Cannon.<sup>8</sup> The animals (species not stipulated) did not survive the operation, and the report was so brief that it lacked a title or a description of the methods.

Orthotopic transplantations of the dog liver were initiated in 1958 by Moore and his associates<sup>9</sup> and by us.<sup>10,11</sup> The technical problems of liver replacement and the features of rejection in untreated canine recipients were delineated.<sup>9-12</sup> Several years later, using immunosuppression with azathioprine<sup>13-15</sup> and antilymphocyte serum (ALS) or its globulin derivative (ALG),<sup>13,16-19</sup> chronic survival was achieved in several mongrel dogs, of which one lived for almost 12 subsequent years.<sup>20</sup> Garnier et al.<sup>21</sup> observed in 1965 that rejection of orthotopic pig liver homografts was mild in comparison with that seen in dogs. Several of their porcine recipients lived for long times without immunosuppression. Other investigators promptly confirmed Garnier's work<sup>13,22,23</sup> Since then, the value of the pig for transplantation research has been demonstrated frequently. Numerous experimental studies of auxiliary and orthotopic liver transplantation in various species were subsequently published. Some of these have influenced clinical practice, but none has had the impact of the original investigations.

For clinical application, orthotopic transplantation has been the most promising procedure. For that reason, most of the following remarks will pertain to this approach.

**Clinical Trials of Orthotopic Transplantation.** Transplantation of a human liver was first attempted on March 1, 1963.<sup>24</sup> In the succeeding 10 months, 6 more such operations were performed, 4 by us<sup>6,7,24</sup> and 2 at other institutions.<sup>25,26</sup> The longest survival was 23 days.

The 7 consecutive failures in 3 institutions led to a 3-year moratorium on clinical trials. The first extended survival of a human recipient was achieved in 1967.<sup>27,28</sup> The patient, a 1½ year old girl with a large primary hepatocellular carcinoma, lived for more than 13 months after the procedure before dying of metastases. Since then, efforts at liver transplantation have been persistent.<sup>29</sup> The yearly frequency of liver transplantation is shown in Figure 176-2. The number of transplan-



**Figure 176-2.** Yearly number of liver transplantations at the University of Colorado (1963 to 1980) and the University of Pittsburgh (1981 to 1982). The projection of 68 transplantations for 1982 fell short of the 82 transplantations actually performed in that year. Note that retransplantation has been attempted. (From Starzl TE et al. *Hepatology* 1982; 2:614-36. Reproduced with permission of the American Association for the Study of Liver Disease and Williams & Wilkins.)

tations in 1982 was predicted to be 68 (Fig. 176-2); the actual total during that year was 82. Calne and Williams<sup>30,31</sup> treated their first patient in 1968, and the English series has now grown to more than 125. Between 1968 and 1978, other single attempts or small series were reported from all over the world.<sup>32-44</sup> Since 1978, several programs have been reopened or initiated. Series of 6 or more cases each have been reported or are in preparation from Holland,<sup>45</sup> East Germany,<sup>46</sup> West Germany,<sup>47,48</sup> France,<sup>49</sup> and the Republic of China.<sup>50</sup> The West German series<sup>48</sup> numbers more than 50, but the results have not been published.

Of 237 patients we treated through April 1982, 112 were children and adolescents (Table 176-1) ranging in age from 5 months to 18 years. The 125 adults (Table 176-2) were 19 to 68 years old.

**Indications for Orthotopic Transplantation.** None of the disorders for which transplantation has been attempted should be excluded categorically from future trials. At the same time, a fairly complete understanding has evolved with respect to many specific diseases about what advice to give to prospective recipients and their families, when and if the operation should be decided upon, how much risk there is of deterioration and death during the search for a donor organ, and what technical difficulties are to be anticipated during the transplantation.

Candidacy is restricted to patients who are less than 55 years old, who are free of extra-

hepatic infection, and who do not have an extrahepatic malignancy. Within this group, the 2 main principles in case selection concern the propriety of a decision to proceed and the feasibility of an attempt. The propriety issue had been the dominant theme because of anxiety that meaningful life might be foreshortened by a dangerous and unpredictable surgical undertaking.<sup>13</sup> Our general guideline was that transplantation for non-neoplastic liver disease became justifiable with the advent of social and vocational invalidism.<sup>51</sup> This condition usually was reflected in repeated hospitalizations for encephalopathy, variceal hemorrhage, hepatorenal syndrome, uncontrolled coagulation disorders, intractable ascites, and other complications of hepatic disease.

Houssin et al.<sup>49</sup> found that all of their patients with alcoholic cirrhosis who had 2 or more of the complications just mentioned died in 1 month or less. Their study, which also contained data on results of tests of liver function, often has been cited as providing criteria for candidacy. However, an effort to develop a clinical or biochemical profile that can be applied generally to such heterogeneous liver diseases as those listed in Tables 176-1 and 176-2 is meaningless. Instead, disease-specific criteria need to be developed.

The feasibility component of patient selection has received inadequate attention. Desperate attempts have been made with transplantation to rescue patients who were bleeding to death, were in Stage 4 coma, had

**Table 176-1. INDICATIONS FOR LIVER TRANSPLANTATION IN PEDIATRIC PATIENTS ( $\leq 18$  YEARS OLD) (FROM MARCH 1, 1963, THROUGH APRIL 1982)**

Disease	No. Cases
Biliary atresia	62*
Inborn metabolic errors	21†
Non-alcoholic cirrhosis	15
Hepatocellular carcinoma	3‡
Neonatal hepatitis	3
Secondary biliary cirrhosis	3§
Byler's syndrome	2
Congenital hepatic fibrosis	2
Budd-Chiari syndrome	1
	112

\*2 had Alagille's syndrome.

†Inborn errors

Alpha-1-antitrypsin deficiency	13
Wilson's disease	3
Tyrosinemia	2
Type I glycogen storage disease	1
Type IV glycogen storage disease	1
Sea-blue histiocyte syndrome	1

21

‡Seven other patients had incidental malignancies (6 hepatocellular carcinoma and 1 hepatoblastoma) in their excised livers. The principal diagnoses in these 7 cases were biliary atresia (3 examples), congenital tyrosinemia (2 examples), alpha-1-antitrypsin deficiency (1 example), and sea-blue histiocyte syndrome (1 example). The diagnosis of the neoplastic change was known in advance in 4 of the 7 cases.

§Secondary to choledochal cyst (2 examples) or trauma (1 example).

anuria, or had lung fields made opaque by pneumonitis or pulmonary edema. This reflected the lateness of referral in some cases; in others, the patients were vital candidates early on but deteriorated during work-up or during the search for a liver donor. The compassion and affection for the candidates by the medical and surgical staffs caring for them during this period of physical and mental decay created an almost irresistible compulsion to proceed when an organ finally arrived, despite hopeless metabolic and technical conditions.

Aside from the medical state of the patient, the question of technical feasibility also must receive increased attention. We have learned from experience that transplantation is relatively easy for some hepatic diseases and exceptionally difficult on the average for others. Whatever the underlying diagnosis, patients who have had earlier adhesion-forming operations in the upper abdomen have an increased perioperative mortality,<sup>29</sup> especially if the porta hepatis has been dissected for

portal diversion procedures or biliary tract reconstruction.

Earlier, a devastating finding in almost 10% of operations was a thrombosed or hypoplastic portal vein. All candidates must be studied with ultrasonography to rule out this possibility. When the results are equivocal, portal venograms are obtained after superior mesenteric arteriography or by transhepatic techniques (Fig. 176-3). Despite these precautions, errors regarding portal vein anatomy continue to be made.

The work-up performed at the University of Pittsburgh<sup>29,52</sup> includes confirmation of the prior diagnosis, analysis of residual liver function, measurement of the recipient's intellectual and psychiatric state, assessment of abnormalities of extrahepatic organ systems, and determination, insofar as possible, of whether liver replacement will be anatomically possible. The mass of resultant data is considered at a weekly conference attended by physicians and surgeons of all specialties, psychologists, nurses, social workers, and lawyers. In the final decision, the questions of propriety and feasibility increasingly have been influenced by the nature of the hepatic disorder and by the difficulties or advantages

**Table 176-2. INDICATIONS FOR LIVER TRANSPLANTATION IN ADULT PATIENTS ( $> 18$  YEARS OLD) (FROM MARCH 1, 1963, THROUGH APRIL 1982)**

Disease	No. Cases
Non-alcoholic cirrhosis	47
Primary malignancy	24*†
Alcoholic cirrhosis	15
Primary biliary cirrhosis	12
Sclerosing cholangitis	10
Secondary biliary cirrhosis	6‡
Alpha-1-antitrypsin deficiency	4
Budd-Chiari syndrome	3
Acute hepatitis B	1
Adenomatosis	1*
Hemochromatosis	1
Protoporphyrria	1
	125

\*One patient in each group had previous (1 and 4½ years earlier) right hepatic trisegmentectomy. At transplantation, the regenerated left lateral segment was replaced with a whole liver.

†Thirteen hepatocellular carcinomas, 7 duct cell carcinomas (Klatskin), 2 cholangiocarcinomas, 1 hemangioendothelial sarcoma, 1 unclassified sarcoma.

‡Two examples each of choledochal cyst and trauma; 1 example each of duct hypoplasia and Caroli's syndrome. All 6 patients had had previous multiple operations.





Figure 176-3. Hypoplastic portal vein (35-mm diameter) demonstrated by transhepatic portography. The patient was 55 years old. PV = portal vein; CV = coronary vein; SV = splenic vein.

encountered with specific diseases that have been clarified by hard experience (Table 176-3).

**Non-Alcoholic Cirrhosis.** Sixty-two patients with this diagnosis have come to transplantation; 47 were adults (Table 176-2) and 15 were adolescents (Table 176-1). Experience has taught the urgency with which each candidacy must be viewed. In our entire experience, no patient with non-alcoholic cirrhosis who was accepted for transplantation and for whom the procedure was not carried out has lived for more than a few months. Referral for consideration of transplantation usually was late, but in several cases our own judgment was that deterioration was not yet severe enough to preclude proceeding in spite of jaundice and manifold evidence of inadequate hepatic function. Such dilatory tactics, or even the inability to find a liver donor promptly after a decision to go forward was reached, often have borne bitter fruit. Further hepatic decompensation usually has been swift, leading to coma, anuria, lethal bleeding into the gastrointestinal tract and elsewhere, and multiple infections. Many of the patients who eventually had transplantation have required prolonged ventilatory support and renal dialysis before coming to the operating room, and the few survivors

in this unfavorable subgroup usually have required the same care for long periods afterwards.

The technical difficulties in replacing the livers of these patients may be extraordinary (Table 176-3). Because the livers are predictably shrunk, a donor with a smaller stature than that of the recipient must be found. Otherwise, closing the incision may be impossible. Without previous abdominal operations, the main structures of the hepatic hilum are relatively normal except for the presence of collaterals. However, the hepatic veins at the upper part of the liver are so distorted by fibrosis and so surrounded with collaterals that special techniques often are required to develop an outflow cuff of vena cava (see section on surgical technique). Collaterals inferior to the liver are of huge size. Even though ties are placed on every bit of tissue that is cut, perfect hemostasis can never be achieved until the hypertensive portal system is decompressed through the new liver, after which the second vital factor of improved coagulation can be expected within a few hours if a well preserved liver has been transplanted.

The legendary marathon operations with dozens or even hundreds of units of blood transfused are commonplace in these patients. The adhesions from previous abdominal operations other than portal-systemic shunts may create so many additional friable collaterals that there is little chance of succeeding. The largest blood loss ever incurred in a patient who survived was 110 liters. The recipient returned to his university departmental chairmanship several months later, but only after spending the preoperative period and the first 2 postoperative months on a ventilator.

The technical problems in patients with previous portal-systemic shunts have been different but no less trying. Although the massive collaterals involute in proportion to the effectiveness of the shunt, the perihepatic area and hepatic ligaments usually are full of troublesome fine arterial collaterals. With loss of the venous collaterals, many such patients have cardiovascular collapse during occlusion of the interconnected portal and inferior vena caval systems (obligatory during the anhepatic phase). The patient may require veno-venous bypass during the anhepatic phase to survive the insult of the reduced venous return to the heart. If the portal

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Table 176-3. METABOLIC, OPERATIVE, AND OTHER FEATURES OF SPECIFIC DISEASES IN 237 LIVER TRANSPLANTATION RECIPIENTS

Disease	No. Cases	Decision about Propriety of Transplantation	Incidence of Prior Abdominal Surgery	Average Technical Difficulty	Usual Metabolic Abnormalities	Disease Recurrence
Non-alcoholic cirrhosis	62	Previously difficult until moribund, easier now	52%	Extreme	Severe	Usual with HBsAg
Biliary atresia	62	Easy	100%	Easy to extreme	Moderate	None
Hepatic malignancy	27	Easy at first, difficult now	96%	Easy to moderate	Minimal to moderate	Common
Inborn metabolic errors	25	Easy until now	24%	Easy to moderate	Moderate to severe	None
Alcoholic cirrhosis	15	Difficult	13%	Extreme	Severe	Unknown
Primary biliary cirrhosis	12	Relatively easy	58%	Easy	Moderate to severe	Has been described
Sclerosing cholangitis	10	Relatively difficult	90%	Moderate to extreme	Moderate to severe	None, but unknown
Secondary biliary cirrhosis	9	Easy	100%	Extreme	Moderate to severe	None
Budd-Chiari syndrome	4	Relatively difficult	75%	Moderate	Moderate to severe	Has been described
Neonatal hepatitis	3	Easy	33%	Easy to moderate	Severe	None
Congenital hepatic fibrosis	2	Easy	50%	Moderate	Severe	None
Byler's syndrome	2	Easy	50%	Easy	Moderate to severe	None
Hemochromatosis	1	Easy	100%			
Protoporphyrria	1	Easy	100%			
Adenomatosis	1	Easy	100%			
Acute hepatitis B	1	Difficult	0%			

diversion has been with a portacaval shunt, the anastomosis must be taken down in order to revascularize the homograft; 2 patients have bled to death when portal veins were found to be too sclerotic to be sutured. When portal diversion has been with a mesocaval or splenorenal shunt, the shunt must be closed surgically to prevent the "steal" that would otherwise partially deprive the new liver of a vital component of its blood supply.

Lethal recurrence in the homograft of the disease that destroyed the native liver has been well documented in patients with preoperative HBs antigenemia.<sup>29,53,54</sup> The antigen titer in the best studied patient was temporarily reduced after operation, indicating that the excised liver was the principal but not the sole reservoir of the virus.<sup>53</sup> Complete clearing of the virus perioperatively was achieved in only 1 of 5 recipients; in the 4 who survived operation, the HBs antigen returned to high titer within a few weeks despite treatment with standard quantities of

hyperimmune globulin immediately postoperatively. Two patients died of liver failure after 5 months and 14½ months, respectively, and a third has poor graft function after 13 months. Recurrent chronic aggressive hepatitis was present in each case. A course of preoperative immunization with HBsAg vaccine is planned in future patients to stimulate an antibody response before the advent of immunosuppression, and immunoglobulin will be administered in much larger doses. Johnson et al.<sup>55</sup> of Cambridge, England, achieved long-term clearing of the antigen with globulin therapy after transplantation in a patient with primary cancer. Nevertheless, the English team considers hepatitis B antigenemia a contraindication to transplantation.<sup>56</sup>

Recurrence of disease in patients with chronic aggressive hepatitis complicated by cirrhosis who do not have HBsAg has not been described, but such an eventuality would not be surprising. The potentially ad-

verse role of recurrence coupled with the enormous difficulty of the operation could lead to a decision against treating patients with underlying chronic aggressive hepatitis. In fact, continued efforts to treat non-alcoholic cirrhosis would be foolish were it not for some encouraging signs. Of 46 patients treated with conventional immunosuppression between 1963 and the end of 1979, 16 lived for at least 1 year<sup>29</sup> and 10 are still alive after 3¼ to 9 years. Whether survival of these high risk patients can be greatly improved by use of cyclosporine and steroids is under study.

Risks to medical personnel have been substantial. All but one of the surgeons of the 1963 Colorado liver team had one (and in one case, 2) bouts of acute hepatitis, and the chief research technician in that effort died of the disease. Within the last year, one of the surgical fellows in Pittsburgh has had B-virus hepatitis. A program has been in place to protect personnel with isolation techniques in and outside the operating room, to treat them with hyperimmune globulin after overt exposure, and to carry out active immunization of those who elect to participate in this potentially hazardous patient care program.

The need has been acknowledged for policy changes in our decision to continue these efforts. We are now recommending operation at an earlier time and with as short an interval as possible between acceptance to candidacy and transplantation, particularly for recipients whose livers are demonstrated to be tiny by ultrasonography and computed tomography. The liver size, as estimated by these imaging procedures, has been within 10% of the actual volumes of the eventually excised livers.

As new hepatic transplantation centers are established, their responsibility will be to treat patients from their regions who have underlying chronic aggressive hepatitis. However, prudence may dictate that trials at a new center begin with the less difficult diseases summarized in Table 176-3. Otherwise, the indelible image may be left with the participants and onlookers that liver transplantation is a murderously difficult and hopelessly complex enterprise that exceeds the capabilities of the sponsoring institution.

**Biliary Atresia.** Sixty-two patients have been treated to date. The prevalence of biliary atresia in Europe and the United States has

been estimated as between 1 in 7000 and 1 in 13,000 births (Chapter 178). With approximately 3.7 million births each year in the United States,<sup>57</sup> the annual number of new patients with biliary atresia should be approximately 400 to 500. Not all would be *bona fide* candidates for liver transplantation, since severe associated anomalies of other organ systems have been estimated to occur in about 15% of these children.

Several patients with biliary atresia have died after liver transplantation because of unexpected intra-abdominal anomalies that jeopardized performance of a technically satisfactory transplantation.<sup>13,29</sup> The most serious variations have included an absent inferior vena cava, a pre-duodenal portal vein, a hypoplastic portal vein, and an hepatic arterial blood supply that was unsuitable for arterial reconstruction. Three patients had a complex of anomalies that included intestinal malrotation, a pre-duodenal portal vein, an absent retrohepatic inferior vena cava, and a small hepatic artery that originated from the superior mesenteric artery.<sup>13,58</sup> One of these recipients had a successful transplantation and is still living 8½ years postoperatively.

The propriety question has never been an issue in deciding upon transplantation (Table 176-3), and the question of feasibility has been clarified by experience. Since 1975, most of the infants and children who have come to transplantation have had a previous attempt at porticoenterostomy (Kasai procedure) with the construction of a Roux-limb of jejunum. Partly because of cholangitis, common after porticoenterostomy, an increasing number of patients with biliary atresia have had multiple operations, including diverting skin jejunostomies. These, in turn, have often required later closure because of bleeding or ulceration. The consequence has been that the ultimate step of liver replacement has become increasingly difficult. Under such circumstances, extensive and highly vascular adhesions are almost always present in the hilar area and frequently around the entire liver surface as well.

Despite these technical disadvantages, the care of children with biliary atresia can be a rewarding experience. The interval between the realization that a porticoenterostomy has failed and death usually is many months. Thus, the transplantation can be planned in a relatively elective fashion and carried out before profound clotting abnormalities and

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When hepatic transplantation was carried out under conventional immunosuppression, the 1-year survival of patients with biliary atresia was only 27%;<sup>29</sup> most of the deaths occurred in the first 3 months. The situation has drastically changed since the introduction of cyclosporine and steroids; the majority of patients treated since then are living with excellent or completely normal liver function with follow-ups of as long as 3 years.<sup>29</sup>

**Hepatic Malignancy.** When clinical liver transplantation was first performed, a primary malignant neoplasm of the liver that could not be removed by a conventional operation was thought to be an ideal indication for liver replacement. The outcome without excisional therapy was highly predictable. The patients were in generally good condition and did not deteriorate rapidly while waiting. Hepatic function, including coagulation, usually was not gravely deranged. Because portal hypertension seldom was severe and because the native livers were of normal size or enlarged, the technical demands of the transplantation were relatively simple in comparison with the standards required in cirrhotic recipients. However, the great frequency of subsequent metastases after total hepatectomy and transplantation,<sup>13,29,51,59,60</sup> as well as the recognition that immunosuppression could theoretically accelerate metastatic growth,<sup>13</sup> quickly dampened enthusiasm for this procedure. The consequence has been that decisions about candidacy are more controversial than ever (Table 176-3).

At the same time as the specter of metastatic disease was emerging,<sup>13</sup> other evidence was developing that recurrence was not inevitable. One of Calne's patients who died of biliary tract complications 5 years after transplantation for primary carcinoma had no detectable disease at necropsy.<sup>31,61</sup> Two of the children we operated on, one with biliary atresia and the other with alpha-1-antitrypsin deficiency, had unsuspected incidental carcinomas in their excised livers and are well after 5 and 13¼ years respectively.

**PRECYCLOSPORINE ERA.** From 1963 to the end of 1979, we performed liver transplantation in 20 patients for the purpose of removing a known primary malignancy. Eight of the recipients died in less than a month

and only one had metastases at necropsy; thus, the preoperative screening for extrahepatic tumor spread had been relatively accurate. Of the other 12 who lived long enough for occult residual tumor to grow, 10 (83%) developed metastases. Recurrent disease was the main cause of death in 5 survivors who eventually died after 11, 13, 14, 24, and 54 months; the other 5 died primarily from other complications. The early and late metastases were from primary hepatocellular carcinoma, duct cell carcinomas, and one hemangioendotheliosarcoma.<sup>29,59</sup> One patient with an unclassified sarcoma is still well after more than 6 years. During this same period, Calne et al.<sup>56,60,61</sup> reported a 50% to 65% frequency of metastases, which were particularly common and aggressive from primary duct cell tumors; the frequency of recurrence may have been misleadingly low, since deaths occurred so early that metastases that might have been inapparent even at necropsy were not stratified out of the computations.

**CYCLOSPORINE ERA.** Later results with cancer patients have been less bleak. Between March 1980 and April 1982, 8 more patients had transplantation for known primary carcinomas. Three of the neoplasms were massive and were in livers that had no other disease; 2 were associated with chronic aggressive hepatitis; and one each was associated with the cirrhosis of alpha-1-antitrypsin disease, tyrosinemia, and sea-blue histiocyte syndrome. The other 3 patients had duct cell carcinomas. All 11 recipients had immunosuppression with cyclosporine and steroids. Seven of the 8 patients with primary carcinoma recovered fully from the operation. One died of recurrence 2¾ years later (discussed later). None of the other 6 has developed metastases after follow-ups of 11, 12, 13, 17, 19, and 20 months.

Unwarranted conclusions should not be drawn from these results. Special pathologic features could have conspired for success; the primary carcinomas that were associated with other diseases were localized enough so that they might have been removed by subtotal hepatic resection were it not for the coexisting cirrhosis. The 3 massive tumors in otherwise normal livers were "fibrolamellar" carcinomas, neoplasms that are characterized by indolent primary growth and late metastases.<sup>62,63</sup> Although draconian measures were required for their removal, recurrences have developed from only one of these tumors. In

this recipient (mentioned earlier), who died of carcinomatosis 2¾ years after liver replacement, a large tumor thrombus originating in a hepatic vein was extracted from the vena cava and right atrium at the time of transplantation. A second patient operated upon 1¾ years ago had complete obstruction of the portal vein by tumor but has had no recurrence. A third patient developed recurrences in the residual lateral segment after a right trisegmentectomy performed 4½ years earlier. The tumor-laden hepatic remnant and left diaphragm were removed in the course of an 18-hour transplant operation, and she has been well for 11 months.

The results in 3 patients who were treated for duct cell carcinomas during the same period and under the same immunosuppression provide a stark contrast. One of the 3 died early of surgical complications. The other 2 had a good convalescence but died of widespread metastases in the 9th and 13th postoperative months. To our knowledge, no patient has ever been cured of duct cell carcinoma by liver transplantation.

More patients with primary hepatic malignancy will be treated with transplantation, but the numbers will be kept small by increasingly scrupulous case selection.

#### Inborn Errors of Metabolism

**ALPHA-1-ANTITRYPSIN DEFICIENCY.** This inborn error of metabolism was seen in our series in 4 adults and 13 children (Tables 176-1 and 176-2). The issues of case selection and surgical technique were the same as in those with chronic aggressive hepatitis. In fact, several of the patients carried the latter diagnosis until examination (or re-examination at a later time) of the surgical specimen. The difference is that the hepatic disease does not recur and the pulmonary complications of the disorder are probably aborted as well. After successful operation, the Pi (protease inhibitor) type converts to that of the donor and depressed serum alpha-1-antitrypsin levels become normal.<sup>29,64,65</sup> The longest survival of a patient with this diagnosis has been more than 6½ years.

**OTHER INBORN ERRORS.** Five other diseases have been treated in 8 patients (Table 176-1). Decisions about proceeding were easy because of the extent of hepatic failure or because the liver contained a neoplasm (Table 176-3). Although cirrhosis was present, the operations were technically easy, even in

a patient with *type I glycogen storage disease* (GSD) who had undergone an end-to-side portacaval shunt 8 years previously.

Metabolic "cure" of the original metabolic disease has been proved or presumed in all of the recipients except a child with *type IV GSD* who died too soon to permit the appropriate studies. Although the enzyme defect of *Wilson's disease* (if an enzyme deficiency is the etiology) is not known, the 3 boys with this disorder underwent total body decapitating.<sup>66-68</sup> One died after 6 years of biliary tract complications. The other 2, who are well after 1½ and 12 years, had complete reversal of severe pre-existing neurologic disability. A liver biopsy after several years in the longest survivor revealed a normal copper concentration.<sup>67</sup>

Stabilization of severe neurologic disease has also been seen during 13 months after transplantation in a child with the *sea-blue histiocyte syndrome* (in spite of the fact that the explanation for this lipid storage disease is unknown<sup>68</sup>). However, a follow-up liver biopsy showed some deposition of lipid granules in the new liver, which may signal recurrence. Daloze et al.<sup>35</sup> have demonstrated restoration of depressed sphingomyelinase for more than a year in a child with *Niemann-Pick lipid storage disease*, but the patient's pre-existing neurologic damage was too great and irreversible to permit survival. The hepatic enzyme defects in *congenital tyrosinemia* (tyrosinase) and *type I glycogen storage disease* (glucose-6-phosphatase) are known. All of the characteristic metabolic perturbations of these disorders are rectified within a few hours after transplantation.<sup>29,68-70</sup>

Now that the feasibility of such "metabolic engineering" has been established, the indications for this approach should proliferate and transplantation be carried out earlier.

**Alcoholic Cirrhosis.** A decision to perform transplantation for alcoholic cirrhosis should be made free of illusions about the surgical difficulties that can be expected. Replacement of the rock hard and frequently small liver presents problems that are similar to or even worse than those already described for non-alcoholic cirrhosis. A depressing number of candidates already have had a portal-systemic diversion or some other intra-abdominal procedure to control variceal hemorrhage.

The screening of candidates for such a herculean effort is by no means easy (Table

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176-3). A surprising number of patients sent to us with the diagnosis of alcoholic hepatitis have had some other disease. A *bona fide* candidate with non-alcoholic hepatic disease who is beyond help by conventional therapy might be someone whose physical condition is relentlessly deteriorating; who has progressive jaundice, hypoproteinemia, prothrombin depression, and other worsening indices of liver function; and whose mental competence is failing. Even if the liver is shrunken, how much survival time remains, and how urgent is the need to find a donor are difficult to estimate. Finally, since many alcoholic patients follow other avenues of self-abuse, disease of the lungs and other organ systems is common.

If transplantation is successful, non-compliance and recidivism may be a problem. Of the first 9 alcoholics in our series, 8 died too soon to evaluate this potential problem.<sup>71</sup> Three of the next 6 had prolonged survival. Of the 4 who lived for at least a year, 3 are still alive and "dry" with follow-ups of 5½, 6, and 9 years. The late death was after 55 months in a young man who resumed drinking and IV drug abuse and developed fatal pneumonitis. Of the 15 alcoholics listed in Table 176-2, none have been treated in the last 3 years.

Despite these characteristics, alcoholic cirrhosis probably will become a more frequent indication for transplantation. If so, the upper age limit probably should be lowered from 55 years and a significant period of alcohol abstinence should be mandatory. The latter step alone will cull the candidacy list, either by making the patient too well to be considered further or by proving the infeasibility of reform. Those who adhere to a rehabilitation program without improving should be offered transplantation much earlier than has ever been done in the past.

**Primary Biliary Cirrhosis (PBC).** Because the natural history of this disease has been so well documented<sup>72,73</sup> and is so predictable, transplantation can be used before an agonal phase is reached. If the serum bilirubin concentration begins a steady rise and exceeds 10 mg/dl average survival is limited to about 18 months.<sup>72,73</sup> Further ways are available to identify those patients who cannot meet or can be expected to exceed this average.<sup>72</sup> The final events of the disease move slowly enough that there is reasonable time (sometimes many months) to search for a donor after selection as a candidate.

Transplantation for PBC is easier than for any other disease (Table 176-3). The liver is of normal size or enlarged, the venous collaterals are not excessive, and occlusion of the recipient portal vein and vena cava during the anhepatic phase is well tolerated. Recurrence of PBC after transplantation has been described.<sup>74</sup> However, we have not seen this complication in recipients followed for as long as 4½ years despite the invariable reappearance of mitochondrial antibodies.<sup>75</sup>

**Sclerosing Cholangitis.** Because the final stages of this disease have not been as well studied as those in PBC, decisions for transplantation have come late. Another adverse factor has been the frequency of previous biliary tract procedures, including choledochenterostomies (Table 176-3). Transplantation in such patients may be technically impossible if not decided upon before the development of serious metabolic perturbations.

As more liver transplantation centers are opened and liver transplantation is recognized as an option at the end of the line, the attitudes of gastroenterologists and surgeons may become more conservative about minimally effective palliative operations such as choledochenterostomy, which may make definitive treatment with transplantation impossible. Further impetus toward non-operative management has already been provided by the ability to achieve biliary decompression by non-surgical means (Chapters 195 and 196).

Whether recurrence of the cholangitis will be a problem is not known. However, the overwhelming prevalence of associated and presumably causal disease in the intestinal tract (especially ulcerative colitis) and elsewhere portends an added risk. If quiescent ulcerative colitis is present, the question of colectomy to prevent recurrence of the liver disease in the transplant will be a consideration, but no experience indicates if or when this should be done. Our present opinion is that colectomy should be put off until after transplantation to avoid the intra-abdominal adhesions and possible ileostomy that would jeopardize liver replacement. Only 4 of the 10 recipients with sclerosing cholangitis in our series have had long survivals. Two of them died after more than a year with no evidence of recurrent disease in the homografts at necropsy.

**Secondary Biliary Cirrhosis.** The initiating event in each of our 9 cases of chronic biliary

obstruction (see footnotes in Tables 176-1 and 176-2) precipitated a series of attempts at biliary reconstruction. If such patients are accepted as transplant candidates, the technical risks must be recognized as enormous (Table 176-3). Four of the 9 recipients died during or just after operation. Yet, disease does not recur if the procedure is successful.

**Budd-Chiari Syndrome.** The possibility that portal-systemic diversion can help these patients may lead to a decision for such an attempt and could thereby preclude subsequent transplantation. However, 2 of our 4 patients had undergone side-to-side portacaval shunts that were successfully taken down at the time of transplantation. Recurrent lethal Budd-Chiari syndrome has been described by Calne et al.<sup>56</sup> and in one of our patients who died after 15 months.<sup>76</sup> In both cases, anticoagulation had recently been discontinued. A second of our 4 recipients died after 20 months, a few days after retransplantation for chronic rejection. The other 2 are alive after 2¾ and 8½ years; the longest survivor has had 2 children.

**Miscellaneous Indications** (Tables 176-1 to 176-3). Finding an organ for patients with acute disease after no hope other than transplantation remains for survival is rare. The patient with acute hepatitis in our series was the only example of a recipient with acute hepatic failure in our first 237 cases of orthotopic transplantation.<sup>29</sup> Other patients were considered but developed evidence of brain stem herniation and died within a few hours after admission.

**Tissue Matching.** Waiting for good matches at the A, B, and DR loci is not practical and probably never will be because of the precarious condition of the recipients. Usually time is not sufficient to determine the presence in the recipient serum of the T-warm antidonor antibodies that cause hyperacute rejection of kidney homografts. Hepatic transplantation often has been performed by us<sup>29,51,71,77</sup> and by the Cambridge-King's College team<sup>78,79</sup> despite positive cytotoxic cross-matches. To our knowledge, hyperacute rejection of the liver has never been seen.

Much more experience is required before concluding that acceptance of positive cross-matches caused by T-warm recipient antibodies is without jeopardy. Patients for whom cross-matches could not be performed or whose sera crossmatched negatively with donor lymphocytes had better results than

those who crossmatched positively.<sup>29</sup> Although hyperacute rejection was not observed in the latter recipients, the postoperative courses tended to be stormy, and at least 2 of the livers developed delayed massive necrosis.

The liver is resistant to hyperacute rejection. However, in animal xenograft models in which the recipient has pre-formed hetero-specific cytotoxins, humoral antibody rejection of the liver is merely slower than that of the kidney<sup>80</sup>; the mechanisms of destruction are the same. The extent (if any) to which the outcome after clinical liver transplantation is degraded by pre-formed antibodies will be important to observe. Many liver transplant candidates have widely reacting T-warm cytotoxic antibodies reflecting sensitization by previous blood transfusions. These make it difficult to find a cross-match-negative donor but we continue to treat such highly sensitized patients.

If donor-recipient ABO blood group incompatibility exists, renal grafts can be destroyed by isoagglutinins.<sup>81</sup> Liver grafts, however, are resistant to this kind of hyperacute rejection.<sup>71</sup> ABO-incompatible donors were used in only 2 of our Pittsburgh patients.<sup>29</sup> One of these patients had a good recovery and now is alive 2 years postoperatively; the other died of aspergillosis. We have tried to avoid violating blood group barriers, since group-compatible donors usually can be found.

**The Donor Operation.** Removal of a satisfactory liver for transplantation begins with wise screening of donors and elimination of those whose physiologic situation could jeopardize vital organ function in advance of procurement. Aside from abnormalities in hepatic function, signals that it may be dangerous to transplant the liver of a given donor to a recipient are donor cardiovascular instability, a need for excessive vasopressor support, an excessive period (several days) between injury and the pronouncement of brain death, or deterioration of renal function, which may suggest poor perfusion of other organs.<sup>13,82</sup> The most common explanation for transplantation of an inadequately preserved liver is pre-existing hepatic injury, rather than poor harvesting or preservation techniques.

Assuming that donor selection has been appropriate, removal of an adequate liver depends upon: (1) performing a good operation, including recognition and protection



from injury of anomalies of the hepatic arterial supply (Fig. 176-4); (2) avoiding hepatic warm ischemia; and (3) minimizing hepatic cold ischemia. The first of these provisos is dependent on the knowledge and skill of the donor surgeon. The second can be met by avoiding occlusion of the blood supply during dissection and by efficient infusion of cold solutions into the liver as the donor operation is terminated. The third requires careful timing of the donor and recipient operations, which often take place across great geographic distances. When the new liver arrives at the operating room of the recipient, the team there should be ready within a few minutes to begin its insertion. With the preservation techniques available today,<sup>85,86</sup> an ischemic interval greater than 6 or 8 hours is not safe.

**Contingency Vascular Grafts.** After the organs are out, the distal aorta and vena cava, the iliac veins, and the iliac arteries are removed and stored separately in balanced electrolyte solution.<sup>87</sup> Often these vascular segments have been desperately needed for the subsequent performance of a renal or hepatic transplantation (Fig. 176-5).

**The Recipient Operation.** A bilateral subcostal incision is used with an upper midline extension through which the xiphoid process is excised (Fig. 176-6). The midline extension with xiphoid removal provides badly needed

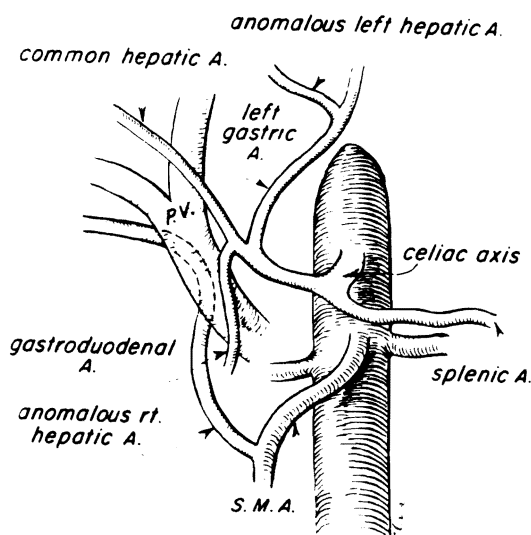


Figure 176-4. Anomalies of hepatic supply. (From Shaw BW Jr et al. *Surg Gynecol Obstet* 1982; 155:321-5. Reproduced with permission.)

exposure for dissection of the hepatic ligaments and the suprahepatic inferior vena cava. If removal of the liver will be a struggle, another extension should be made immediately into the right seventh intercostal space (Fig. 176-6). This is most commonly needed if the liver is unusually shrunken. In such cases, special techniques may be needed to construct vena caval cuffs for later anastomoses.<sup>88,89</sup>

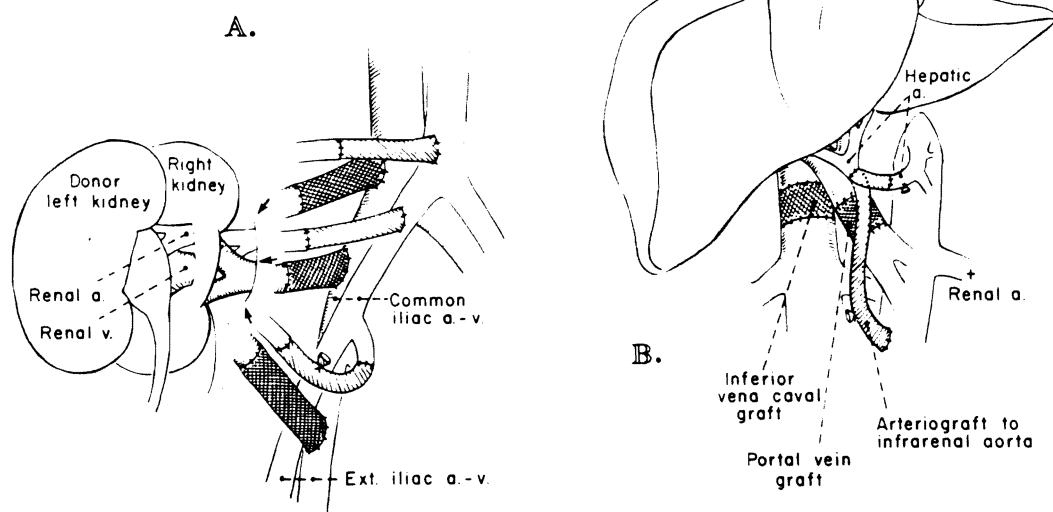


Figure 176-5. The uses to which aortic, vena caval, and iliac vascular grafts have been put in renal (A) and hepatic (B) transplantation. (From Starzl TE et al. *Surg Gynecol Obstet* 1979; 149:737. Reproduced with permission.)



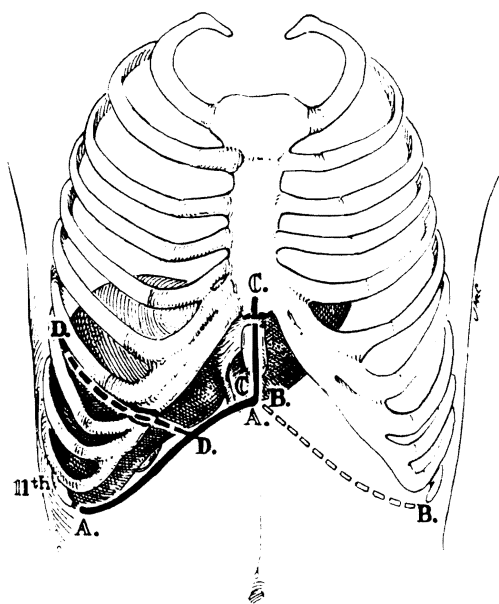


Figure 176-6. Incisions for orthotopic liver transplantations and for hepatic resections, right or left. Note that several extensions may be made from the basic right subcostal incision, A to A, that is almost always used. More than one of the depicted extensions may be required in a given patient. (From Starzl TE et al. *Surg Gynecol Obstet* 1975; 141:429-37. Reproduced with permission.)

With the liver out, the wound is checked for major sites of bleeding, realizing that total hemostasis of the bare area and elsewhere is not possible at this time. The suprahepatic and infrahepatic vena caval anastomoses are performed first, followed usually by reconstruction of the portal vein. At a convenient time, air and the potassium-rich preservation fluid in the graft should be washed out (Fig. 176-7) to prevent air embolism or hyperkalemia with revascularization. Portal blood flow is usually restored first. After checking for major anastomotic leaks, the hepatic arterial anastomosis is performed. Special techniques<sup>91,92</sup> have been developed for the various vascular anastomoses, which often must be performed intraluminally or in close quarters.

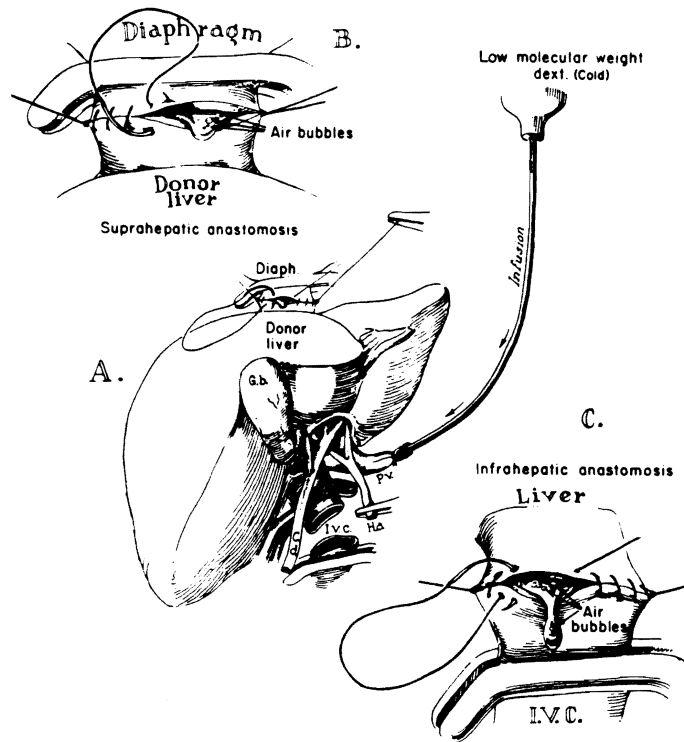
Frequently, the new liver is at first swollen and hard, with diffuse hemorrhage from all raw areas. With time and the administration of platelets and fresh frozen plasma, the problems are usually reversible, provided a major bleeder has not been missed. Efforts at mechanical hemostasis are continued until it is thought safe to perform the biliary tract reconstruction.

**Venous Bypasses.** Portal and vena caval occlusion usually is reasonably well tolerated during a 45- to 90-minute anhepatic phase despite major declines in cardiac output and variable hypotension.<sup>93</sup> The relative safety of the occlusions depends on the collaterals that develop with human liver disease. The same thing has been demonstrated in dogs subjected to chronic bile duct obstruction.<sup>94</sup> Because of this, we abandoned the venous bypasses that we used in all of our first cases.<sup>7,24</sup> However, some patients can be gravely jeopardized by the venous cross-clamping. If severe hypotension occurs after cross-clamping, Calne et al.<sup>56,95</sup> have recommended femoral vein to femoral artery bypass with an intervening oxygenator. About 10% of the English patients are so treated. One death during the last year in our series could have been avoided by this precaution, as could a cardiac arrest that was successfully treated.

The fact that most patients can recover from portal and inferior vena caval cross-clamping may have created a false impression about the safety of this practice. Usually the intestine grossly swells during the period of portal occlusion. Subsequently, many patients suffer from third space fluid sequestration and from postoperative renal failure. The extent to which these complex physiologic events have contributed to the high perioperative mortality of liver transplantation has not been delineated. For this reason we have returned in some cases to the practice of venous bypass, which we abandoned long ago. Cannulas are placed into the inferior vena cava through an iliac or femoral vein and into the portal system through the open end of the transected portal vein. During the anhepatic phase the blood is returned to a reservoir and pumped to one of the large veins in the neck or arm. This bypass requires total body heparinization, and the amount of bleeding that is induced may be so excessive and unresponsive to protamine reversal as to result in death on the operating table. The possibility of using pump-driven venous bypasses without heparin is being evaluated in dogs. The canine experience thus far has been encouraging.

If venous bypass without heparin becomes feasible, liver transplantation will be possible with maintenance of better homeostasis and without as much stress on the anesthesiologists and surgeons. Removal of the devas-

**Figure 176-7.** Initial steps in the implantation of a new liver. *A*, Infusion with lactated Ringer's solution in order to wash out the potassium-rich Collins' solution. *B*, Completion of suprahepatic anastomosis. *C*, Completion of infrahepatic vena cava anastomosis. *B* and *C*, Note the escape of air bubbles that, if not expelled, could lead to air embolism. (From Starzl TE et al. *Ann Surg* 1978; 187:236-40. Reproduced with permission.)



cularized liver in a meticulous and deliberate way, as well as more leisurely performance of the vascular anastomoses, could for the first time make transplantation a pleasant operation instead of a desperate race against the clock.

#### *Technical Problems and Solutions*

**"FROZEN" LIVER HILUS.** Patients with previous operations may have such severe right upper quadrant adhesions that it is virtually impossible to enter the abdomen. Developing an exact plane on the undersurface of the liver with sharp dissection is essential in such recipients to eventually encircle the porta hepatis. If the lesser omental sac can be found and entered through the avascular gastrohepatic ligament, the encirclement usually is easiest from the left side. If dissecting the individual structures of the porta hepatis is then impossible, the triad can be transected after the mass placement of a vascular clamp. The individual structures can be identified at the cut surface and traced back for the development of cuffs.

**ARTERIALIZATION OF GRAFT ANOMALIES.** Problems posed by homograft arterial anomalies (Fig. 176-4) have been described along with various technical solutions.<sup>13</sup> A double

arterial supply originating from the celiac axis and superior mesenteric artery once was thought to be too troublesome to warrant an effort at reconstruction. In several cases, the celiac axis and superior mesenteric artery have been connected (Fig. 176-8), and one or the other end of the superior mesenteric artery has been anastomosed to the recipient hepatic artery.<sup>96</sup>

**INADEQUATE RECIPIENT ARTERY.** Contingency plans should be made in the event that a recipient hepatic artery is too small or too inconveniently located to permit an effective anastomosis. The most common cause is an anomalous recipient arterial supply. Attempts were made in our earliest experience in such recipients to perform an anastomosis of the graft aorta or celiac axis to the aorta of the recipient above the recipient celiac axis. The dissection required to clean off the recipient aorta in this inaccessible area was difficult, and aortic cross-clamping, which was usually required during the anastomosis, had devastating physiologic effects. Consequently, this approach has been abandoned.

The easiest solution is to attach the homograft blood supply to the recipient abdominal aorta, inferior to the origin of the renal arteries (Fig. 176-9). The extra length of graft

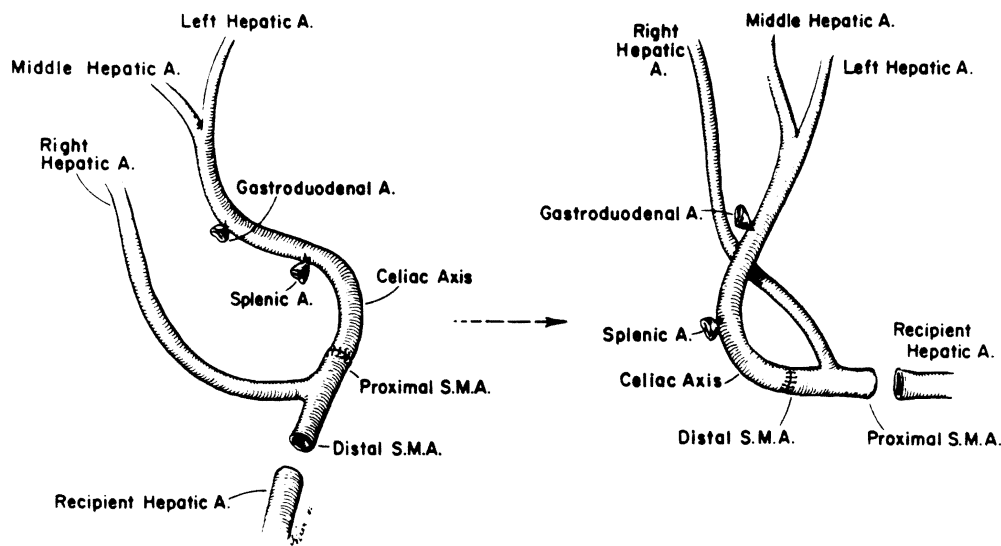


Figure 176-8. The management of a common graft anomaly in which part of the hepatic blood supply is derived from the superior mesenteric artery. Note that the celiac axis is anastomosed to one end of the main superior mesenteric artery and the other end is used for anastomosis to a recipient vessel. (From Shaw BW Jr et al. Surg Gynecol Obstet, in press. Reproduced with permission.)

vessel necessary to reach this location can be provided by retaining the thoracic aorta of the donor in continuity with the celiac axis and by turning the aorta 180° (Fig. 176-9). The occasional need for this technical deviation has prompted the donor team to retain the thoracic aorta with the specimen whenever possible.

Another option to obtain the needed length<sup>96</sup> is to anastomose the free common iliac artery graft to the same location in the recipient aorta with ligation of the hypogastric artery (Fig. 176-9). The external iliac artery is almost a perfect match for anastomosis to the graft celiac axis (Fig. 176-9).

**THROMBOSIS OR HYPOPLASTIC PORTAL VEIN.** One of the great tragedies of liver transplantation has been the discovery at operation of an unsuspected thrombosis or hypoplasia of the portal vein. If effective revascularization of the homograft portal vein has not been accomplished, survival has never been obtained. In 2 patients, the suprarenal inferior vena cava was anastomosed to the graft portal vein, providing the liver with systemic venous inflow, as with a portacaval transposition. This anastomosis thrombosed in one patient, who died of massive hemorrhage from esophageal varices a month later; the other patient died of massive graft necrosis.

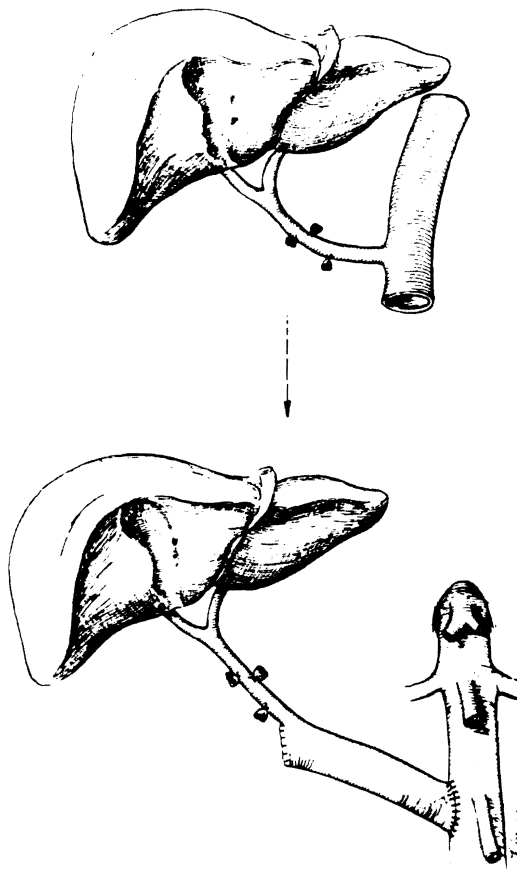
If the thrombosis (or hypoplasia) has not involved the splenic and superior mesenteric

veins, the confluence of these portal tributaries can be dissected free from beneath the pancreas. We have then developed a cloaca at this junction to which an iliac vein graft has been anastomosed to provide added length. The use of an interposition host graft under these circumstances (Fig. 176-5) has been life saving. If thrombosis of the portal vein has been recent, thrombophlebotomy has been accomplished on several occasions. Although a rough intimal surface has been left, the portal venous system has remained open.

**BILIARY TRACT RECONSTRUCTION.** The most common technical complications in the early days of liver transplantation originated from defects in biliary tract reconstruction.<sup>31,97,98</sup> These were often not recognized and led to the death of many patients. Because of its convenience, the now abandoned procedure of cholecystoduodenostomy was frequently used (Fig. 176-10E). Obstruction at the homograft cystic duct occurred in almost half the cases. Even without obstruction, the biliary tract became the site of entry of bacteria. The frequency of bacteremia was astonishing, sometimes occurring in asymptomatic patients. The organisms recoverable from the bloodstream were those indigenous to the gastrointestinal tract.<sup>13</sup> We envisioned that the liver was being frequently contaminated with enteric contents, followed by systemic dissemination of the bacteria.

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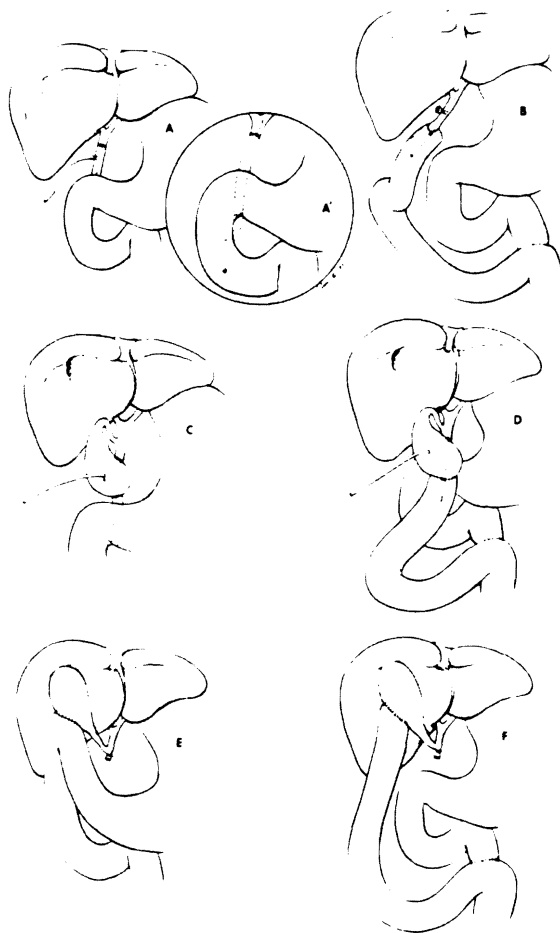


**Figure 176-9.** Technical solution if an adequate recipient artery cannot be found in the area of the portal triad. A piece of graft aorta in continuity with the graft celiac axis can be anastomosed to the abdominal aorta of the recipient. Alternatively, an iliac artery graft can be attached to the recipient aorta with a distal anastomosis to the celiac axis. The latter technique depends upon the availability of contingency grafts procured at the time of liver harvest (Fig. 176-5). (From Shaw BW Jr et al. *Surg Gynecol Obstet*, in press. Reproduced with permission.)

The results were improved with the systematic use of a defunctionalized jejunal limb (Roux-en-Y) to which the gallbladder was anastomosed (Fig. 176-10F). However, the problem of cystic duct obstruction in more than one-third of the recipients remained (Fig. 176-11), necessitating frequent secondary revisions with conversion to choledochojejunostomy (Fig. 176-10B). Our present practice if biliary-enteric anastomosis is necessary (as is invariably the case with biliary atresia) is to perform a choledochojejunostomy (Roux-en-Y) at the first operation (Fig. 176-10B). This is done with a single layer of continuous absorbable suture; a few tacking sutures can be used for reinforcement and an internal stent is used. When choledocho-

jejunostomy is performed, the gallbladder is removed.

Biliary tract reconstruction by duct-to-duct anastomosis was used by us at first and then was temporarily abandoned because of a large number of biliary leaks, which were lethal in the patients treated 15 to 20 years ago. The duct-to-duct anastomosis is performed with interrupted absorbable sutures (Fig. 176-10A). A T-tube stent is used whenever possible, and the T-limb is brought out through a choledochotomy in the recipient portion of the composite duct. In small children, and occasionally in adults, the available T-tubes are too small and an internal stent is used with the distal tip passed into the duodenum. The homograft common duct must



**Figure 176-10.** Methods of biliary tract reconstruction that have been used with liver transplantation. The techniques shown in E and F are so defective that they have been abandoned. Depending upon the anatomic and clinical circumstances, each of the other methods may be useful in individual cases (see text for discussion).

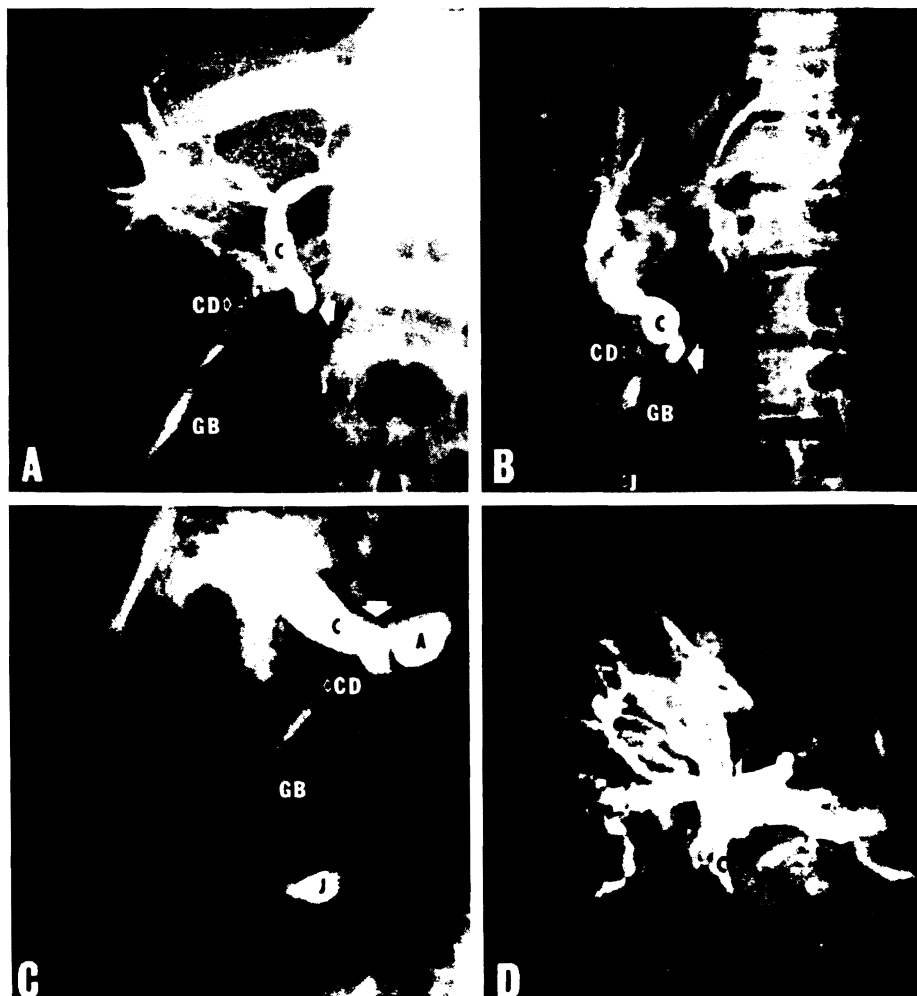


Figure 176-11. Transhepatic cholangiograms in 4 patients whose original biliary reconstructions were with Roux-en-Y cholecystojejunostomy. *A*, Minimal obstruction. *B*, Moderate obstruction. *C*, Severe obstruction with leak and abscess formation. *D*, Very severe obstruction; at reoperation the common duct was necrotic. *A* = leak and abscess formation; *C* = common duct; *CD* = cystic duct; *GB* = gallbladder; *J* = jejunum; large arrow = site of common duct ligation. (From Starzl TE et al. *Surgery* 1977; 81:212-21. Reproduced with permission.)

be cut high enough that its tip is well arterialized. Studies have shown that the blood supply of the graft is dependent upon retrograde perfusion from hilar vessels.<sup>99</sup>

Waddell and Grover<sup>100</sup> recommended that the homograft duct be anastomosed to the graft gallbladder as part of the biliary reconstruction in liver transplantation. Calne has used this technique extensively, and for him it is the method of choice.<sup>79,101</sup> The distal anastomosis with the fundus of the homograft gallbladder is made either to the recipient common bile duct (Fig. 176-10C) or to a Roux-limb of jejunum (Fig. 176-10D). In either case, both of the anastomoses are stented with a T-tube, which can be used for

irrigation. We have used the Waddell-Calne procedure only when the extra length provided by the gallbladder was necessary to bridge a gap between the graft and the distal anastomosis.

An assessment of the various forms of biliary tract reconstruction used by us in 78 consecutive cases has been published by Iwatsuki et al.<sup>102</sup> Choledochocholedochostomy and choledochojejunostomy have both provided excellent results. Our experience with the Waddell-Calne procedure has been too limited to warrant comment, but the Cambridge team has been pleased with the results.<sup>56</sup>

**CONTROL OF HEMORRHAGE.** The most im-

portant mechanical basis for bleeding in patients undergoing liver transplantation is portal hypertension with extensive venous collaterals. Coagulation defects must be anticipated, with depletion of clotting factors produced by the liver constituting a baseline condition. The situation may be aggravated by fibrinolysis, which may begin shortly before the revascularization of the homograft and which can assume crisis proportions shortly afterwards. The series of events in coagulation after liver transplantation was worked out before 1979.<sup>13,24,103,104</sup> Developments in the coagulation field since that time may make the assessment and control of coagulation easier in the future. For example, there may be a place for the controlled use of antifibrinolytic agents such as epsilon-amino-caproic acid (EACA), a drug that was abandoned more than a decade ago because its use was associated with the frequent occurrence of secondary clotting of the graft blood supply. Intraoperative changes in clotting need to be reassessed by modern technology with a view to therapeutic modifications.

Control of bleeding must start with the mechanical means of ligation, suture ligation, and cautery. With the new liver in place, the portal system is decompressed through the new organ with elimination of one adverse mechanical factor, i.e., portal hypertension. If the liver functions well, the perturbations in clotting can be expected to be self-correcting, but this may require hours. Meanwhile, platelets, fresh frozen plasma, and blood constituents may be used as a temporary expedient. Some patients have lost as much as 200 units of blood during surgery but have left the operating room dry.

**Postoperative Care.** Because grave metabolic abnormalities predate operation in most patients, the postoperative care has often been an exercise in resuscitation. The most common early difficulties have been with pulmonary insufficiency (requiring mechanical ventilation for several months in some cases), renal failure (at the same time that massive fluid shifts are occurring), and persistent clotting abnormalities. These problems are managed with conventional methods of intensive care with great emphasis on biochemical and hemodynamic monitoring. Recovery can be expected from encephalopathy and the hepatorenal syndrome.<sup>105</sup>

The ability to survive this critical period

depends on what has just transpired in the operating room. Patients who have received well-functioning livers can have an almost miraculous recovery, but defective performance by the graft at the outset may preclude recovery unless another organ can be quickly found for retransplantation.

The list of later complications is a long one<sup>13</sup> and includes peritonitis with or without bowel perforation, pancreatitis, pulmonary embolus, extra-abdominal infections, and psychosis. Many of these may be directly or indirectly related to the concomitant immunosuppressive therapy. With an initially well-functioning liver, the most important prognostic factor is the ability to control later rejection.

**Immunosuppression.** All of the methods to prevent or reverse rejection of whole organs have been developed with the simpler procedure of renal transplantation. These are summarized in Table 176-4, exclusive of the earlier trials with total body irradiation<sup>106</sup> which was never used for liver transplantation.

**Azathioprine-Prednisone.** Because the first genuinely promising drug, azathioprine, was ineffective when given alone,<sup>107</sup> azathioprine and prednisone, which have additive or possibly synergistic effects,<sup>108-111</sup> were given together.<sup>81</sup> For organ transplantation, this has been the most commonly used immunosuppression throughout the world for almost 20 years. Our first 5 liver recipients and occasional later ones were treated with these drugs. The same treatment was used for almost all of the patients in the Cambridge series from 1968 until 1979.

Under double drug treatment, irreversible rejection of cadaveric kidneys or their loss for other reasons during the first postoperative year has been about 50%, even in later multicenter compilations.<sup>112,113</sup> Double drug therapy is even less optimal in liver recipients, for whom cadaveric donors are obligatory and who do not have the option of fallback maintenance on an artificial organ therapy analogous to renal dialysis.

**Triple Drug Therapy.** Alternative therapeutic programs introduced for renal transplantation between 1963 and 1979 (Table 176-4) were all modifications of or additions to the original double drug therapy. The most useful was lymphoid depletion with antilymphocyte globulin (ALG),<sup>17</sup> which was given IM or IV as an adjunct to azathioprine and pred-

Table 176-4. CLINICAL IMMUNOSUPPRESSIVE DRUG REGIMENS DEVELOPED WITH KIDNEY TRANSPLANTATION

Agents	Year Described and Reported (References)	Place	Deficiencies	Use for Liver Transplantation
Azathioprine	1962 <sup>107</sup>	Boston	Ineffective, dangerous	No
Azathioprine-steroids	1963 <sup>108-111</sup>	Denver, Richmond, Boston, Edinburgh	Suboptimal	Yes
Thoracic duct drainage as adjunct	1963 <sup>115</sup>	Stockholm, pretreatment	Nuisance; requires 20-30 days	Yes
Antilymphocyte globulin as adjunct	1966 <sup>17</sup>	Denver	Still suboptimal	Yes
Cyclophosphamide substitute for azathioprine	1970 <sup>114</sup>	Denver	No advantage except for patients with azathioprine toxicity	Yes
Total lymphoid irradiation	1979 <sup>119, 120</sup>	Palo Alto, Minneapolis	Dangerous; extensive preparation; not quickly reversible	No
Cyclosporine alone	1978-1979 <sup>128, 129</sup>	Cambridge	Suboptimal	Yes
Cyclosporine-steroids	1980 <sup>130, 131</sup>	Denver	Under evaluation	Yes

\*It was not realized until much later that pretreatment for 3 to 4 weeks before transplantation was a necessary condition.<sup>116</sup>

nisone during the first few weeks or months after transplantation, when the risk of rejection was known to be the greatest. Such "triple drug therapy" has been the second most commonly used immunosuppression worldwide. Cyclophosphamide could be substituted for azathioprine.<sup>114</sup> One-year graft survival after cadaveric renal transplantation under triple drug therapy was improved in most, but not all, centers in which trials were conducted. After the discontinuance of ALG, the rate of delayed rejection became unacceptable. The alternative of temporary lymphoid depletion with *thoracic duct drainage* (TDD)<sup>115</sup> in the preparation of patients for cadaveric renal transplantation<sup>116</sup> proved to have the same disadvantage.<sup>117</sup>

The original triple drug treatment with azathioprine, prednisone, and variable courses of intramuscular ALG was used for the great majority of our liver recipients from 1966 through 1979.<sup>13,29</sup> The duration of ALG therapy was usually limited to a few weeks because of sensitization of the recipients to the horse, rabbit, or goat globulin, but in some patients the globulin treatment could be continued for 6 to 12 months. Cyclophosphamide was used instead of azathioprine in 16 patients<sup>118</sup>; later, all of the surviving patients were switched to azathioprine.<sup>29</sup> In 1978 and 1979, TDD was used as an adjunct to therapy with azathioprine and prednisone in 21 patients.<sup>29,54</sup> TDD is ineffective in renal

transplantation unless applied at least 3 weeks in advance of grafting,<sup>116</sup> but potential liver recipients could not tolerate the high volume thoracic lymph drainage associated with hepatic disease for this long. Hence, the procedure was abandoned.

*Total lymphoid irradiation*<sup>119,120</sup> has been too dangerous to use for any kind of clinical transplantation.

**Cyclosporine.** Cyclosporine, an extract of the fungi *Cylindrocarpum lucidum* and *Trichoderma polysporum*, was shown to be immunosuppressive by Borel et al.<sup>121,122</sup> in mice, rats, and guinea pigs. It was unusually effective in preventing or delaying rejection of mouse skin homografts; both humoral and cellular immunity were depressed, with a quickly reversible action. These effects were not accompanied by the bone marrow depression that had frequently limited the doses of azathioprine and cyclophosphamide. Analogous observations indicated that heart, kidney, liver, and pancreatic grafts were also protected in rats, dogs, and pigs.<sup>123-127</sup>

When cyclosporine A was first used in patients by Calne and co-workers,<sup>128,129</sup> the hope was that no other drug would be routinely required. Our experience has been that cyclosporine should be combined with steroid therapy from the outset,<sup>130-132</sup> although the steroid component with this version of double drug therapy has been smaller than

in the past. With cyclosporine and steroids, kidney survival of greater than 80% can be expected 1 year after primary cadaveric transplantation.<sup>131,132</sup>

Nephrotoxicity is the most serious side effect of cyclosporine.<sup>128-137</sup> Fortunately, the renal complications are promptly reversed with the reduction of the cyclosporine doses. Most of the other side effects of cyclosporine<sup>128-132</sup> have not been serious; among them are gum hyperplasia, tremor, regional flushing or vague abdominal discomfort just after drug ingestion, and the development of breast fibroadenomas in women. Although hepatotoxicity has been seen in about one-fifth of cases,<sup>138</sup> this has rarely been serious and can be controlled by dose reduction.

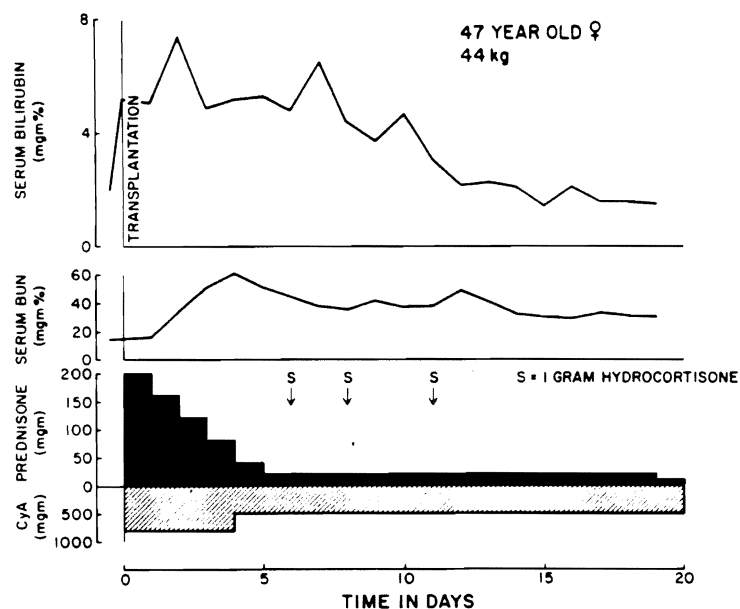
The most publicized question about cyclosporine has concerned its role in causing lymphomas.<sup>129</sup> Lymphoma development with use of cyclosporine and steroids is not much (if at all) greater than with conventional immunosuppression. The evidence is that these lymphomas result from infections with the Epstein-Barr virus.<sup>131,132</sup> The risk of *de novo* epithelial malignancies may be less than with conventional immunosuppression, and, in fact, no such tumors have been reported, a striking but preliminary observation. Under conventional immunosuppression, epithelial tumors account for about 75% of the "new" malignant tumors.<sup>139</sup>

Cyclosporine and steroids for liver trans-

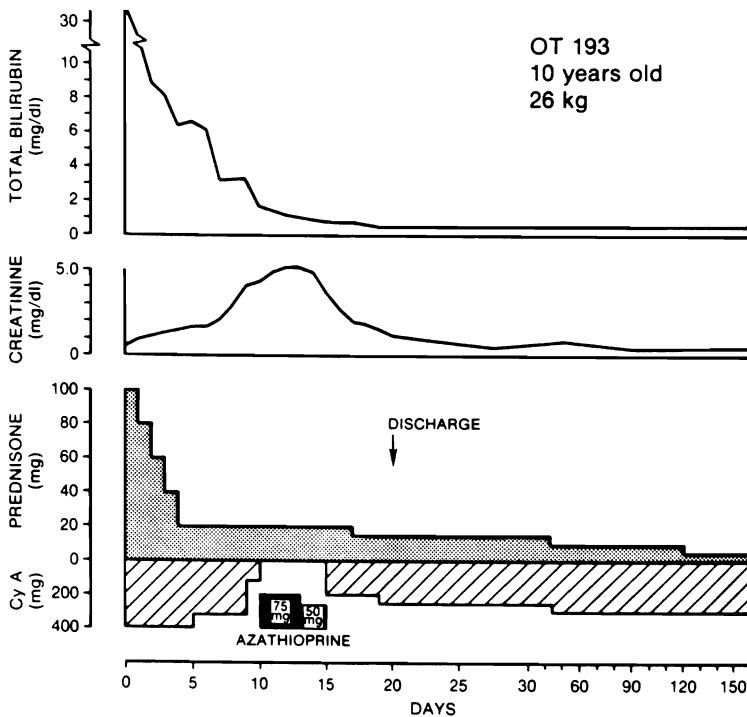
plantation have been adapted from the practices that first were standardized for kidney grafting.<sup>140-142</sup> Cyclosporine is started a few hours preoperatively with an oral dose of 17.5 mg/kg (Figs. 176-12 to 176-14). Cyclosporine is continued daily, but with reduced IM doses (Figs. 176-12 and 176-13) or IV doses (Fig. 176-14) until diet is resumed. Subsequently, an oral dose of 17.5 mg/kg/day is given, usually divided into twice daily doses. The doses are reduced subsequently if nephrotoxicity develops (Figs. 176-12 and 176-13). Steroids also are started on the day of operation. For adult patients who leave the operating room in relatively good condition, a 5-day burst of prednisolone is given, starting at 200 mg and stopping with a maintenance dose of 20 mg/day (Fig. 176-12). Further reductions of cyclosporine and steroid doses are made on an individualized basis in the ensuing months. Initial maintenance therapy with steroids is scaled down in infants and children (Fig. 176-13).

If the patient is in poor postoperative condition, the initial burst of high dose steroid therapy is omitted for a few days or greatly reduced (Fig. 176-14). A few patients suspected of having nephrotoxicity from cyclosporine have been switched temporarily to azathioprine with resumption of cyclosporine treatment after improvement of renal function (Fig. 176-13). With less severe renal impairment (Fig. 176-12 and 176-14), the

Figure 176-12. Double-drug immunosuppression with cyclosporine and steroids. The patient had a hepatocellular carcinoma,  $\alpha_1$ -antitrypsin deficiency, and chronic active hepatitis. The reduction of the cyclosporine dosage after 4 days was because of the increasing azotemia. The boluses of hydrocortisone were given because of a possible unwarranted suspicion of early rejection. (From Starzl TE et al. *Hepatology* 1982; 2:614-36. Reproduced with permission of the American Association for the Study of Liver Disease and Williams & Wilkins.)







**Figure 176-13.** Immunosuppression with cyclosporine and steroids (plus temporary azathioprine) in a 10-year-old girl. Note that the 5-day opening burst of prednisone therapy was scaled down because of her small size. The temporary discontinuance of cyclosporine and replacement with azathioprine between postoperative days 10 and 15 was because of probable cyclosporine nephrotoxicity. The patient, who was of B blood type, was given the liver of an A donor. (From Starzl TE et al. *Hepatology* 1982; 2:614-36. Reproduced with permission of the American Association for the Study of Liver Disease and Williams & Wilkins.)

doses of cyclosporine can be reduced. Only one of our patients has been changed to azathioprine permanently.

If rejection occurs in spite of this beginning therapy, the principal responses have been to administer intermittent large doses of hydrocortisone (or prednisolone) IV (Fig. 176-12 and 176-14), to repeat the original 5-day burst of steroids (Fig. 176-14), or to settle at a higher maintenance level of steroids. Although cyclosporine is not a drug that permits much dose maneuverability, increasing the amounts given has sometimes been possible, the limiting factor being nephrotoxicity. Dose adjustments of cyclosporine can be aided by pharmacologic monitoring of plasma or blood levels.<sup>143,144</sup>

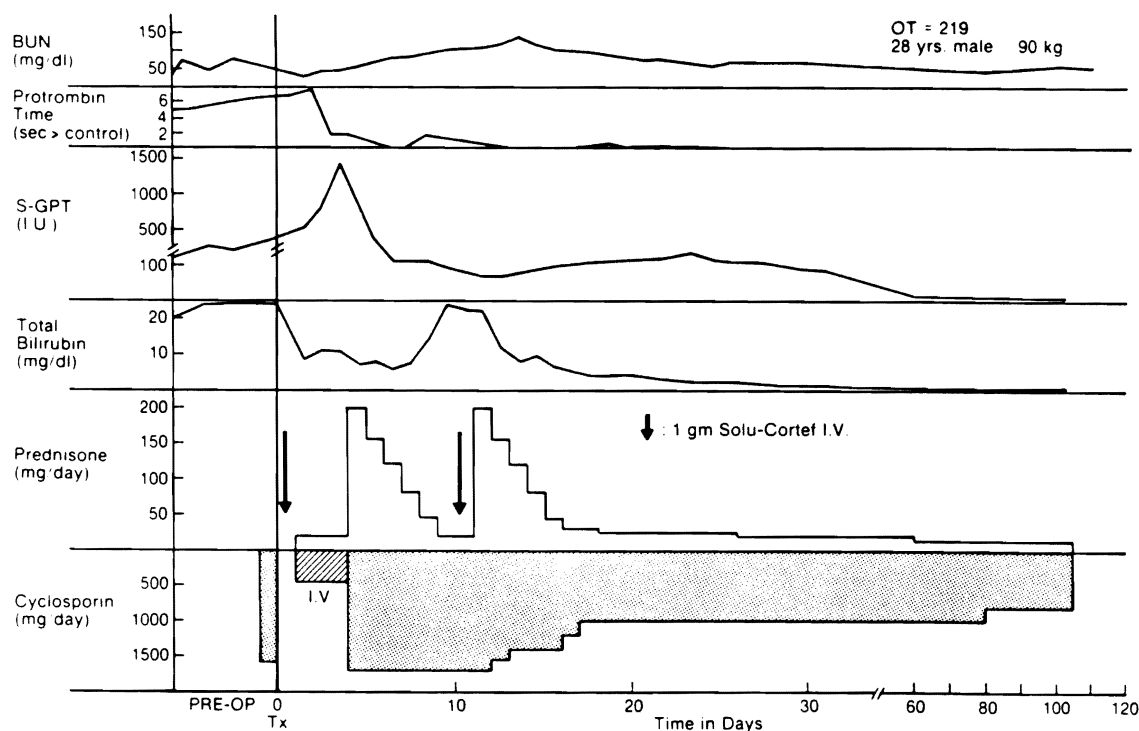
Most of the experience of Calne et al.<sup>56</sup> has been with delayed administration of this drug. Azathioprine (1.5 mg/kg/day) and prednisolone (0.4 mg/kg/day) were used by them until renal and hepatic function were adequate. Then 10 mg/kg/day of cyclosporine was begun, and the steroid dose was slowly reduced to zero. The supervision of acute rejection during the interval of treatment with azathioprine and prednisone had been troublesome; Calne et al.<sup>56</sup> recommend shortening this period.

**Rejection Under Immunosuppression.** Porter,<sup>145</sup> of London, studied the problem of

hepatic rejection and immunosuppressive therapy in a variety of species, including man, and pieced together a clear picture in 1969 that remains unchallenged today. The concepts that came from his descriptions were developed with conventional immunosuppression, but in any given case they apply without revision when cyclosporine-steroid therapy is used.

The first sign of rejection in untreated animals or in human recipients is the appearance in the liver of lymphoid cells (many with pyroninophilic cytoplasm) that leave the portal vein ramifications and probably the small arterial branches throughout the graft, accumulate in the portal tracts, and enter the central vein and the endothelial lining of the sinusoids. The cells invade the spaces of Disse, and some insinuate themselves between hepatocytes. With cellular infiltration, many of the sinusoids disintegrate, the blood flow through the liver begins to decrease,<sup>12</sup> and some centrilobular cells die. Centrilobular necrosis progresses to mid-zonal necrosis, and liver function begins to deteriorate. At this late time (but not before), immunoglobulins and complement can be found in the walls of small arteries, some of which develop fibrinoid necrosis.

Most of the foregoing studies were in dogs. When rejection is mild, as in pigs,<sup>146</sup> or when



**Figure 176-14.** Deviation from standard steroid therapy in a patient whose perioperative condition was frail. The 5-day burst of postoperative steroids was begun several days postoperatively but had to be repeated when rejection supervened. Before operation, the patient had the hepatorenal syndrome and encephalopathy and had been on a ventilator for more than 1 week. Because of defective clotting, efforts to place central venous lines before starting transplantation resulted in uncontrolled hemorrhage with loss of 20 liters of blood. The subclavian and innominate vessels were explored through cervical and thoracotomy incisions, and the bleeding was mechanically controlled before transplantation was started. The blood loss from placement of the vascular lines exceeded that incurred during transplantation. The patient survived because of prompt correction of the coagulation abnormalities. (From Starzl TE et al. *Hepatology* 1982; 2:614-36. Reproduced with permission of the American Association for the Study of Liver Disease and Williams & Wilkins.)

it is modified by treatment with immunosuppressive agents, as in dogs, rats, and man,<sup>145,147-149</sup> the destruction of hepatocytes ceases, cellular infiltration diminishes and may disappear, and the central part of the lobular reticulin framework often collapses. Marked accumulation of bile in the surviving centrilobular hepatocytes and the bile canaliculi occurs, accounting for the hyperbilirubinemia that is characteristic of subacute and chronic rejection. A precise explanation of the cholestasis has not been established. Larger intralobular bile ducts become scarce in some patients as modified rejection becomes chronic.<sup>78,79,145,150</sup>

The progression from acute modified rejection to chronic rejection is not precise. Connecting bands of reticulin are often laid down between the central areas subdividing the lobules. On this framework, fibrosis may develop that can progress to true cirrhosis. Another characteristic feature of chronic re-

jection is intimal and subintimal thickening of the kind that has been seen in the arteries of renal and cardiac grafts. These vascular changes may or may not be associated with the intramural deposition of immunoglobulins and complement.<sup>151</sup>

The clinical manifestations of these pathologic changes have been varied, prompting attempts at classification by us<sup>13,29</sup> and by Williams and Calne.<sup>31</sup> The systemic manifestations can include fever, malaise, anorexia, and depression. The grafts can become swollen and hard, and the patients may complain of right upper quadrant tenderness. Liver scans, whether involving parenchymal or reticuloendothelial function, show poor uptake of the isotope. Poor synthetic function of the graft is detected most easily by measurements of prothrombin time. Jaundice usually develops and may increase very slowly or with astonishing rapidity. Elevations in activity of the aminotransferases usually are seen

and, if these are extreme, prognosis is guarded. Occasionally, we have seen all of the manifestations of rejection but with minimal or no increases in serum bilirubin concentration; biopsies in these cases have shown marked cellular infiltration. This has been called "anicteric" rejection.<sup>13</sup>

The clinical syndrome just described, with any or all of its permutations, is non-specific. Hepatic injury, biliary obstruction, cholangitis, hepatitis, and drug toxicity have been proved to be alternative explanations. For this reason, if the postoperative evolution has not been satisfactory, diagnostic procedures such as cholangiography and needle biopsy must be promptly considered. Meanwhile, the steroid dosage is temporarily increased with the understanding that it will be returned to baseline if a diagnosis other than rejection can be made. The possibility of an error in diagnosis is greatly increased and management made more difficult if good initial graft function is not achieved.

Hepatic blood flow is drastically reduced with severe rejection,<sup>12</sup> making the ischemic liver unusually susceptible to bacterial invasion. Interaction has been shown in animal<sup>152</sup> and in human<sup>13,153-155</sup> studies between rejection and homograft bacterial colonization. Paradoxically, one of the important ways to prevent transhepatic infection of this kind is to protect the graft with potent immunosuppression, especially during the early postoperative period. In addition, systematically designed antibiotic therapy should be given intraoperatively and for several days afterwards.

The clinical diagnosis of chronic rejection has been restricted to patients whose graft biopsies showed the arterial intimal thickening, hepatic fibrosis, and other findings alluded to before. The morphologic findings of chronic rejection have not been directly related to the postoperative interval, since they have been seen within the first few months. The clinical manifestations of chronic rejection have been similar to those with chronic liver failure from end-stage liver diseases of different causes. In contrast to acute rejection, chronic rejection cannot be effectively treated with increased immunosuppression.

**Survival After Liver Replacement.** The introduction of cyclosporine-steroid therapy has had a major influence on the results after orthotopic liver transplantation.

*The Precyclosporine Era.* From 1963 to

1979, 170 patients underwent orthotopic liver transplantation with conventional double drug or triple drug therapy. The 1-year survival ranged between 28.8% and 50% throughout this time, but without an identifiable trend of improvement. The results during this 16-year period are summarized in Figure 176-15.

Of the 170 patients in this series, 56 lived out the first postoperative year, 23 of whom subsequently died.<sup>29</sup> Although 13 of the 23 late deaths were in the second postoperative year, losses occurred as late as 6 years. Of the original 170 patients, 33 (19.4%) are still alive after follow-ups of 3½ to 13½ years. Adult and pediatric recipients were almost equal (Tables 176-1 and 176-2). From the sixth month onward, the younger patients had about a 10% survival advantage.

Occasional spectacular successes interspersed with a larger number of failures were also the experience of the Cambridge-King's College trials from the beginning of that program in 1968 through early 1980.<sup>56, 60</sup> In the English series, 22 (23.7%) of the first 93 recipients lived for at least 1 year, with 11 subsequent deaths during the second to sixth years; at the time of last reporting, the 11 survivors had been followed for 1 to 6 years.

*The Cyclosporine Era.* The predictability and reliability with which liver transplantation could be carried out improved abruptly with the first trials of cyclosporine-steroid

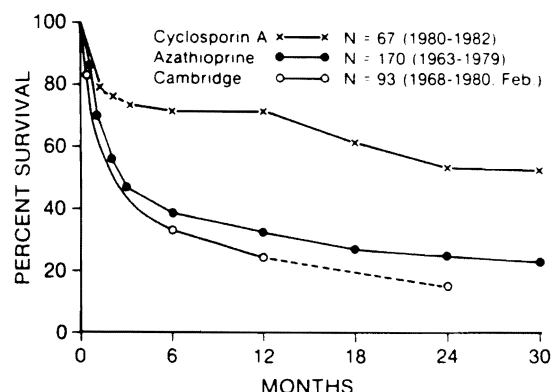


Figure 176-15. The actuarial survival of patients treated with cyclosporine and low-dose steroids compared with the actual 1-year survival obtained under conventional immunosuppression. The data for the Cambridge curve were obtained from published reports.<sup>56, 60</sup> (From Starzl TE et al. *Hepatology* 1982; 2:614-36. Reproduced with permission of the American Association for the Study of Liver Disease and Williams & Wilkins.)

therapy,<sup>29,140-142</sup> and this improvement has been sustained. Since 1980, the majority of liver recipients have been able to leave the hospital for out-patient care. By May 1, 1982, 40 recipients had been treated with this new immunosuppressive agent, with the survival projections shown in Figure 176-15. Since then, the survival of pediatric recipients has been maintained at about the same level, although less favorable results in adults have brought the 1-year survival curve down. In addition, 3 of the patients treated with cyclosporine and steroids who reached or passed the 1-year mark died in their 13th, 16th, and 20th postoperative months. The causes of the late deaths were recurrent carcinoma, recurrent Budd-Chiari syndrome, and chronic rejection (with unsuccessful retransplantation).

The influence of cyclosporine upon survival in the Cambridge-King's College trials has not been clearly defined, in part because the drug has not been used regularly and in part because it had been started late in most cases after an initial course of azathioprine and steroids. Nevertheless, improved results have been attributed by Calne et al.<sup>56</sup> to the better immunosuppression which they can now provide with delayed cyclosporine.

**Causes of Mortality.** The principal mortality after liver transplantation has been early in both the initial trials of liver transplantation under conventional immunosuppression and those with cyclosporine-steroid therapy. Detailed analyses of the causes for this mortality have been published.<sup>13,29,51,54,88</sup> Throughout the years, the causes of failure have included the use of grafts damaged by ischemia, massive operative hemorrhage, thrombosis of the reconstituted homograft blood supply, intraoperative cerebral air embolism, unsuspected recipient abnormalities (particularly of the porta hepatis structures), hopeless anatomic situations created by multiple previous operations, irreversible pre-existing debilitation, and defective biliary tract reconstruction. Acute or subacute homograft rejection was also a factor, but its dimensions could not be clearly delineated. At necropsy, histopathologic findings of acute rejection have been found in a minority of cases. This prompted speculation in the earlier days, when biopsy was not often performed, that excessive immunosuppression, especially with prednisone, may have been responsible for unnecessary deaths.

However, when serial biopsies were obtained in later cases,<sup>29,51,54</sup> this view had to be revised. Many of the biopsy specimens contained unmistakable findings of rejection for which the appropriate response had been more steroids. Yet, after death, which was most commonly caused by terminal infection, findings of rejection were absent. This same chain of deadly events is still seen, but less frequently than before.

Assessment of the reasons for late deaths, by contrast, has been less ambiguous. Recurrent liver failure was responsible for the deaths of three-quarters of the 26 patients who died after 1 year, if the 5 who died after attempted retransplantation are included.<sup>29</sup> The dominant pathologic diagnoses in late failing grafts have been chronic rejection in the majority of cases, with biliary obstruction, recurrent carcinoma, chronic hepatitis, portal vein thrombosis, and recurrent Budd-Chiari syndrome being progressively more distant contenders.<sup>29</sup>

These findings in long-term surviving patients are remarkably different from those reported by Calne et al.<sup>56</sup> in 11 patients who died after 1 year. Recurrent carcinoma was the main homograft abnormality in 5 of their patients. Biliary sludge and cholangitis were found in the other 6 grafts. Chronic rejection was not mentioned. Reconciliation of this divergence of observation will be important. Our findings suggest that ongoing problems with immunologic control will continue to take a gradual toll long after transplantation, whereas the interpretation of the pathologic findings in the English recipients diminishes the importance of chronic rejection.

**Steps to Reduce Mortality.** A glance at the life survival curves from the earlier days of our experience, or even later (Fig. 176-15), shows that the highest priority for improved management is reduction of the perioperative mortality. However, the fact that the survival curves continue to decline even after 3 or 4 months means that strategies to circumvent late mortality will also be important. Consideration of policy adjustments that may have an impact in both periods is, therefore, of importance.

**Recipient Selection and Work-up.** The way in which the original disease dictates the technical difficulty of transplantation (see earlier section on Indications) was not clearly perceived until relatively recently. The consequent hidden risk factor could be improved

by trying to treat patients with "dangerous" diseases (such as postnecrotic cirrhosis, alcoholic cirrhosis, and secondary biliary cirrhosis) at an earlier time. When such patients have had previous operations at or near the hepatic hilum (such as repeated biliary tract reconstructions or, especially, portacaval shunts) liver transplantation is no longer a reasonable option in some cases, especially if the patient's physical and metabolic deterioration is extreme. Almost all of our deaths on the operating table, and many not long afterwards, have been in such patients.

The question of veno-venous bypasses during removal of the recipient liver and implantation of the new organ was discussed earlier. If candidates are accepted who have undergone a previous portacaval shunt, standby provisions should be made for the bypass, since the venous collaterals that usually make it safe to occlude the inferior vena cava and portal vein are apt to have undergone involution. Occasional other patients may be candidates for veno-venous bypasses, but none with the predictability of the patient with previous portacaval shunt.

Reservations were also expressed earlier about liver transplantation for postnecrotic cirrhosis in hepatitis B-virus carriers and patients with hepatic cancer. Evidence is insufficient to foreclose this avenue of treatment, but workers in the field must pool data to arrive at a consensus. Too many late deaths have occurred from recurrence of these diseases.

Incomplete knowledge of recipient anatomy cannot be accepted in future cases. Of all the adverse possibilities, an inadequate recipient portal vein is the most serious and the only one for which there usually is not a technical remedy. The means available to detect a defective portal vein must be employed to the fullest.

**Improvements in Criteria for Acceptable Donor Livers.** Defective vascular or biliary tract anastomoses have become uncommon. The single most common problem is now the marginally functioning donor liver. When this has occurred, the orderly stages of donor liver removal have been found to be abridged or otherwise changed from the standard procedure. Another contributory factor has been acceptance of a physiologically unstable donor who frequently has required large amounts of vasopressor medications for maintenance of blood pressure. The investment of so much time and effort by the

physicians who obtained permission to remove the liver or by the donor team (which frequently has flown to a distant city) may create a powerful compulsion to proceed in spite of warning signs. Abandonment of the donor effort under questionable circumstances will be increasingly necessary.

**Retransplantation.** When a transplanted liver fails from rejection reaction or other causes, aggressive attempts at retransplantation usually offer the only chance for survival. One of the most common judgment errors we have made is to hope vainly for improvement in hepatic function until the chance for reintervention is lost. Despite this, more than 30 patients have undergone retransplantation since 1968.<sup>29</sup> These efforts have become encouraging. More than a dozen patients treated in 1980 to 1982 had retransplantation a few days to 20 months after primary grafting and the majority are surviving with subsequent follow-up periods of up to 1½ years.

The performance of retransplantation has usually been surprisingly easy. The procedure has been greatly simplified by retaining cuffs from the suprahepatic and infrahepatic vena cava and from the portal vein of the first graft. Usually, performing the arterial anastomosis proximal to the previous site of anastomosis has been necessary.

**Option of Auxiliary Liver Transplantation.** Clinical efforts to transplant an extra liver (auxiliary transplantation) without removal of the diseased native organ have been discouraging.<sup>156</sup> Of more than 50 well-documented auxiliary transplantations, only 2 could be pronounced unequivocal successes—one in New York City<sup>156</sup> and the other in Paris.<sup>157</sup>

Auxiliary liver transplantation may be useful in patients with potentially reversible hepatic disease. The extra liver could be used as a temporary support organ and later removed. We are seeing more patients with chronic disease whose portal veins have clotted in the hepatic hilum, making it technically impossible to consider liver replacement. Auxiliary liver transplantation might be an option in such patients or in patients with extensive previous surgery in the right upper quadrant for whom orthotopic transplantation would be excessively difficult or impossible.

**Potential Role of Liver Transplantation.** A plan to organize a network of liver transplantation centers is in the embryonic stages of

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development. The required surgical techniques are within the grasp of many practicing surgeons, and the improvements in immunosuppression of the last few years should make postoperative management a reasonable exercise. Moreover, the number of *bona fide* candidates for this procedure per year will probably be in the thousands even if more rigid criteria of selection are imposed than in the past. All of these could influence decisions about treatment earlier in the course of several hepatic diseases.

Avoidance of major and often futile surgical operations that can jeopardize the ultimate candidacy for transplantation will be increasingly important. Fortunately, alternative approaches are available. Sclerosing therapy for the control of variceal hemorrhages instead of portal diversion has become increasingly accepted. Bile duct strictures in sclerosing cholangitis and other diseases may now be managed, at least palliatively, by non-surgical means. Better guidelines will need to be developed for procedures such as porticoenterostomy (Kasai operation) so that infants with biliary atresia who might benefit from this operation, but who could be rendered non-transplantable by extensive or multiple and futile procedures, could be selected out from those whose chances of palliation are poor.

Much new basic knowledge about the liver should become available as a result of transplantation. Information has already been gathered about the synthesis of proteins whose origin previously was not clear.<sup>7,32,158-160</sup> In the same context, information is accruing about several inborn errors of metabolism. Rarely has such an opportunity been possible to combine meaningful and basic scientific inquiry with the humanitarian pursuit of improved patient care.

### Partial Hepatectomy

The stimulus for the development of methods of partial resection of the liver was the referral for transplantation of many patients whose hepatic tumors involved most (but not all) of the liver. Hence, treatment of patients who had extensive but resectable lesions became a peripheral function of the liver transplantation service. During a 17-year period from October 1964 to March 1982, 150 subtotal liver resections were performed on our service.<sup>161</sup>

### Work-up of Localized Hepatic Lesions.

We have become increasingly partial to CT scans as the imaging procedure to help decide the extent of the lesions and to plan how much liver must be removed. By viewing tomograms at different levels, a 3-dimensional picture of the lesion can be constructed, and from this, how the mass relates to the anatomic segments of the liver may be determined. Also, cystic lesions can be distinguished from solid masses and vascularity revealed with adjunctive use of IV contrast infusion. Thus, our dependence on other imaging and diagnostic techniques has lessened and we no longer routinely obtain pre-operative angiograms. A variant arterial blood supply to the liver can easily be identified at the time of operation.

We do not recommend blind or radiographically guided needle biopsy of localized hepatic lesions prior to surgery. Biopsies by referring surgeons or physicians have precipitated emergency operations in several of our patients who had hemangiomas, adenomas, or highly vascular malignancies. Aside from the risk of hemorrhage and the possibility of tumor spread, the small specimen obtained by a needle biopsy may not be adequate to differentiate a malignant tumor from a benign one.

Past medical history, review of operative records, and re-examination of previously obtained tissue should not be neglected prior to operation. Detailed history, careful physical examination, and proper use of laboratory tests such as the hepatitis screen and assays of carcinoembryonic antigen (CEA) and alpha-fetoprotein are often helpful in making a correct diagnosis. The work-up to identify a primary tumor of non-hepatic origin that may have spread to the liver or a tumor that may represent spread from a primary cancer of the liver is described in other chapters, in which these tumors are the subject of prime concern.

**Kinds of Hepatic Resections.** The term "local excision" has been used for resections that do not follow intersegmental or lobar planes. Many benign lesions are ideally treated this way, since a clean plane can often be developed where the mass has compressed adjacent liver tissue. However, the word "local" can be misleading because the masses can be enormous in size, replacing most of the liver. Thus, a local excision can be as difficult and time-consuming as a formal resection.

The 4 anatomic resections commonly practiced<sup>162</sup> consist of removal of the true right lobe, the true left lobe, the lateral segment of the left lobe, and the right lobe plus the medial segment of the left lobe (*right hepatic trisegmentectomy*) (Fig. 176-16).

A fifth resection has been described,<sup>163</sup> in which the full left lobe plus the anterior segment of the right lobe is excised (*left hepatic trisegmentectomy*). With this operation, lesions involving predominantly the left lobe but extending into the anterior portion of the right lobe (previously considered unresectable) can be removed.

The liver segmental anatomy that was the basis for these resections was clarified by Healey and Schroy,<sup>164</sup> Goldsmith and Woodburne,<sup>165</sup> and Couinaud,<sup>166</sup> whose studies, in turn, were founded on previous ones by American and European workers.<sup>167,168</sup> McIndoe and Counseller<sup>167</sup> first showed that the division between the true right and left lobes of the liver is not at the falciform ligament, but rather at a line going through the bed of the gallbladder and projecting posteriorly toward the venae cavae (Fig. 176-16). Each lobe is further divided into 2 segments: the right lobe into anterior and posterior segments and the left lobe into lateral and medial segments. The branches of the portal vein, hepatic artery, and bile duct conform to this

segmental organization. Many of the ramifications of the larger hepatic veins are distributed between rather than within segments and lobes.

All of the major hepatic resections, except left trisegmentectomy,<sup>163</sup> were actually performed before the segmental and lobar anatomy was understood. Because of this, accurately establishing priority for the first right or left lobectomy and left lateral segmentectomy has not been possible.<sup>169</sup> Right trisegmentectomy was first performed more than 30 years ago by Wangenstein,<sup>170</sup> Lortat-Jacob and Robert,<sup>171</sup> and Quattlebaum,<sup>172</sup> but its forbidding mortality prevented wide use. In 1975, we described in detail a safe technique of right trisegmentectomy<sup>162</sup> and demonstrated its relation to other resections. A modification of the original technique was later reported that has been particularly useful for bulky superior and posterior hepatic tumors, including those that invade the diaphragm.<sup>173</sup>

With any of these resections, bleeding at the site of parenchymal transection can be severe. If so, the porta hepatis can be temporarily cross-clamped (the Pringle maneuver). Huguet and co-workers<sup>174</sup> reported that normothermic ischemia of the human liver usually can be tolerated for more than an hour, far longer than the previously accepted 15- or 20-minute time limit.

**Drainage and Other Care.** The subphrenic space must be adequately drained after partial hepatectomy. Multiple closed-system suction drains can be placed in the huge dead space, or open drainage may be performed with multiple 1-inch Penrose drains. T-tube biliary drainage is not necessary unless the biliary system has been injured. An exception is left trisegmentectomy, after which T-tube drainage should be instituted with the upper limb of the tube passing into the remaining posterior segmental duct; this duct otherwise tends to become angulated.<sup>163</sup>

Prophylactic antibiotics are started preoperatively and continued for several days. Intraoperative correction of coagulopathy is important when transfusion of a large amount of blood is required. Fear of hypoglycemia has been overemphasized. Usually, infusion of a 5% glucose/electrolyte solution is sufficient to maintain an adequate blood glucose level during and after operation. Transient jaundice and depression of multiple hepatic functions are often seen after right triseg-

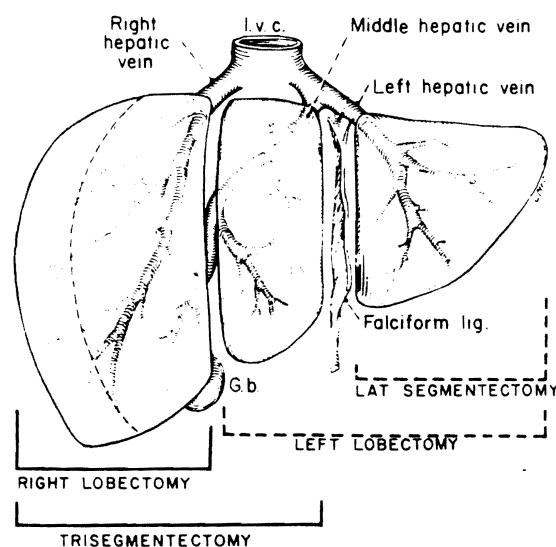


Figure 176-16. The 4 usual kinds of partial hepatectomy. A fifth resection, left trisegmentectomy, involves removal of the true left lobe plus the anterior segment of the right lobe. (From Starzl TE et al. Surg Gynecol Obstet 1975; 141:37. Reproduced with permission.)



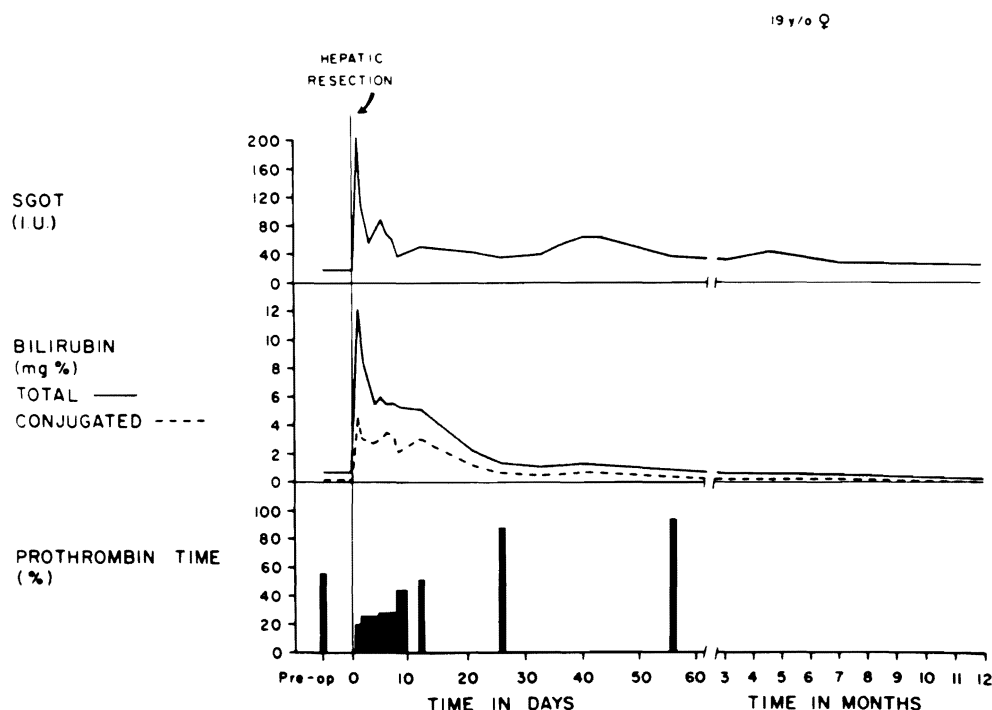


Figure 176-17. Postoperative evolution after an unusually extensive right trisegmentectomy. (From Starzl TE et al. *Am J Surg* 1975; 129:587-90. Reproduced with permission.)

mentectomy, but even after an 85% resection,<sup>175</sup> relatively complete recovery may occur within 3 or 4 weeks (Fig. 176-17). Jaundice has been unusual in the other kinds of resections.

**Indications for Hepatic Resection.** The diseases for which 150 resections were carried out in our institutions are listed in Table 176-5. Most of the hepatic lesions requiring partial hepatectomy are represented. As shown, the majority were primary or metastatic malignant tumors, but 64 (43%) were histopathologically benign lesions.

#### Benign Lesions

**CAVERNOUS HEMANGIOMA** (see Chapter 172). Of the 32 patients who underwent resection for this lesion, 3 had spontaneous hemorrhage and 2 more had emergency resection for bleeding after unwise needle biopsies. The others had significant complaints related to the tumor, including pain, pressure symptoms, and early satiety with weight loss. Most of the tumors were large and qualified for the term "giant cavernous hemangioma" introduced by Adam et al.,<sup>176</sup> in that they were at least 4 cm in diameter. The majority of the hemangiomas could be excised locally, but 18 required anatomic re-

moval of a segment, lobe, or (in 6 cases) 3 segments, all without mortality.

Cavernous hemangiomas are the most common benign neoplasms of the liver,<sup>177</sup> (Chapter 172) and judgment is important in recommending their removal. Most are asymptomatic and are found incidentally during investigation or at operation for other conditions. We have recommended that most asymptomatic cavernous hemangiomas be observed, provided the diagnosis is certain<sup>178</sup>; CT scans with contrast injection and arteriography can give such assurance with almost total accuracy.<sup>179,180</sup> Failure to assess presumed hemangiomas completely can lead to tragedy. We have seen 2 lesions misdiagnosed as cavernous hemangiomas, one of which turned out to be an adrenocortical carcinoma and the other an angiosarcoma.

**ADENOMA.** (see Chapter 172). Of the 14 patients in our series with this type of tumor, 11 were women of child-bearing age and 3 were men aged 25, 34, and 67 years. Most of the tumors were symptomatic, usually with pain or vague sensations of right upper quadrant pressure, and 5 had ruptured, necessitating immediate operation because of intra-abdominal hemorrhage. Three patients had multiple adenomas in all 4 segments of the



Table 176-5. INDICATIONS FOR 150 LIVER RESECTIONS

Disease	No. Cases
<i>Benign Diseases</i>	<i>64 cases</i>
Hemangioma	32
Adenoma	14
Cysts:	7
Simple (4)	
Polycystic (2)	
Echinococcal (1)	
Focal nodular hyperplasia	4
Trauma	3
Abscess	1
Fibroma	1
Leiomyoma	1
Regenerative nodule	1
<i>Malignant Diseases</i>	
Primary malignant neoplasms:	<i>43 cases</i>
Hepatocellular carcinoma	29
Squamous cell carcinoma of cyst wall	3
Hepatoblastoma	2
Cholangiocarcinoma	2
Rhabdomyosarcoma	2
Leiomyosarcoma	1
Angiosarcoma	1
Sarcoma, undetermined cell type	1
Cholangiocarcinoma of bile duct	1
Adenocarcinoma of gallbladder	1
Metastatic neoplasms:	<i>43 cases</i>
Colorectal adenocarcinoma	24
Carcinoid tumor	3
Adrenocortical carcinoma	3
Wilms' tumor	3
Adenocarcinoma of kidney	2
Spindle cell sarcoma of intestine	2
Leiomyosarcoma of stomach	1
Glucagonoma	1
Neuroblastoma of adrenal	1
Melanoma of eye	1
Hemangiosarcoma of breast	1
Medullary carcinoma of thyroid	1
Squamous cell carcinoma of endocervix	1
Ovarian carcinoma	1
<i>Total</i>	<i>150</i>

liver with massive hepatomegaly and complications that singly or in combination included pain, disabling pressure symptoms, or hemorrhage.

Most authorities agree that adenomas require resection in all but exceptional cases<sup>181,184</sup> (Chapter 172). A conservative approach carries too great a risk of rupture or hemorrhage and in addition the distinction between adenoma and minimum deviation hepatocellular carcinoma may be difficult. Anatomic hepatic resection is usually advisable, but smaller adenomas can be excised

locally (Table 176-6). In the 3 patients who had multiple adenomas in all 4 sections of the liver, right trisegmentectomy was performed with the expectation that the remaining adenomas in the left lateral segment would not grow rapidly. This hope was not realized in 1 of the 3 patients who, within 14 months, redeveloped the portal vein and inferior vena caval obstructions that had precipitated the resection. The residual lateral segment was removed and replaced with a liver homograft and the patient is well 1 year later. The 2 other patients whose liver remnants contained adenomas are now 12 and 20 months postoperative, respectively.

Return of adenomas has not been seen in any of the patients who had single lesions. All of the women in this group were advised not to use oral contraceptive pills, although less than half of the women had ever been on oral contraceptives before the development of adenomas. The connection between contraceptives and hepatic adenomas was made by Baum<sup>185</sup> and confirmed by others, but Guzman et al.<sup>186</sup> questioned if the incidence of these lesions has actually increased while conceding that their growth and propensity to hemorrhage may be related to the pill.

Terblanche<sup>187</sup> recommended a more conservative approach to treatment, including arterial embolization of the adenomas. Others<sup>188-192</sup> have recommended discontinuance of oral contraceptives with subsequent watchful waiting, but this may be a dangerous management principle.

**FOCAL NODULAR HYPERPLASIA.** Such lesions do not have a high occurrence rate of spontaneous hemorrhage<sup>192</sup> and are usually small and asymptomatic. They are often found incidentally at the time of operation or during diagnostic work-ups for abdominal symptoms. Diagnostic uncertainty may lead to exploratory surgery and resection. We have seen very large and symptomatic focal nodular hyperplasias, necessitating resections of the magnitude of right trisegmentectomy.

**CYSTS.** (see Chapter 170). The treatment of symptomatic non-parasitic simple cysts is still controversial. Some advocate that the solitary cysts with clear fluid be unroofed and drained into the peritoneal cavity and that cysts with bile-stained fluid be drained with a Roux-en-Y jejunal limb.<sup>193</sup> We recommend resection of such cysts. They can be excised locally or removed by anatomic resection

Table 176-6. EXTENT OF LIVER RESECTION, ITS INDICATIONS AND OPERATIVE MORTALITY (150 RESECTIONS)

	Right		Left		Right Lobectomy		Left Lobectomy		Left Lateral Segmentectomy		Local Excision	
	No. pts.	No. operative deaths*	No. pts.	No. operative deaths	No. pts.	No. operative deaths	No. pts.	No. operative deaths	No. pts.	No. operative deaths	No. pts.	No. operative deaths
Benign Diseases	14	1	1	0	18	1	5	0	4	0	22	0
Hemangioma	5	—	1	—	8	—	1	—	3	—	14	—
Adenoma	6	—	—	—	6	—	1	—	—	—	1	—
Focal nodular hyperplasia	1	—	—	—	—	—	—	—	1	—	2	—
Cysts	1	—	—	—	1	—	2	—	—	—	3	—
Trauma	—	—	—	—	2	—	1	—	—	—	—	—
Others	1	1	—	—	1	1	—	—	—	—	2	—
Malignant Diseases	50	3	3	0	13	1	8	0	9	0	3	0
Primary	26	3	2	—	5	1	5	—	3	—	2	—
Metastatic	24	—	1	—	8	—	3	—	6	—	1	—
Total	64	4 (6.3%)	4	0	31	2 (6.5%)	13	0	13	0	25	0

\*Operative death is defined as any death within 30 days as well as any death during the initial hospitalization for liver resection regardless of time.

(Table 176-6). Although malignant change in the cyst wall is uncommon, we have treated 3 patients who developed squamous cell carcinoma in the cyst wall (Table 176-6); 2 of the 3 were previously operated upon with the Roux-en-Y internal drainage technique.

The pressure symptoms of polycystic disease of the liver can sometimes be palliated with multiple needle aspirations. Operative marsupialization, incisional drainage, or aspiration of large cysts cannot relieve the symptoms better than can simple percutaneous needle aspirations. Therefore, operation for polycystic disease is rarely justified. However, occasional patients have a dominance of normal tissue in the lateral segment of the liver. We have treated 2 such patients by right trisegmentectomy with prolonged symptomatic relief (Table 176-6). Hydatid cysts may be an indication for hepatic resection (see Chapter 232).

**OTHER BENIGN LESIONS.** Rare benign tumors, such as *fibroma*, *rhabdomyoma*, and *leiomyoma*, have been treated by hepatic resection. Anatomic resection is sometimes the best surgical procedure to control hemorrhage if severe trauma has involved an entire lobe.<sup>194</sup>

**Malignant Lesions** (see Chapters 173, 174, and 175). As long as the malignant lesion is localized in 3 or 4 segments of the liver, curative subtotal hepatectomy theoretically can be achieved. Forty-three of the 150 patients in our hepatic resection series had primary malignant lesions; hepatocellular carcinoma was by far the most common (Table 176-5). Localized metastatic tumors have also been resected whenever possible with an aggressive approach particularly directed at metastases from primary colorectal cancers (Table 176-5).

### Results of Hepatic Resection

**Mortality.** Any death within 30 days of operation or during the hospitalization for surgery, regardless of time, should be counted as an operative death. Intraoperative deaths have become unusual. Deaths caused by hepatic insufficiency are usually postponed for more than a month with good supportive therapy. The mortality of hepatic resection is influenced significantly by the indication and the underlying liver disease as well as the extent of the resection.

Six of our 150 patients who underwent liver resection died, an operative mortality of

4.0%. Details of the mortality after various kinds of resections are given in Table 176-6. The mortality after resection for benign and malignant disease was 3.1% (2 of 64) and 4.7% (4 of 86), respectively. The circumstances of the deaths are summarized in Table 176-7. Four of the 6 deaths were in patients with severe underlying liver disease (including 3 with cirrhosis). Six of the 150 patients who underwent liver resection were cirrhotic patients. Since 3 of them died, they accounted for half of our operative mortality. Some patients with compensated cirrhosis can tolerate conservative hepatic resection, as has been documented by Asian surgeons.<sup>195-200</sup>

The operative mortality of liver resections reported in the English literature since 1970 is summarized in Table 176-8. According to Foster's review,<sup>201</sup> the operative mortality of liver resection for primary liver cancer was 24% before 1970. Since then, the operative mortality reported from major centers has decreased substantially (Table 176-8). The operative mortality of liver resection for metastatic tumor may be even less. We have treated 43 patients with metastatic liver tumor without a death in spite of the fact that 36 of the resections were of one or more lobes (Table 176-6). By contrast, Morrow et al.<sup>202</sup> reported an operative mortality of 20%. Anatomic resections for metastatic tumor will soon be performed in major centers for liver surgery with an operative mortality of less than 5%.

**Morbidity.** Transient hyperbilirubinemia (Figure 176-17), ascites, and edema occasionally develop after major hepatic resection. Prolonged prothrombin time and hypoalbuminemia may also occur (Fig. 176-17), but they usually are self-limited and not clinically significant. If the abnormal values are not spontaneously corrected within a week or 10 days, surgical complications should be looked for. The complications encountered in our 150 resections (Table 176-9) are similar to those reported by others.

Three of the 150 patients required re-exploration for postoperative bleeding. The hemorrhage, which was from the raw liver surface, was controlled in each case, but a patient whose resection was for a misdiagnosed giant hyperplastic nodule died subsequently of hepatic insufficiency (Table 176-7). Twelve patients had abscesses form in the right subphrenic space. The pus collections

Table 176-7. TIME AND CAUSE OF OPERATIVE MORTALITY FOLLOWING LIVER RESECTION

Case	Original Diagnosis	Final Diagnosis	Procedure	Time of Survival (days)	Cause of Death
1	Hepatocellular carcinoma*	Same	RTS†	20	Hepatic failure; thrombosis of celiac axis
2	Hepatocellular carcinoma in cirrhotic (Thorotrast) liver	Same	RTS	58	Hepatic failure; pulmonary metastases
3	Infected hepatocellular carcinoma	Fungal and bacterial abscess; thrombosis of intrahepatic portal and hepatic veins	RTS	32	Hepatic failure; stress ulcer hemorrhage
4	Hepatoma	Same	RTS	45	Hepatic failure; stress ulcer hemorrhage
5	Hepatoma in cirrhotic liver	Same	RL‡	0	Unrecognized perforation of central venous catheter into mediastinum; hypovolemia and mediastinal tamponade
6	Ruptured hepatocellular carcinoma in cirrhotic liver	Giant regeneration nodule in cirrhotic liver	RL	4	Hepatic failure

\*Case previously reported.\* A reversed vena caval graft had been used to drain the residual lateral segment after the remaining left hepatic vein had been resected.

†RTS: right trisegmentectomy.

‡RL: right lobectomy.

were drained in 6 instances by reopening prematurely closed anterior drain tracts at or near the body wall. Six abscesses were drained posteriorly by removing the right twelfth rib. Posterior drainage procedures were carried out in 6 other patients in the early postoperative period because of difficulty in effectively irrigating deeply placed cavities from the anterior approach. The complications occurred almost uniformly after right trisegmentectomy.

Major bile leaks occurred after 2 right and 2 left trisegmentectomies. A portion of the bile duct to the residual liver had been involved with tumor in each instance and had been resected, the bile ducts being reconstructed over a T-tube or U-tube stent. The bile leaks ceased spontaneously without further operative intervention. Minor bile leaks through the drain were common, but these all closed spontaneously. Two patients developed bile duct obstruction several months after right trisegmentectomy in one and left lobectomy in the other; the cause was recurrent tumor in both cases. The obstruction was distal in the patient with left lobectomy and was relieved by anastomosing the unin-

involved proximal common duct to a Roux-en-Y jejunal loop.

Two patients had major stress ulcer hemorrhage and hepatic insufficiency after right trisegmentectomy. Both of these patients died (Table 176-7). Another patient developed a small bowel obstruction 2 weeks after right lobectomy, requiring lysis of the responsible adhesions.

**Survival.** The 62 patients with benign disease who survived the operation were alive and relieved of symptoms as of October 1982 (minimum follow-up of 6 months). Only one had late complications—a woman who developed hepatic adenomatosis in the residual left lateral segment after right trisegmentectomy and who was treated with orthotopic liver transplantation.

The actuarial survival of our 86 patients with hepatic malignancy is shown graphically in Figures 176-18 and 176-19. The 3-year survival in patients with primary hepatic malignancy was 56% (Fig. 176-19), and with metastatic liver neoplasms the survival was 66%. Actuarial survival 5 years after liver resection for primary hepatic malignancy was 46% and for metastatic neoplasms it was

Table 176-8. OPERATIVE MORTALITY AND LONG-TERM SURVIVAL AFTER LIVER RESECTION

Investigators	Indications	No. Patients	Operative Mortality*	Survival			
				1 Year	2 Years	3 Years	5 Years
Foster <sup>201</sup>	Primary liver cancer	296	24.0% (A)		33.3%		14.0%
		Asian	24.0% (A)		23.0%		6.0%
		Non-Asian	22.0% (A)		59.0%		36.0%
		400					
Foster <sup>207</sup>	Metastatic tumors	400	11.0% (A)				
	Colorectal cancer	192			44.0%		22.0% †
Lin <sup>195, 196</sup>	Primary liver cancer	118	11.8% (B)	35.0% †	24.4% †	20.0% †	19.0% †
Lee et al. <sup>197</sup>	Primary liver cancer	165	20.0% (A)	45.0% †	30.0% †	20.0% †	20.0% †
Joishy and Balasegaram <sup>198, 199</sup>	Malignant and benign	288	11.8% (A)				
	All malignancy	133	12.8% (A)				
	Primary liver carcinoma	94	14.9% (A)				
Wu et al. <sup>200</sup>	Primary liver carcinoma	181	8.8% (B)	55.9% †	36.8% †	38.9% †	16.0% †
Almersjo et al. <sup>203</sup>	All malignancy	46	30.0% (B)		31.0% †		
Smith <sup>205</sup>	Primary liver malignancy	60	6.7% (D)		26.7%		
Bengmark et al. <sup>204, 210</sup>	Primary liver malignancy	21	14.3% (A)	47.6%	38.1%		
	Colorectal cancer	32	6.3% (B)			20-25% †	
Longmire et al. <sup>183</sup>	Malignant and benign	75	9.3% (C)				
	All malignancy	41	12.2% (C)				
	Primary liver malignancy	19	21.2% (C)				
Fortner et al. <sup>182, 206</sup>	Malignant and benign	137	9.3% (B)				
	All malignancy	113	10.6% (B)				
	Primary liver cancer	42	16.7% (B)	85.0% ††		50.0% ††	37.0% ††
	Colorectal cancer	43	9.3% (B)	87.0% ††			
	Colorectal cancer	25	8.0% (B)	88.0% ††	48.0% ††	48.0% ††	
Adson and Weiland <sup>181</sup>	Primary liver neoplasm	60	6.7% (B)			65.0% ††	36.0% ††
	Primary liver malignancy	46	4.3% (B)				
Wilson and Adson <sup>208</sup>	Colorectal cancer	60	1.7% (B)				28.0% ††
Adson and Van Heerden <sup>209</sup>	Colorectal cancer	34	5.9% (B)	82.0% †	58.0% †	41.0% †	
Morrow et al. <sup>202</sup>	Metastatic tumors	64	20.0% (B)		45.0% ††		34.0% ††
	Colorectal cancer	29			67.0% ††		27.0% ††
Iwatsuki et al. <sup>161</sup>	Malignant and benign	150	4.0% (A & B)				
	Malignant tumors	86	4.7% (A & B)				
	Primary liver malignancy	43	9.3% (A & B)	77.8% †	59.5% †	55.7% †	46.0% †
	Metastatic tumors	43	0.0% (A & B)	85.3% †	66.7% †	66.7% †	57.2% †
	Metastatic colorectal	24	0.0% (A & B)	91.3% †	73.0% †	73.0% †	52.1% †

\*Definition of operative mortality: A = death in initial hospitalization, B = death in 30 days, C = death in 60 days, D = intraoperative death.

†Operative death excluded.

‡Actuarial survival.

57%. The difference in survival up to 5 years was not statistically significant between those with primary and metastatic liver neoplasms, nor were differences significant in subgroups of either of these 2 major categories.

Long-term survival data have been given in only a handful of reports, and the most complete information has been for primary hepatic malignancy. Foster<sup>201</sup> collected 296 cases of primary liver cancer from the pre-1970 literature; the 2- and 5-year determinant survival rates were 33.3% and 14% overall, respectively; but they were 59% and 36% for non-Asians as compared with 23% and 6% for Asian patients. Four large Asian series have been reported in the English literature since Foster's review. Lin<sup>195, 196</sup> reported 3- and 5-year actual survival of 20% and 19%, respectively, in 1976, and Lee et al.<sup>197</sup> reported 1- and 3-year actuarial survival of 45% and 20%, respectively. Balasegaram and

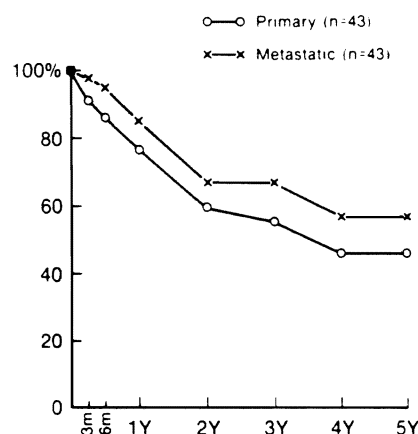
Joishy<sup>198, 199</sup> reported a possible survival of 58.5% and 43.6% at 1 and 3 years after resection; however, not all of their patients could be followed. Wu et al.,<sup>200</sup> reporting the largest series from a single institution in 1980, recorded 1- to 5-year actual survival rates of 55.9%, 36.8%, 28.9%, 21.8%, and 16%, respectively (excluding an 8.8% operative mortality). Seventy per cent of their patients had cirrhotic livers. Almersjo and Bengmark and co-workers<sup>203, 204</sup> in Europe reported 2-year actual survival of 31% (excluding an operative mortality of 30%), and in 1979 Smith<sup>205</sup> reported a 27% survival 2 years after resection. In the United States, Fortner et al.<sup>182, 206</sup> reported 1-, 3-, and 5-year actuarial survivals of 85%, 50%, and 37%, respectively (excluding the operative mortality of 16.7%). Adson and Weiland<sup>181</sup> reported 3- and 5-year actuarial survival of 65% and 36%, respectively, (excluding operative deaths). Our 1- to 5-

**Table 176-9. SURGICAL COMPLICATIONS IN 150 RESECTIONS**

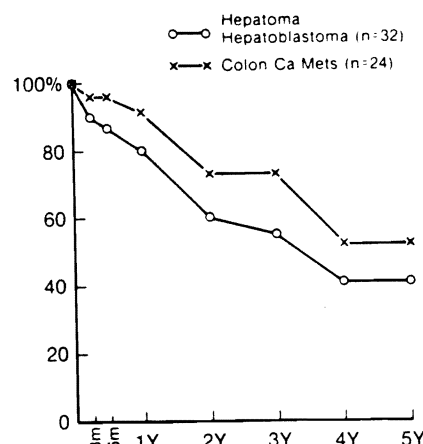
Complication	No. Cases
Postoperative bleeding	3
Supphrenic abscess:	12
Anterior drainage	(6)
Posterior drainage	(6)
Subphrenic collection:	6
Posterior drainage	(6)
Major bile leak	4
Bile duct obstruction due to recurrent tumor	2
Major gastrointestinal bleeding	2
Small bowel obstruction	1

year uncorrected actuarial survivals for primary malignancy are 77.8%, 59.5%, 55.7%, 46%, and 46%, respectively.

The results of liver resection for metastatic liver tumors also have been encouraging, particularly since such resections can be performed with minimum mortality. Foster<sup>207</sup> reviewed the hospital records of more than 400 patients with metastatic liver tumors from colorectal cancer who underwent liver resection, and in 1978 reported 2- and 5-year determinant survival of 44% and 22%, respectively (excluding operative deaths). Fortner et al.<sup>182,206</sup> reported 1-, 2-, and 3-year actuarial survival of 88%, 48%, and 48%,



**Figure 176-18.** Actuarial survival after liver resection. Comparison between primary liver malignancies and metastatic liver tumors. There are no statistically significant differences between the 2 at any point of time. (From Iwatsuki S et al. *Ann Surg* 1983; 197:247-53. Reproduced with permission.)



**Figure 176-19.** Actuarial survival after liver resection. Comparison between hepatoma/hepatoblastoma and metastatic colorectal cancer. There are no statistically significant differences between the 2 at any point of time. (From Iwatsuki S et al. *Ann Surg* 1983; 197:247-53. Reproduced with permission.)

respectively (excluding an operative mortality of 8%). Wilson and Adson<sup>208</sup> reported a 5-year survival of 28% among 60 patients with metastases from colorectal cancer, two-thirds of whom were treated by wedge resection of the liver. Later, Adson and Van Heerden<sup>209</sup> reported 1-, 2-, and 3-year actual survival of 82%, 58%, and 44%, respectively, among 34 patients who had major hepatic resections (excluding operative deaths of 5.9%). Morrow et al.<sup>202</sup> reported 1- to 5-year actuarial survival of 76%, 45%, 43%, 39%, and 34%, respectively (excluding an operative mortality of 20%) among 64 patients with metastatic liver tumors; for metastatic tumors from colorectal cancer, they reported 2- and 5-year actuarial survival rates of 67% and 27%, respectively. We have obtained 1-, 3-, and 5-year actuarial survival of 91.3%, 73%, and 52.1%, respectively, in metastatic colorectal cancer without any operative mortality. Although our survival figures seem to be higher than those of others, differences between them are not statistically significant. If our higher survival figures hold for several more years, they may, at least partly, reflect our policy of extensive liver resections as opposed to local excision for metastatic tumors.

### Portal-Systemic Diversion

One of the dominant themes in the medical literature in the era of hepatic surgery that is

ending has been how portacaval and other portal-systemic shunts can be used to treat complications of portal hypertension. During the same time, information about the physiologic effect of such procedures has accumulated that has called into question the probity of their continued use. This new information, which collectively has been called *hepatotrophic physiology*,<sup>211,212</sup> has removed much of the mystery about the complications and expectations after portal-systemic shunting procedures.

**Hepatotrophic Physiology Before 1973.** In 1877, Eck described the operation of the completely diverting portacaval shunt in dogs.<sup>213</sup> Although only one of his animals survived the perioperative period, Eck was convinced that the procedure was safe and would have clinical application. Only 16 years later, Pavlov and his associates<sup>214</sup> described injurious effects from the Eck fistula, including weight and hair loss, hepatic encephalopathy, and liver atrophy.

**Liver Changes.** Three-quarters of a century passed before it was realized that hepatic atrophy caused by Eck's fistula occurs with astonishing rapidity, being 90% complete within 3 to 4 days.<sup>215,216</sup> Electron micrographic techniques made it possible to develop a clear picture of the organelle changes caused by portacaval shunt in the hepatocytes of previously normal rats,<sup>217-220</sup> dogs,<sup>215,216,221,222</sup> sub-human primates,<sup>222,223</sup> and man.<sup>224,225</sup> The most striking and specific ultrastructural changes are depletion and disruption of the rough endoplasmic reticulum and reduction in the membrane-bound polyribosomes.<sup>215,216,221-225</sup> Other features are fatty liver, reduction of glycogen granules, and deterioration of the mitochondria. Oudea and Bismuth<sup>218</sup> noted an increase in smooth endoplasmic reticulum in rats, but this is not prominent in dogs, baboons, or man.<sup>223,225</sup>

Another feature of the Eck fistula liver that escaped notice for a long time was a marked increase in hepatocyte renewal, which has been described in rats,<sup>219</sup> dogs,<sup>215,216</sup> and baboons.<sup>222,223</sup> After portacaval shunt, the mitotic index and the rate of thymidine incorporation, as measured with autoradiography, rise within a few days to a new and stable level 3 or 4 times higher than the preoperative resting level. The stimulus for the low-grade hyperplasia is unknown. It may represent a response to an increased death rate of hepatocytes. Since hepatic hyperplasia and

hypertrophy are parallel in most situations of liver regeneration, the combination of atrophy and hyperplasia after Eck's fistula is a special situation that has generated much discussion.<sup>216,219</sup>

**Flow Hypothesis.** Rous and Larimore<sup>226</sup> were intrigued with the possibilities that portal venous blood contained special factors and that the extrahepatic diversion of these factors by portacaval shunt was responsible for the hepatic atrophy and the poor health of animals with Eck's fistula. Unfortunately, their experimental models did not permit decisive experiments with which to support this suspicion.

A contrasting hypothesis was championed by Mann,<sup>227</sup> who did not believe that the portal blood had special qualities that were important for liver health. He envisioned the liver mass as a by-product of, or a kind of encrustation upon, its complex capillary bed, which in turn was controlled solely by the volume of blood presented to it. He wrote ". . . restoration of the liver depends . . . upon the flow of portal blood through the organ and . . . the primary stimulus is the [quantity of] the portal blood itself"—the flow hypothesis.

Studies by Child et al.,<sup>228</sup> using portacaval transposition in dogs as the experimental model, were erroneously but generally interpreted as crucial evidence favoring the flow hypothesis and disproving the hepatotrophic concept. By replacing the diverted splanchnic venous blood with an inflow to the portal vein from the inferior vena cava, most of the adverse effects of Eck's fistula were avoided.<sup>228</sup> The concept became rooted that the quality of portal venous blood was not a prime determinant of good hepatic structure, function, or capacity for regeneration.<sup>228,229</sup> Nevertheless, the flow hypothesis did not satisfy everyone's curiosity. Bollman (Mann's associate) wrote, "In the 83 years since it was first reported, the Eck's fistula has been reasonably successful in hiding its secrets as well as giving rise to many additional questions fundamental to an understanding of the functions of the intestine, liver, and brain."<sup>230</sup>

**Hepatotrophic Concept from Studies of Liver Transplantation.** The flow hypothesis was demolished by investigations that had their origin in studies of auxiliary liver transplantation. The seminal observations<sup>7,231</sup> were that an hepatic graft transplanted as an extra

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liver underwent rapid and remarkable atrophy if it was not provided with a portal venous inflow from the recipient splanchnic bed (Fig. 176-1), but that if this kind of splanchnic venous flow was given to the graft at the expense of the dog's own liver the atrophy now affected the native liver.

Later, non-transplant models were developed that allowed study of the fate of liver fragments given different kinds of portal venous inflow but that in all other respects were equivalent. In one such model,<sup>232</sup> splanchnic venous blood was provided for one portal branch of the liver, whereas the other portal branch was supplied with blood from the inferior vena cava. The side receiving the high flow of vena caval input invariably underwent atrophy; the atrophy could not be prevented even by arterializing the disadvantaged side.

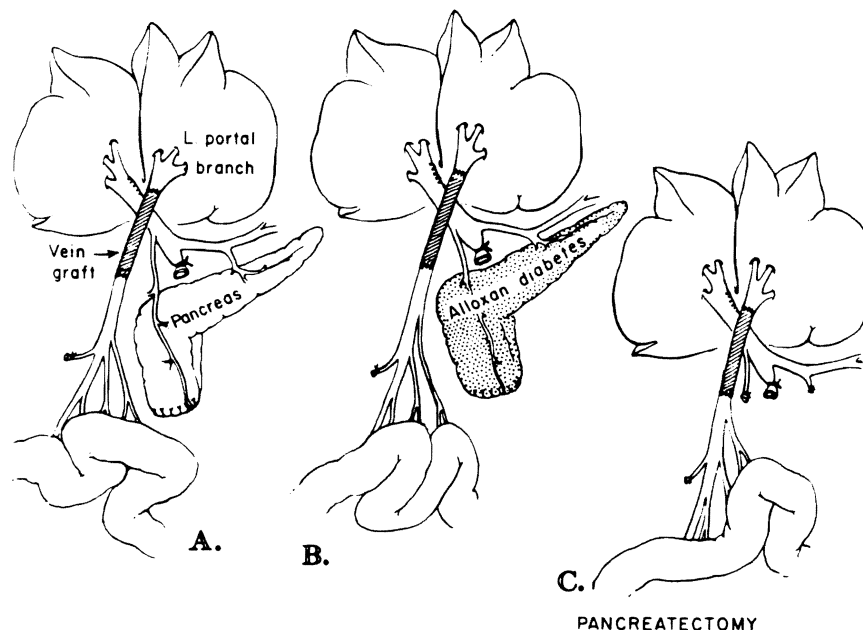
#### Hormonal Nature of Hepatotrophic Substances

**"Double Liver" Experiments.** Another kind of "double liver" model was used in an effort to pinpoint the splanchnic organs from which the so-called hepatotrophic factors came. In this preparation, blood returning from the pancreas, duodenum, stomach, and spleen passed to one portion of the liver while the

other liver fragment was being perfused with venous blood returning from the small intestine (Fig. 176-20).

The results were unequivocal.<sup>233</sup> The liver fragment perfused with blood returning from the upper abdominal viscera remained healthy. By contrast, the liver provided with intestinal blood became atrophic, deglycogenated, and fatty. The organelle structure of the atrophic fragment was like that after portacaval shunt, including disruption and depletion of the rough endoplasmic reticulum. Such histopathologic studies in the splanchnic division experiments made the pancreas suspect as a major hepatotrophic source and made insulin the most likely major hepatotrophic substance.<sup>233</sup>

The morphologic observations were bolstered in the so-called "double liver" preparations (Fig. 176-20) by numerous biochemical studies of the 2 liver sides, including determinations of glycogen, glucokinase, cyclic adenosine monophosphate (cyclic AMP), active phosphorylase, and lipids.<sup>233</sup> The major differences in the liver fragments related to the nature of the portal venous inflow. The details of the biochemical disassociation are beyond the scope of this chapter, but the reasonable inference was that the 2 liver sides were living in different metabolic



**Figure 176-20.** Splanchnic division experiments. In these dogs, the right liver lobes received venous return from the pancreaticogastrroduodenosplenic region, and the left liver lobes received venous blood from the intestines. A, Non-diabetic dogs. B, Alloxan-induced diabetic dogs. C, Dogs with total pancreatectomy. (From Starzl TE et al. Surg Gynecol Obstet 1975; 140:549-62. Reproduced with permission.)



worlds in which hormone control was the dominant factor.

The nature of the biochemical differences suggested that endogenous insulin, which was being efficiently extracted by the first liver tissue to which it was exposed, played the most important role. The significance of endogenous insulin was further highlighted when the advantages enjoyed by the lobes perfused by splanchnic venous blood were greatly reduced, although not eliminated, by either total pancreatectomy or alloxan diabetes.<sup>222,234,235</sup> While emphasizing the role of insulin, these investigations showed equally clearly that non-pancreatic hormones or other substances also contributed to the total hepatotrophic effect of splanchnic venous blood. Although the influence of these extra-pancreatic factors remains unchallenged, they have not been identified.

Complicated though they were, the double liver fragment models were crucial to an understanding of the enigmatic Eck fistula. If insulin was a vital hepatotrophic factor, the reason for its unmasking by the double liver fragment experiments became understandable. The well-known efficiency of insulin removal during a first pass through hepatic tissue<sup>236</sup> made the insulin relatively unavailable for a second liver or a liver fragment and thus exaggerated the effect of portal blood deprivation in the disadvantaged hepatic tissue.

At the same time, the protection afforded after portal diversion by flow augmentation procedures, such as Child's portacaval transposition<sup>228</sup> or Fisher's portal arterialization,<sup>229</sup> was explained. If insulin and other hepatotrophic substances were bypassed around a single liver, they would be returned to it in a diluted form in direct relation to the total hepatic blood flow, which these procedures increased.

**Hormone Infusion Experiments.** We suspected by this time that the secrets of Eck's fistula were explained mainly by the liver's being deprived of direct access to endogenous insulin. The experiment shown in Figure 176-21 was designed as a direct test of that hypothesis. Non-hypoglycemic infusions of insulin, glucagon, and other substances were made for 4 days into the ligated left portal vein after Eck's fistula.<sup>215,216</sup> The experiment was designed to evaluate any direct protective effect of hormones on the left lobar hepatic tissue, as well as to assess a spillover effect on the right lobes after recirculation. The results were unequivocal: insulin greatly reduced the atrophy that otherwise halved the size of the cells within 4 days, and it preserved the hepatocyte ultra-structurally. Glucagon in small doses did not potentiate the action of insulin, and in large doses it may have reduced the insulin benefit. Glucagon alone in large or small doses had no effect.<sup>215,216</sup>

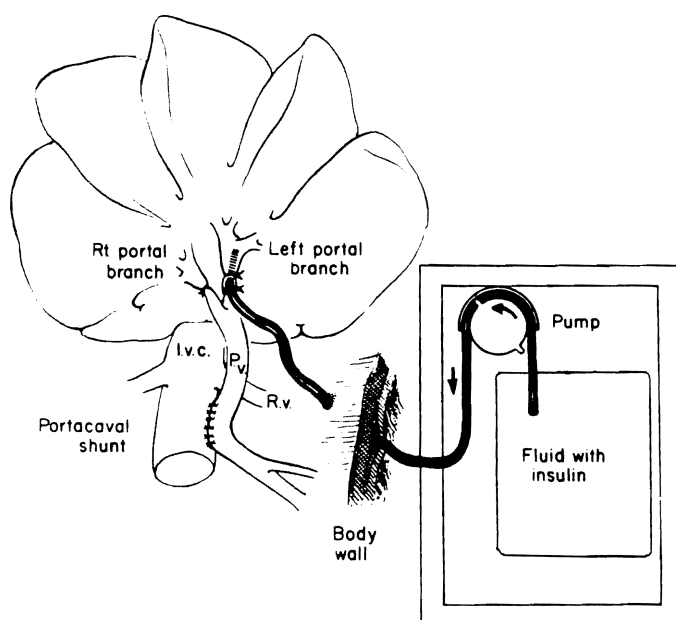


Figure 176-21. Experiments in which Eck's fistula is performed and postoperative infusions are made into the left portal vein. (From Starzl TE et al. *Lancet* 1976; 1:281-5. Reproduced with permission.)

The effect of insulin on hepatocytic proliferation in these experiments was also striking. After Eck's fistula, the mitotic rate was already increased to about 3 times normal (from 1.6 to 4.8/1000 hepatocytes). Insulin more than tripled this cell renewal with no spillover to the contralateral lobes. Glucagon alone had no effect, nor did it potentiate the action of insulin.<sup>215,216</sup>

**Evisceration and Hepatocyte Culture Experiments.** The foregoing observations established relative "hepatic insulinopenia" as the most important element in the liver injury of Eck's fistula. However, the clarity with which insulin has emerged as the principal portal hepatotrophic substance has not diminished interest in the search for contributory hepatotrophic factors. The observation that the insulin protection was not complete in our infusion experiments was interpreted as a reflection of ancillary substances.<sup>215,216</sup> Evidence that multiple hepatotrophic factors exist has been uncovered with all of the experimental models used by us.<sup>215,216,222,233-235,237,238</sup>

However, the probability that control of hepatocytic integrity is multifactorial has not de-emphasized the central role of insulin in maintaining liver cells. This was again demonstrated after removal of all non-hepatic splanchnic viscera including the pancreas.<sup>237,238</sup> The intraportal infusion of insulin alone prevented most of the atrophy and other structural deterioration of hepatocytes that otherwise occurred and preserved the rate of spontaneous renewal of hepatocytes that was otherwise depressed. The hepatic protection in eviscerated animals<sup>237</sup> was similar to that observed with intraportal insulin therapy after portacaval shunt.<sup>215,216</sup>

Many investigators have described analogous insulin effects in hepatocyte tissue culture systems.<sup>239</sup> The role of insulin in maintaining hepatocytic mitochondrial metabolism has also been emphasized.<sup>240</sup> No potentiating effect of glucagon has been demonstrated in any of these models.

**Function of the Portoprival Liver.** The discovery of the hormonal nature of the hepatotrophic substances has been coincident with, if not responsible for, better insight into the changes in hepatic function caused by portal diversion. Liver function after Eck's fistula, or after the better tolerated portacaval transposition of Child et al.,<sup>228</sup> was long thought to be essentially normal, the main defect being inefficient clearance of ammonia.<sup>241,242</sup> Only in the past 10 or 15 years have

subtle but cumulatively massive changes in hepatic function caused by portal diversion been realized. These alterations are so sweeping that an all-inclusive description undoubtedly would require a discussion of virtually every facet of hepatic physiology and metabolism.

A relatively specific effect of portacaval shunt described earlier is the qualitative and quantitative loss of rough endoplasmic reticulum (RER) and its lining polyribosomes. Since RER is the "factory" of the cell,<sup>243,244</sup> many biosynthetic processes are consequently reduced.

Portacaval shunt reduces the serum concentration of cholesterol in animals<sup>222</sup> and in man.<sup>245</sup> This effect can be explained by the reduction in hepatic lipid synthesis demonstrated in dogs,<sup>222,246</sup> rats,<sup>247</sup> swine,<sup>248</sup> and baboons.<sup>246</sup> As discussed later, data about hepatic lipid synthesis also are available from patients treated by us with portacaval shunt for familial hypercholesterolemia.

Bile acid synthesis is greatly reduced by portacaval shunt.<sup>247,249</sup> The hepatic urea (Krebs-Henseleit) cycle has been shown by Reichle et al.<sup>250</sup> to be depressed by Eck's fistula in rats and dogs.

Other hepatic synthetic or metabolic processes probably follow the same pattern after portacaval shunt. This possibility is supported by many studies showing that portacaval shunt lowers the activity of the hepatic microsomal mixed-function oxidase system.<sup>251-255</sup> In addition to illustrating the principle of wide-ranging decline of hepatic synthetic functions after portacaval shunt, these observations are of importance because the microsomal mixed-function oxidase system, for which multiple cytochrome P-450 and P-448 species serve as terminal oxidases, metabolizes a variety of drugs and foreign chemicals as well as endogenous compounds such as steroids and fatty acids.

The evidence is overwhelming that the changes in hepatic function following Eck's fistula are caused mainly by depriving the liver of endogenous insulin. Reaven et al.<sup>256</sup> have shown that the disruption and disorganization of the RER that are characteristic after portacaval shunt can be caused by the production of alloxan diabetes and can be reversed by treating the diabetes with insulin. Similarly, Kato<sup>255</sup> has shown that activity of the mixed-function oxidase system is depressed in rats given alloxan diabetes in the same way as can be caused by portacaval

shunt. Pector et al.<sup>252,257</sup> have shown that the hepatic alterations in the mixed-function oxidase system are the same if the tied-off central portal vein is arterialized or revascularized with systemic venous blood using the transposition technique. These latter experiments showed that the mere restoration of the "wrong" kind of hepatic blood flow could not prevent the changes that are specific from portal diversion.

**Relevance of Animal Studies to Man.** As already noted, the histopathologic alterations caused by portacaval shunt are not demonstrably different in rats, dogs, swine, monkeys, baboons, and man.<sup>223</sup> Whether the lethal consequences of portacaval shunt represented more than a species peculiarity of the dog was not known until about the early 1950s. The dearth of information began to end with the classic clinical articles of McDermott et al.,<sup>258,259</sup> which were seemingly confirmed by Hubbard<sup>260</sup> a few years later. Unfortunately, misinterpretation of the observations in these reports actually delayed an understanding of the physiology of human portacaval shunt for almost 2 decades.

**The McDermott-Hubbard Artifact.** McDermott et al.<sup>258,259</sup> and Hubbard<sup>260</sup> each reported on 2 patients who had carcinomas of the head of the pancreas and grossly normal livers, except for the findings of biliary obstruction. To perform a pancreaticoduodenectomy, resection of the portal vein was necessary, and in all 4 patients the end of the transected superior mesenteric vein was anastomosed to the side of the inferior vena cava. Within a few weeks or months, all 4 patients developed episodic hepatic encephalopathy, malnutrition, fatty liver, and hypoalbuminemia. When the patients died 4 to 20 months postoperatively, none had recurrent tumor. The conclusions were reached that these were the first examples of Eck's fistula in man, that human patients were even more sensitive than dogs to the metabolic complications of Eck's fistula, and that the ability of patients to tolerate portal diversion was inversely related to the quality of pre-existing hepatic function.

None of these conclusions was valid. The errors were caused by the failure to appreciate that the operations were not pure Eck's fistulas. In addition to the portal diversion, all 4 of the patients also had removal of variable amounts of the pancreas. The latter organ was subsequently proved to be the single most important source of hepatotrophic substances.

**Species Encephalopathy Factor.** The encephalopathy (usually associated with weight loss and alopecia in experimental animals) that was first described in dogs has been variable in swine,<sup>248,261,262</sup> severe in subhuman primates,<sup>223,246,263,264</sup> and minor in rats.<sup>265-267</sup> Glial proliferation and central pontine myelinolysis have been found in the brains of rats, monkeys, and baboons.<sup>223</sup>

Fortunately, the remarkable encephalopathic complications produced after the subhuman primate operations have not been duplicated in human patients with previously normal livers. The human experience with Eck's fistula in the presence of normal hepatic function has been in patients with types I, III, and VI glycogen storage disease (GSD) and familial hypercholesterolemia.

Patients with GSD generally tolerate portacaval shunt well in spite of the fact that their well functioning livers usually have significant pre-existing structural abnormalities.<sup>224,245</sup> Of 9 patients followed by us for 4¾ to 19½ years after portal diversion, only 1 developed hepatic insufficiency and encephalopathy 8 years after portacaval shunt. This girl was successfully treated with orthotopic liver transplantation;<sup>70</sup> it was possible to take down the portacaval anastomosis and to use the portal vein to revascularize the new liver. None of the other patients with glycogen storage disease treated with portal diversion is known to have developed encephalopathy.

The picture was even clearer in patients who had portacaval shunts for familial hypercholesterolemia (FH). Characteristically, patients with this disease start with completely normal hepatic structure and function. Only 1 of our 13 patients, and none of the 26 others reported from other centers,<sup>268</sup> has had overt manifestations of the Eck's fistula syndrome with follow-up periods of 1 to nearly 10 years. The exception in our series was a 3-year-old girl who had a single episode of unconsciousness 9 months after portacaval shunt at a time when her blood ammonia level was 85 µg/dl (normal <55). Encephalopathy was accepted as the diagnosis because no other explanation was found. The child is currently well on a low protein diet.

The histopathologic changes caused by portal diversion in the livers of the FH patients<sup>225,268</sup> have been indistinguishable from those in animals. Blood ammonia levels, when measured, were always increased to or beyond the upper limits of normal;<sup>268</sup> low-grade elevations of activities of aminotrans-

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ferases and alkaline phosphatase have been common. Although the patients have been clinically well and on normal diets after portacaval shunt, hepatic function probably has been impaired. Nevertheless, their behavioral and physical development has not been obviously affected.

The only other use of portal diversion in the presence of a normal or nearly normal liver has been in patients with esophageal varices from extra-hepatic portal venous obstruction (presinusoidal block). The thrombosed portal vein in many such patients is replaced with a multitude of collaterals that are frequently so well developed that they have been referred to collectively as "*cavernous transformation*." Flow in the collaterals is hepatopetal<sup>269</sup> and thus important in perfusing the liver with hormone-rich splanchnic blood, albeit by circuitous routes. If a sound portal-systemic anastomosis can be constructed (usually with splenorenal, cavo-mesenteric, or makeshift shunts), control of variceal hemorrhage is almost always achieved. At the same time, the collateral splanchnic venous flow to the liver just described is "stolen" from the liver through the shunt.<sup>269</sup>

Despite this physiologic penalty, clinical results after technically satisfactory shunt procedures in patients with portal vein thrombosis usually have been good.<sup>270</sup> None of the 19 patients reported by Grauer and Schwartz<sup>270</sup> developed hepatic failure or encephalopathy after follow-up periods of as long as 2 decades. The observations were consonant with those of previous workers.

Even more reassuring were the results obtained by Alagille's group.<sup>271</sup> Seventy-six children with portal obstruction had portal-systemic shunts (32 central splenorenal, 32 Marion mesocaval, 6 interposition mesocaval, 3 makeshift, 2 distal splenorenal, 1 portacaval). Seventy of the shunts remained patent. Although blood ammonia levels were raised slightly, none of the patients developed encephalopathy as judged by neurologic examinations and electroencephalograms every 6 to 12 months and by analysis of academic performance. Physical growth was not interrupted and may have been accelerated.

Nevertheless, hepatic dysfunction and encephalopathy have been reported<sup>272</sup> with or without portal diversion in patients with extrahepatic portal block; in 2 such patients encephalopathy was reversed after disconnecting the portal-systemic shunts and restoring hepatopetal blood flow.<sup>269</sup> Voorhees

et al.<sup>273</sup> reported a high frequency of psychologic and psychiatric perturbations that they suggested might be occult manifestations of encephalopathy after portal-systemic shunting. These latter conclusions have not been verified, and in patients with familial hypercholesterolemia and portal thrombosis, careful psychologic examinations and intelligence testing after shunt operations have not turned up anything resembling Voorhees' observation.<sup>268, 271</sup>

The resistance of man to encephalopathy after portacaval shunt has not been explained satisfactorily. One possibility is that the natural diet of man is more compatible with the depressed hepatic function of Eck's fistula than that consumed by some of the animal species. In various animals, the clinical manifestations of hepatic encephalopathy can be forestalled or ameliorated with special low protein diets; use of the same kind of dietetic management in man is a logical response if hepatic encephalopathy occurs.

**Human Eck's Fistula Syndrome Versus Pre-existing Hepatic Dysfunction.** The McDermott-Hubbard artifact may have been responsible for the widespread conviction that the risks of the Eck's fistula syndrome in human beings are proportionate to the quality of pre-existing hepatic function, being greatest with a completely normal liver. The rationale frequently has been that severely diseased livers that had already lost hepatopetal portal flow to collaterals would not be much further affected by a portacaval shunt and that such livers would have compensatory increases in hepatic artery flow. By contrast, the argument continued, normal or near normal livers that still retained significant portal venous flow would sustain a major insult by abrupt diversion of this flow.

Clinical experience with various shunting procedures in cirrhosis has been the opposite of the foregoing hypothesis. For 2 decades, the risk of most patients being considered for portal diversion has been stratified by the Child classification according to the quality of hepatic function.<sup>274</sup> Those with the best function (A category) have always had the best results. Those with the worst function (C category) have experienced the worst results, and those with a B classification have had intermediate clinical results. Parenthetically, the A patients are the most apt to have residual hepatopetal flow, although the association is too imperfect to be useful in predicting the outcome.<sup>275, 276</sup>

**Complete Portal Diversion for Metabolic Dysfunction.** End-to-side portacaval shunt has been performed in patients with glycogen storage disease (GSD), familial hypercholesterolemia (FH), and alpha-1-antitrypsin deficiency. In each instance, the liver damage and resulting changes in hepatic function have counteracted some of the lethal or undesirable metabolic features of the original inborn error.

**Glycogen Storage Disease (see Chapter 168).** Portal diversion for glycogen storage disease was first reported in 1965.<sup>277</sup> The objective was to deglycogenate the liver, as had been observed to occur in animals, and to relieve the episodic hypoglycemia and acidosis that were dominant symptoms. The consequences of the procedure proved to be more subtle and wide ranging. The value of portacaval shunt for GSD was confirmed in several centers.<sup>224,245,278-280</sup> However, the need for portacaval shunt was abruptly eliminated in 1976 when an alternative form of treatment, continuous alimentation, became available (see later).

Our own experience with portal diversion was with 10 patients whose specific enzyme deficiencies were of glucose-6-phosphatase (type I, 6 examples), amylo-1,6-glucosidase (type III, 3 examples), and phosphorylase (type VI, 1 example). The first 2 patients had portacaval transposition, and the second of these died when the glycogen-laden liver was unable to transmit the vena caval flow. The other 9 patients survived, and 8 are still living after 7½ to almost 20 years.

Following portal diversion, most of the children who had pre-existing hypoglycemia did not have relief of this symptom or else the relief was not complete. Thus, night feedings usually had to be continued. Studies of plasma insulin and glucagon concentrations were obtained in several of these patients. The flat peripheral insulin curves typical of type I glycogen storage disease<sup>281</sup> became elevated after portacaval shunt, and smaller increases in glucagon were noted.<sup>245</sup> The glucose tolerance curves were the same before and after operation. Liver glycogen concentrations in our patients who later had liver biopsies were not changed, nor were the measures of hepatic enzyme activity. Corbeel et al.<sup>279</sup> found a striking increase of *active* glucose-6-phosphatase after portacaval shunt in a child with type Ib GSD. Portal diversion was thought to have unmasked a non-func-

tional glucose-6-phosphatase by improving the defective transport of this enzyme across microsomal membranes.

Despite failure to alter the hepatic glycogen concentration,<sup>224,245</sup> liver size decreased in several patients, as measured with liver scan planimetry. Even if obvious shrinkage did not occur, postoperative biopsies always showed a diminution in the size of individual hepatocytes,<sup>224</sup> similar to that produced in animals by portacaval shunt.

Compared with the incomplete relief of hypoglycemia, all components of the hyperlipidemia characteristic of the type I disease were corrected permanently. Other metabolic defects also were corrected, including abnormal bleeding, uric acid elevations, and abnormal calcium metabolism.<sup>224,245,278-280,282</sup>

All 10 of our patients had growth retardation before portacaval shunt. Afterwards, height increases, which in most cases had virtually ceased, occurred during the first postoperative year at the rate of approximately 0.5 cm/month. The same thing has been described in all of the other reported cases. Quantitative measures of the phenomenal growth rate were obtained with radiographic techniques.<sup>224</sup> Circulating somatotropin in these patients was normal.<sup>224</sup> The growth spurts may have been at least partly attributable to increased insulin distribution to the periphery, since insulin has been recognized to be a major growth hormone, comparable in potency to somatotropin.

The morbidity from portacaval shunt was not excessive. The one patient already mentioned who developed hepatic encephalopathy 8 years after end-to-side portacaval shunt for type I GSD also had multiple filling defects in her enlarged liver, which proved to be adenomas at the time of transplantation. Another patient who had low levels of blood ammonia died during an angiographic procedure 5 years after portacaval shunt. She had advanced obstructive changes of the pulmonary arterial circulation, similar to changes documented in other patients with type I GSD as well as in those with other liver diseases.<sup>283</sup>

Folkman et al.<sup>280</sup> showed that preoperative parenteral hyperalimentation could reduce the operative risk of portacaval shunt by normalizing pre-existing hepatomegaly, acidosis, and other abnormalities, including hyperlipidemia. Greene et al.,<sup>284</sup> in an extension of this concept, showed how continuous or

frequent feedings (including overnight alim-entation) could achieve the same objectives as portacaval diversion. Since then, continuous alim-entation has been the therapy of choice.

**Familial Hypercholesterolemia.** Patients with this disease have absent or deficient cell membrane lipoprotein receptors,<sup>285</sup> and thus a "switch-off" mechanism to control lipid (especially cholesterol) synthesis is not in place. Patients who are homozygous for the abnormality have serum cholesterol concentrations of 800 to 1000 mg/dl and, because of the resulting lipid deposits in the heart valves and coronary arteries, rarely live beyond the teens.

Complete portal diversion reduces the serum cholesterol and low density lipoprotein (LDL) levels of such patients.<sup>225</sup> By mid-1982, 13 patients with FH had been treated by us in this way.<sup>268</sup> The total serum cholesterol concentrations fell significantly in every patient after portacaval shunt. When measured, LDL cholesterol concentrations were reduced commensurately. The total cholesterol declines were 20 to 55.4 (average 33.8) and were maintained throughout the period of study. High density lipoprotein (HDL) cholesterol and triglyceride levels were variably affected. Tendinocutaneous xanthomas regressed or disappeared in every patient.

The invariable and long-lasting lipid lowering in our 13 patients was achieved without serious morbidity. The physical development of those children who were normal before operation has proceeded, and the growth of those who were stunted before has moved toward normal. Emotional or intellectual deterioration secondary to the portal diversion has not occurred, although one child had an acute episode of encephalopathy that was managed with diet.

Twenty-six additional patients have been treated elsewhere,<sup>268</sup> 13 at one institution in Johannesburg.<sup>286</sup> The results confirmed those obtained by us, with thrombosis of the shunt being the most common cause of failure.

Cholesterol and LDL synthesis is greatly reduced after portacaval shunt,<sup>287,288</sup> and total body cholesterol mass is reduced to half or less within 1 or 2 years after operation.<sup>288</sup> Such data are compatible with the disappearance of tendinocutaneous xanthomas and with the hope that the lethal cardiovascular complications can be slowed or forestalled by portacaval shunt. Despite this possibility, sta-

bilization of the vascular disease may be the best that can be hoped for with portacaval shunt, even in patients whose angina pectoris is relieved, since the serum lipid levels are never restored to completely normal values.

**Alpha-1-Antitrypsin Deficiency.** Patients with this disorder have a low level of plasma alpha-1-antitrypsin (an alpha globulin) and a high rate of occurrence of pulmonary complications.<sup>289</sup> Sharp et al.<sup>290</sup> demonstrated a variable association of alpha-1-antitrypsin deficiency with liver disease.

The basis for the liver injury is the hepatic production of an abnormal alpha-1-antitrypsin that cannot be effectively transported out of the liver cells and that consequently becomes sequestered within the hepatocytes near the rough endoplasmic reticulum. Irritation by the entrapped glycoprotein has been the postulated cause of the cirrhosis, portal hypertension, and hepatic failure that follow.

We have performed end-to-side portacaval shunt in 3 children with the cirrhotic liver disease of alpha-1-antitrypsin deficiency.<sup>291</sup> The first 2 patients had major hemorrhages from esophageal varices and the third had ascites. After follow-up periods for as long as 7 years, liver function in these 3 children has not greatly changed, although the plasma ammonia levels have been elevated whenever this measure was obtained. None of the patients has encephalopathy. The second and third children had liver biopsy at varying times after portacaval shunt and, after 2 or 3 years, semiquantitative morphometric studies indicated that the amount of alpha-1-antitrypsin entrapped in the liver had significantly decreased.

Our assumption is that the portacaval shunt diminished the synthesis of the abnormal alpha-1-antitrypsin, presumably by altering the function of the rough endoplasmic reticulum without commensurately reducing the transport of this glycoprotein. With a better equilibrium between the production and the transport of the alpha-1-antitrypsin, its intracellular accumulation was possibly slowed or even reversed.

**Portal-Systemic Shunt for Complications of Portal Hypertension.** After Whipple<sup>292</sup> and Blakemore and Lord<sup>293</sup> opened the modern era of portacaval shunt, portal diversion was widely used to treat intractable ascites and to stop or prevent hemorrhage from esophageal varices. Although portal diversion



often dries up ascites, its use for this purpose has been all but abandoned because of the mortality and morbidity (especially encephalopathy) of the procedure, because better diuretics have made ascites easier to control, and because the safer peritoneal-venous (LeVeen-type) shunts can be used if medical management of the ascites is unsuccessful<sup>294</sup> (Chapter 159).

Portal-systemic shunts are still being used to control variceal bleeding, but are being recommended far less frequently (Chapter 159). The incongruity of imposing the insult of portal diversion upon a liver that is already laboring under the handicap of intrinsic disease has become increasingly appreciated. Furthermore, the results of randomized clinical trials in patients with or without previous variceal hemorrhage have not demonstrated a statistically significant increase in survival after any kind of portacaval shunt when compared with that achievable without operation. The usual outcome after shunting has been that a decreased mortality after gastrointestinal hemorrhage has been replaced by perioperative deaths or by a subsequent higher death rate from hepatic failure. As a consequence, alternative methods (such as sclerotherapy<sup>295,296</sup> and transhepatic embolization of the left gastric (coronary) vein<sup>297</sup>) to control variceal bleeding non-operatively without changing the pre-existing blood flow patterns have been viewed with increasing acceptance.

A few patients may continue to be *bona fide* candidates for portal-systemic shunts. The techniques from which a choice can be made are shown in Figure 176-22. The literature about the various shunt operations is so voluminous and so frequently contradictory that no effort can be made to review it here. The interested reader can quickly obtain a good idea of what has been written by referring to Chapter 159 and by perusing one of several reviews.<sup>298-300</sup>

**Portal Flow Studies in Shunt Planning.** A logical decision about the type of shunt to be used cannot be reached without knowing if perfusion of the liver by portal blood (hepatopetal flow) persists. Rough estimates of residual portal flow can be made with angiographic techniques, including late phase venograms after selective arteriography.<sup>301</sup> Alternatively, a radiopaque dye can be injected directly into the portal vein by way of the liver<sup>302</sup> or by umbilical venography.<sup>303</sup>

**Completely Diverting Shunts.** By definition, an end-to-side portacaval shunt pro-

vides absolute assurance of complete portal diversion. With the reduction of pressure in the splanchnic venous system, hemorrhage from esophageal varices is practically eliminated, and this with an operation that can usually be done quickly, easily, and with little blood loss. Encephalopathy is a very common complication.

For a long time the various side-to-side shunts (portacaval, cavomesenteric, mesocaval, or conventional splenorenal) were assumed to permit partial continued perfusion of the liver with portal blood. However, all effective side-to-side shunts are merely variants of the common theme shown in Figure 176-22 (middle). All of the blood returning from the distal splanchnic bed is diverted around the liver if the anastomoses are adequate. In addition, a variable amount of blood from the sinusoids of the liver itself can pass into the systemic venous circulation by so-called retrograde drainage. The complications of hepatic failure, including encephalopathy, after the various side-to-side shunts have been as common in controlled series as after end-to-side portacaval shunts.<sup>304-306</sup> The mesocaval H-graft operation<sup>307</sup> is no exception, and in addition the prosthesis used in this procedure has a high rate of late thrombosis.<sup>308</sup>

**Selective Portal-Systemic Shunts.** If the objective is to prevent recurrent hemorrhage from esophageal varices, a decision to perform a selective portal-systemic shunt should be beyond criticism. The selective diversion procedures that have been used clinically include the original Warren-Zeppa-Foman distal splenorenal shunt<sup>309</sup> (Fig. 176-22, bottom), an uncommonly performed modification also described by Warren et al.<sup>310</sup> whereby the distal splenic vein is anastomosed to the inferior vena cava (Fig. 176-22), and the direct anastomosis of the coronary vein (left gastric vein) to the inferior vena cava described by Inokuchi et al.<sup>311</sup> (Fig. 176-22). The selective shunts are technically more difficult and demanding than the conventional completely diverting portacaval shunt. Yet, if it can be accomplished, a distal splenorenal type procedure effectively decompresses esophageal varices while maintaining hepatopetal portal venous flow. Warren's selective procedure is associated with better preservation of hepatic biosynthetic processes such as urea production<sup>312</sup> than after completely diverting portacaval shunt, and it carries a far lower rate of encephalopathy.<sup>298,313-317</sup>

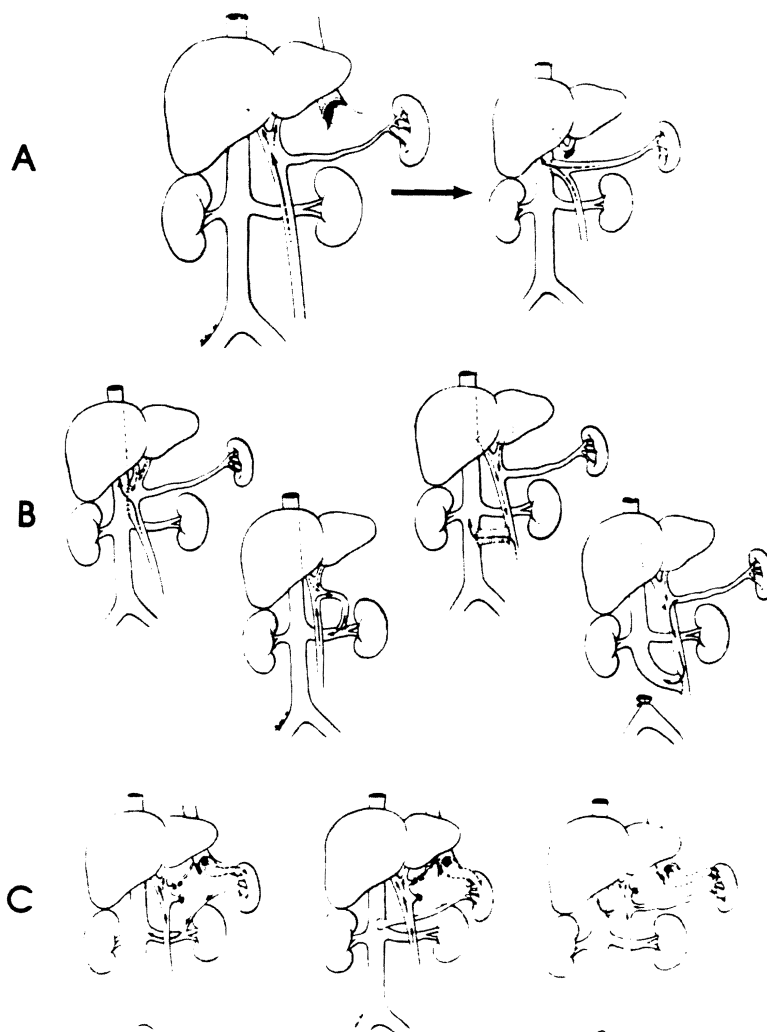


Figure 176-22. Kinds of portal-systemic shunts. A, End-to-side portacaval shunt. B, Variant to side-to-side shunts. C, Selective portal-systemic shunts.

Randomized trials comparing the distal splenoportal shunt with totally diverting shunts have not revealed a striking divergence in the life survival curves.<sup>298,313-317</sup> If this trend continues, maintenance of a better quality of life, including relative freedom from hepatic encephalopathy, may be the only justification for the selective shunts in preference to the completely diverting shunts. If selective shunt procedures fail to provide a better life survival than totally diverting portacaval shunts, the most fundamental reason undoubtedly is that the patients under treatment have progressive hepatic diseases with such an immutable course that the effect of therapeutic intervention cannot be accurately measured. Other factors may play a minor role in masking the superiority of selective shunts, including a higher perioperative mortality while surgeons are learning how to carry out the Warren procedure.

At least in some patients, the residual hepatopetal portal flow that is expected from the Warren procedure is gradually "stolen" from the liver as blood from the high pressure mesenteric bed is recruited into the low pressure area drained by the distal splenoportal shunt.<sup>313,318-320</sup> The loss of portal hepatic perfusion is so gradual after distal splenoportal shunt<sup>313,321</sup> that time (months or years) exists for compensatory physiologic adjustments such as augmentation of the hepatic arterial input.

**The Concept of Portal Arterialization.** After completely diverting portacaval anastomosis, the possibility of replacing the lost portal flow with arterial blood has been examined in many experimental laboratories. Clinical trials have been under way in one American<sup>322</sup> and one European center.<sup>323</sup> Such operations could have a minor beneficial effect, since the hepatotrophic constituents that are diverted around the liver with



a shunt become available in diluted form by way of the arterial system. These diluted hepatotropic substances would be brought to the liver in direct relation to the quantity of hepatic flow. Nevertheless, any benefit from such flow augmentation procedures is limited. The atrophic changes in liver fragments deprived of splanchnic venous inflow could not be prevented by arterializing the liver tissue despite flow augmentation to several times normal volume.<sup>232</sup> Furthermore, the depressed activity of the mixed function oxidase system following portacaval shunt could not be restored by rearterialization of the portal vein stump.<sup>257</sup> Portal arterialization procedures will have little, if any, effect on either morbidity or mortality after completely diverting portal-systemic diversion.

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