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Transplantation of the Liver

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The ultimate therapeutic step in the treatment of any terminal hepatic disease is the provision of a new liver with or without removal of the afflicted native organ. The first clinical trial of liver transplantation took place in 1963.²⁴ In the subsequent decade, more than 150 attempts have been made throughout the world, 74 of these at our own institution. The historical aspects of both animal and human liver transplantation have been summarized in a book in which the world literature was brought up to date as of the spring of 1969.¹⁹

KINDS OF OPERATIONS**AUXILIARY TRANSPLANTATION**

Liver transplantation was first performed and recorded by Welch in 1955.³¹ Welch envisioned treating patients who were dying of cirrhosis or other non-neoplastic diseases for whom the removal of the diseased native liver would not be obligatory. With the Welch operation, the extra canine liver was placed in the right paravertebral gutter or the right side of the pelvis. Its hepatic arterial supply was derived from the aorta or from the iliac artery. Venous inflow was reconstituted by anastomosing the distal inferior vena cava or a distal iliac vein to the homograft portal vein. Outflow was into the inferior vena cava (Fig. 35-1A).

The use of auxiliary homografts for the

treatment of benign hepatic disease initially had a special attractiveness, and still does in the minds of a minority of students of liver transplantation. The adherents of auxiliary transplantation argue that sacrifice of the remaining function of the failing recipient liver could be avoided, providing some reserve in the event of poor initial performance by the homograft, due to ischemia or to a severe but reversible rejection. This might be a particularly significant advantage in patients with biliary atresia, since the synthesizing functions of the liver are often retained until the terminal stages of this disease. Second, it was initially assumed that the placement of an extra liver would be safer and technically less demanding than the orthotopic procedure, an assumption that has not been validated by actual experience.

With auxiliary transplantation, the results in animals have been inferior to those with liver replacement, partly because co-existing livers have the capacity to damage each other to a variable degree according to which organ is the "dominant" one. Factors favoring dominance include a splanchnic source of the blood for portal venous inflow, perfect biliary drainage, optimal total hepatic blood flow, and unimpeded venous outflow. An auxiliary canine liver graft, which does not enjoy these advantages relative to the host liver, undergoes rapid atrophy¹² by mechanisms that have evoked numerous and heated discussions.¹⁰ More recently, evidence has been ac-

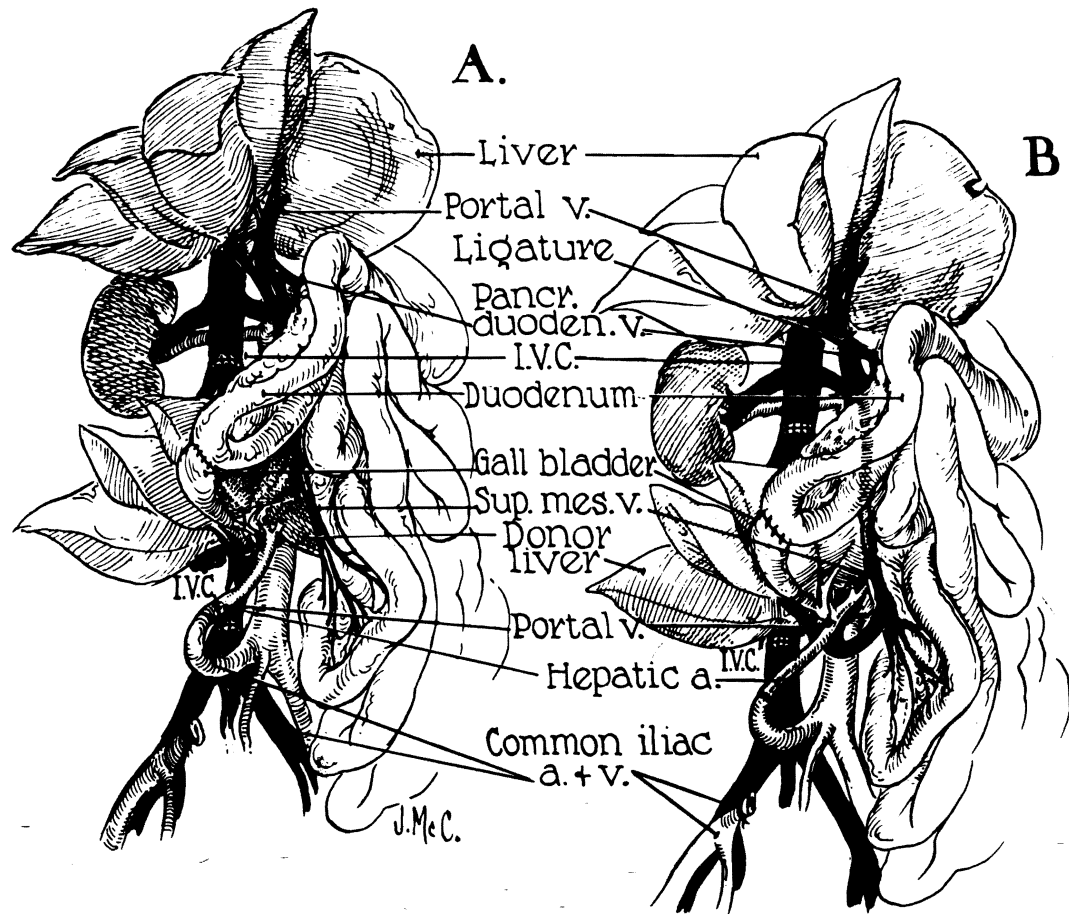


FIG. 35-1. Marchioro's first experiment with auxiliary hepatic homotransplantation, which suggested competition between coexisting livers. A) Modification of Welch-Goodrich technique. The portal blood flow to the transplant was from the systemic venous system. The homograft underwent rapid atrophy. B) The portal venous inflow was obtained from the nonhepatic splanchnic bed. The host liver received only an arterial supply. With these changes, the homograft atrophy was prevented and in some experiments, the shrinkage now involved host livers. (Marchioro, T. L., et al.: *Surg. Gynecol. Obstet.*, 121:17, 1965.)

quired to explain the beneficial effect of perfusing the portal vein with splanchnic venous blood. It has been shown that the "hepatotropic factors" in this kind of venous blood emanate from the pancreas and that the most important constituent is apparently endogenous insulin.²¹ Since insulin is largely removed by a single passage through the liver, the first organ having access to pancreatic blood would deprive the second liver of an adequate supply of this hormone.

Until 1973, clinical auxiliary liver transplantation had never resulted in the significant prolongation of recipient life. The results had been so poor that the number of attempts

at the auxiliary operation declined virtually to zero. A contributory factor was that the placement of an extra organ had often proved to be more difficult, rather than technically simpler, than in liver replacement.

But early in 1973, Fortner lightened the pessimism about auxiliary transplantation by revascularizing a homograft using the principles described by Marchioro *et al.*¹² shown in Figure 35-1B, whereby the splanchnic blood is directed through the heterotopically located liver. The human version of this procedure is shown in Figure 35-2. Fortner's patient suffered from biliary atresia. After operation, the bilirubin fell to normal, the native

liver underwent marked shrinkage, and the splenomegaly and hypersplenism were relieved. The follow-up in the case is now more than six months.⁷ In view of this encouraging experience, additional clinical trials of auxiliary transplantation will probably be forthcoming.

ORTHOTOPIC TRANSPLANTATION

The alternative approach to hepatic transplantation is liver replacement (or orthotopic transplantation). With this operation, the diseased host liver is removed, creating a space into which the graft is transplanted with as normal an anatomic reconstruction as possible. Survival in dogs and humans has been achieved exceeding 9½ and 4½ years, respectively. The remarks in succeeding sections will pertain to the more promising orthotopic transplantation as opposed to the auxiliary operation discussed above.

INDICATIONS FOR HEPATIC TRANSPLANTATION

No matter what the underlying disease, certain criteria should be met before accepting patients for chronic immunosuppression and transplantation. None of the contraindications is absolute, although they may be very strong. For example, pre-existing systemic or local infections would create highly unfavorable conditions. So would diseases of organs other than the liver, for example, co-existing severe heart disease, or a history of sociopathic behavior which would prevent postoperative management. From our experience with renal transplantation, we have learned that people who are more than 45 or 50 years of age frequently cannot withstand the rigors of intensive immunosuppression. They may develop muscle wasting and other physical incapacities, have steroid-induced pancreatitis more frequently than younger patients, and have a

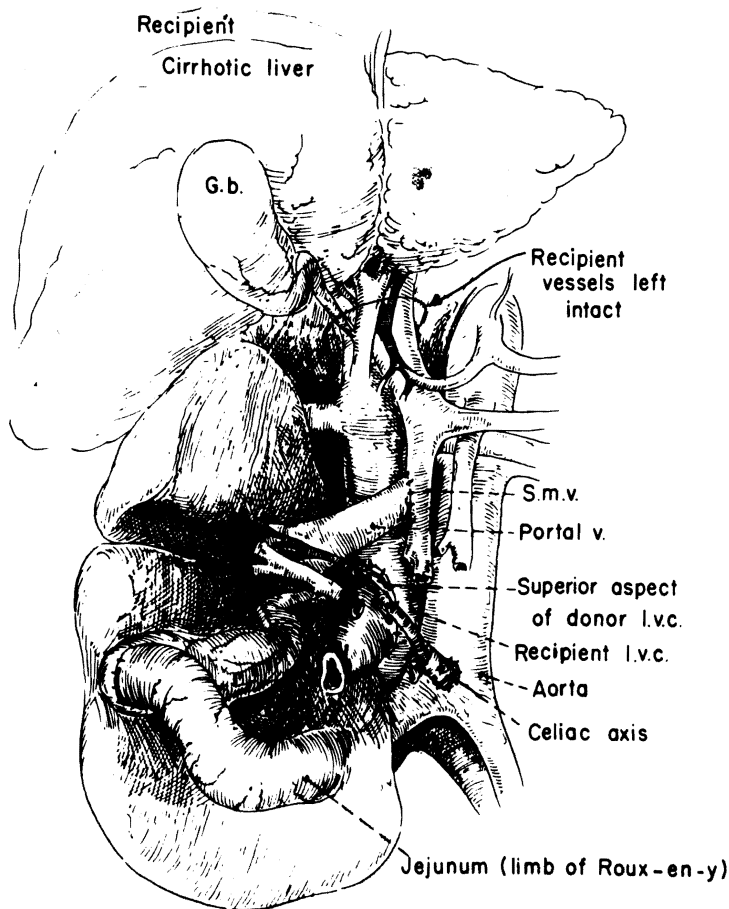


FIG. 35-2. A technique of auxiliary liver transplantation in which the homograft receives through its portal vein venous blood derived from the splanchnic bed. (Starzl, T. E. and Putnam, C. W.¹⁰)

higher incidence of a variety of gastrointestinal complications, including gastroduodenal hemorrhage and colonic problems.¹⁵

BENIGN DISEASE

Any patient with terminal liver disease of non-neoplastic origin is a potential candidate for liver transplantation. Of the various possibilities, extrahepatic biliary atresia is perhaps the least questionable, since death is inevitable after a relatively predictable interval and without any hope in the remaining life for rehabilitation. Because of these considerations, children can be considered for this operation while they are still in relatively good health. With intrahepatic biliary atresia, more conservatism is exercised since some of these children can survive for many years.

The problem of the proper time for liver transplantation may be difficult for almost all other kinds of non-neoplastic liver disease. This is particularly true if alcoholism is a significant etiologic factor that could be eliminated by abstinence. All gastroenterologists of experience have seen occasional patients with Laënnec's cirrhosis who were apparently dying of profound hepatic failure but who recovered and subsequently left the hospital.

Appreciation of this fact has probably been responsible for the rather small number of liver transplantations for the indication of alcoholic cirrhosis.

The outcome is somewhat more predictable in patients with post-necrotic cirrhosis and less common disorders such as primary biliary cirrhosis, medically refractory Wilson's hepatolenticular degeneration, irreparable biliary duct injury, and some of the more lethal in-born errors of metabolism. But even with these diseases, there was initial reluctance to proceed until incontrovertible evidence was obtained that extended survival was possible in humans after liver transplantation. Now that the feasibility of long-term survival has been proven, it will be possible to relax the restrictions on intervention so that treatment may be instituted before the terminal stages of the disease. Otherwise, it is unlikely that the results in future cases will be significantly improved.

At present, it is our belief that all patients who are dying from an otherwise untreatable non-neoplastic hepatic disease should be considered as possible candidates for liver transplantation providing there are no other reasons, such as those discussed at the beginning of this section, against the decision.

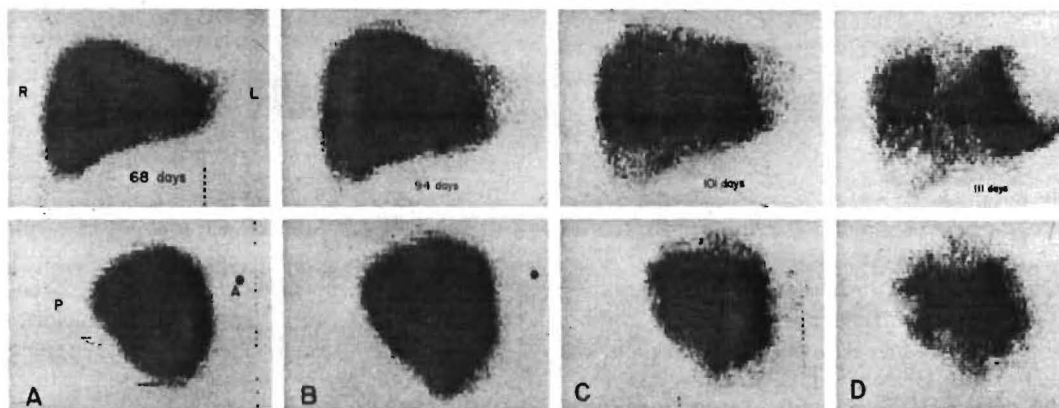


FIG. 35-3. Destruction of the homograft by tumor recurrence in a 15-year-old recipient, whose indication for liver transplantation was hepatoma. The posteroanterior and lateral liver scans were obtained with ^{99m}technetium. A) 68 days: Normal scan. B) 94 days: The patient had become jaundiced. Hepatomegaly is evident. C) 101 days: Multiple areas of poor isotope concentration are now visible. D) 111 days: The process has continued its rapid progression. By the time of death one month later, the homograft was almost completely replaced with carcinoma (see Fig. 35-4). (Starzl, T. E. and Putnam, C. W.¹⁹)

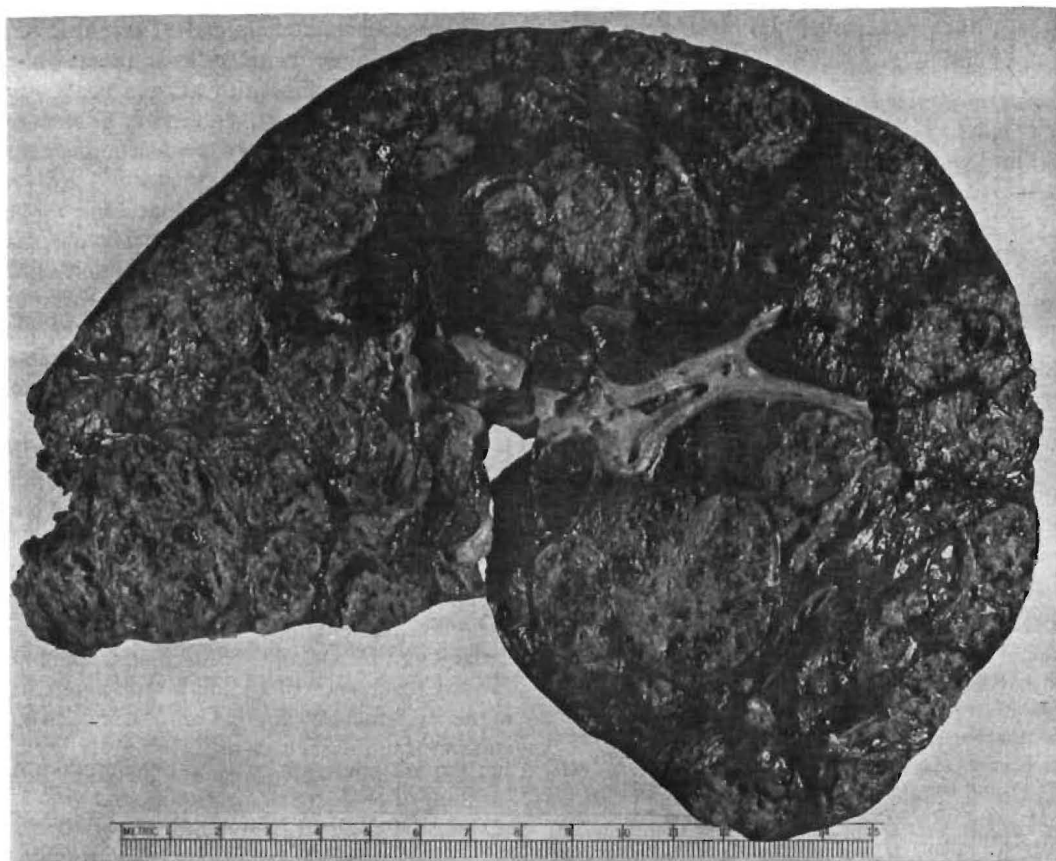


FIG. 35-4. The liver homograft at autopsy, 143 days post-transplantation, of the patient whose scans are depicted in Figure 35-3. The graft has been replaced by tumor except for a very small residual area of hepatic parenchyma (arrow). (Starzl, T. E. and Putnam, C. W.¹⁰)

THE QUESTION OF HEPATIC MALIGNANCY

Orthotopic liver transplantation was first attempted in humans for the indication of primary liver malignancy. The major reason for this policy was that complete removal of the recipient liver was an obligatory component of the undertaking if cure was to be achieved. Thus, liver replacement was conceived as a means for extending the limits of resectability in patients who did not have extrahepatic spread of their tumors.

Actual experience with liver replacement for the indication of primary hepatic malignancy has led us to declare a moratorium on such cases. At the University of Colorado, a total of 13 patients have undergone liver replacement because of the preoperative diag-

nosis of primary hepatic malignancy. In six cases, the attempt was "successful" in a technical sense, with survival for at least 2½ post-operative months. All six recipients developed recurrence of malignancy from two to thirteen months later. Eventually, the six patients died and in most instances, the tumor recurrence either caused death or contributed to it in an important way. Lethal and widespread metastases were responsible for death as early as 143 days after operation and as late as 14 months (Figs. 35-3, 35-4).

Hepatoma was the histopathologic diagnosis in all but one of the foregoing six cases with postoperative follow-ups exceeding 2½ months. The exceptional patient had a heman-
giendotheliosarcoma. Although he made a

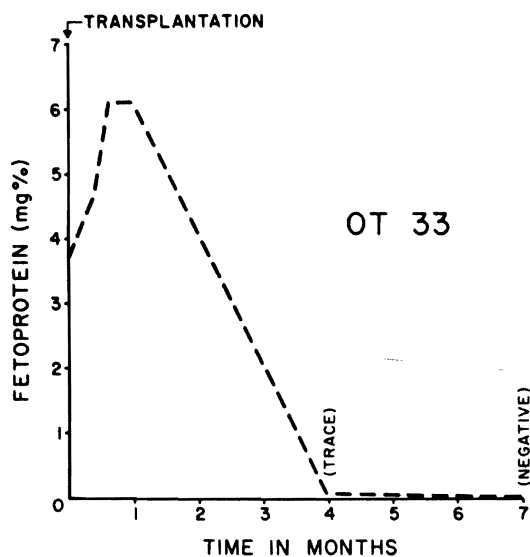


FIG. 35-5. Alpha-fetoprotein determinations in a 3-year-old child who underwent transplantation for biliary atresia. A small hepatoma was discovered within the operative specimen. The child is now 3½ years after transplantation. Alpha-fetoprotein determinations continue to be negative and she remains free of tumor. (Starzl, T. E. and Putnam, C. W. in *Abdominal Operations* (Maingot, R., Ed.). 6th Edition. New York, Appleton-Century-Crofts, 1974, pp. 1247-1271.)

satisfactory recovery from operation, he also developed widespread metastases and died in less than four months.

We have suggested that the immunosuppressive therapy necessary to prevent rejection may itself have contributed to the aggressiveness of the metastatic growth. Such speculations are based in some way on the surveillance hypothesis of cancer proposed by Thomas²⁹ and Burnet³ which holds that the immune system is an important factor in the limitation of growth of mutant neoplastic cells. Whether immunosuppression and the consequent loss of this restraining influence upon tumor growth contributed to the unsuccessful outcome under the specific conditions of liver transplantation cannot be proved, since the results may only have been a reflection of the highly malignant natural history of these neoplasms.

It is conceivable that other kinds of hepatic malignancies with a more indolent natural course may be less prone to post-transplanta-

tion recurrence and spread. Three patients with intrahepatic ductal cell carcinomas have now received transplants at our center for this lesion. Two survived the early postoperative period; neither has evidence of recurrence.

It is too early to conclude once and for all that liver replacement in the face of hepatic malignancy is an unacceptable undertaking. One of our patients, whose primary reason for liver transplantation was biliary atresia, had an incidental hepatoma in the total hepatectomy specimen. Her preoperative serum contained almost 4 mg. per cent of alpha fetoprotein. After operation in 1970, the alpha fetoprotein disappeared from the serum (Fig. 35-5) and has not recurred in the 3½ years of post-transplantation life. Apparently, this child has achieved a cure from her hepatoma. Isolated "cures" of hepatic malignancy after liver replacement have also been reported by Calne⁴ and by Daloz.⁵ Nevertheless, the high rate of recurrence of tumor in our hands has made us reluctant, for the time being, to accumulate more such cases.

DONOR PROCUREMENT

In most transplantation centers in the United States, the criteria of brain death based upon the concept of irreversible brain injury have been accepted for the pronouncement of death. Under these conditions and with an ideal cadaveric donor, the interval of normothermic ischemic injury is reduced essentially to zero, inasmuch as the dissection prior to the removal of the liver or other organs can be carried out or even completed in the presence of an effective circulation. It is of more than passing interest that public acceptance of these conditions of organ removal has been widespread in America with almost no negative outcries.

However, in at least half of the potential cadaveric donors seen by us, there is a need for far greater urgency than under the ideal conditions just discussed. One common circumstance seen by us is the development of an irreversible cardiac arrest in someone already considered to have a hopeless brain injury. When this occurs, the organs can be saved for transplantation by the rapid insertion of cannulas through a femoral artery and

vein into the great abdominal vessels. The cadaver may then be connected to a cardiopulmonary bypass. With a heat exchanger interposed in the circuit, the body may be simultaneously perfused and cooled (Fig. 35-6). Finally, refinements in technology have made possible the successful preservation of canine and human livers for many hours after their excision and insertion into perfusion chambers.² With these various advances, all achieved within the last decade, it is no longer excusable to carry out a liver transplantation with an organ that has been significantly injured either pre- or post-mortem.

DONOR-RECIPIENT MATCHING

With the exception of biliary atresia, most potential recipients of liver homografts have a very brief period of candidacy for transplantation. If an organ cannot be quickly found, death supervenes. Obviously, highly discriminating donor selectivity is not practical under these circumstances and for that matter any selectivity, however supportable on immunologic criteria, may cost the patient his only chance for treatment. It is in the context of such urgency that donor-recipient matching will be considered below.

THE HL-A SYSTEM

Several years ago, it was hoped that clinical results after cadaveric transplantation might be improved by effective donor-recipient matching of histocompatibility (HL-A) antigens. Unfortunately, the results obtained so far with hepatic, cardiac, and renal transplantation have not correlated well with the quality of the matches. These findings in our own experience and in that of others have led us, for the moment, to ignore the question of HL-A matching for liver transplantation. Nor do we even use most favorable matching as an instrument of selection among a given group of candidates for transplantation. At the present time, our major criterion concerns who has the most pressing need.

THE QUESTION OF PREFORMED ANTIBODIES

ABO Matching. When a seriously ill person is identified as a possible organ donor, the ABO blood type is determined. In considering potential recipients for the liver, it is desirable that they have the same ABO group as the donor. Failing this, the rules of tissue transfer summarized in Table 35-1 are followed. The guidelines are designed to avoid the trans-

FIG. 35-6. Technique of extracorporeal perfusion with a heart-lung machine. In the event of an irreversible cardiac arrest in a patient with a hopeless brain injury, catheters are rapidly inserted via the femoral vessels into the aorta and vena cava. The extracorporeal circuit is primed with a glucose or electrolyte solution to which procaine and heparin are added. The cadaver is thus anticoagulated with the first surge of the pump. Temperature control is provided by the heat exchanger. Cross-clamping the thoracic aorta limits perfusion to the lower part of the body. (Starzl, T. E. and Putnam, C. W.¹⁹)

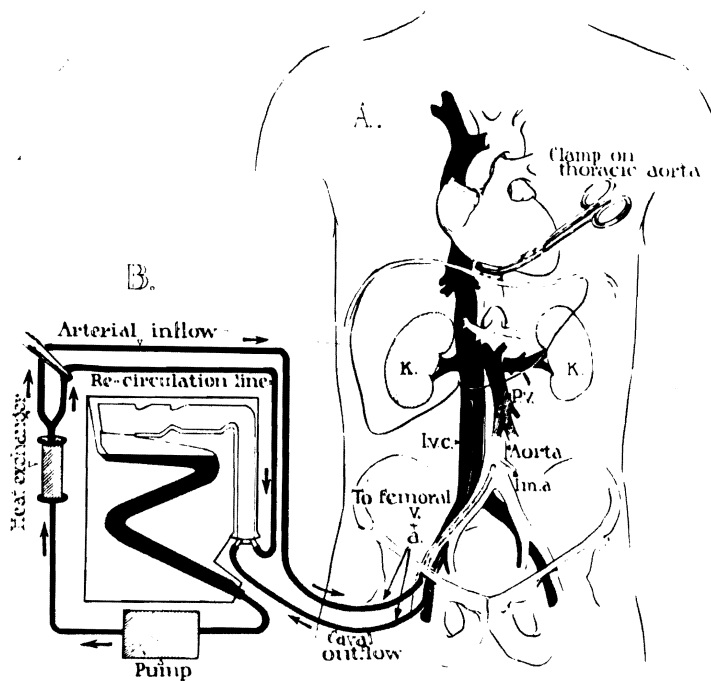


TABLE 35-1. DIRECTION OF ACCEPTABLE MISMATCHED TISSUE TRANSFER *

O to non-O	Safe
Rh- to Rh+	Safe
Rh+ to Rh-	Relatively Safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous

* O is universal donor. AB is universal recipient.

plantation of an organ into a recipient who possesses preformed antidonor isoagglutinins. Red blood cell antigens against which these isoagglutinins react are found not only in red cells but also in most nucleated cells. Thus, violation of the rules of tissue transfer (Table 35-1) can result in an acute immunologic insult to a graft. With kidney homografts, immediate rejection has commonly occurred.¹⁸

Since red cell antigens are also found in hepatocytes, the principles enunciated in Table 35-1 have been scrupulously followed at our center in all cases of liver transplantation until recently. Then, three ABO mismatched livers were used (Table 35-2). Hyperacute rejection did not occur and no obvious adverse consequences were seen. The titers of antigraft isoagglutinins were highly variable and, at least in one case, reached prodigious levels (Table 35-3). This ability of the liver to remain healthy under conditions which would be predictably harmful to most kidneys is a noteworthy feature which has been seen in other preformed antibody situations to be discussed later.

Cytotoxins. For example, in renal transplantation, the presence of antigraft cytotoxic antibodies in the recipient carries an overwhelming risk of hyperacute rejection, even higher than with transplantation across the ABO barrier. The events of hyperacute rejection include clearance by the graft of the antibodies, formed blood elements, and clotting factors.^{16, 20, 23} The result is that the small vessels of the organ become occluded with diffuse thrombi and the graft undergoes infarction. When xenografting is performed between widely divergent species, as from the pig to the dog, organs are hyperacutely rejected by the same mechanism. However, the liver is destroyed more slowly than the kidney.^{11, 16} Thus we have concluded that even in this devastatingly severe experimental model, the liver is relatively resistant to hyperacute rejection.

The resistance to hyperacute rejection probably is a general principle in clinical practice as well. During the last year, three patients have been given livers from donors against which cytotoxic antibodies were found. In all three cases, cytotoxins were also present against most of the donors of an indifferent lymphocyte screening panel. Thus, the prospects of finding a liver without a positive cytotoxic antibody crossmatch were considered nil. As a consequence, a decision was made to proceed despite the potentially adverse prognostic implications.

None of the three patients developed hyperacute rejection, although two of them eventually died (Table 35-4). In Case 3, the

TABLE 35-2. THREE CASES OF TRANSPLANTATION OF ABO INCOMPATIBLE LIVERS

CASE NUMBER	DONOR		RECIPIENT		PRE-OP ISOAGGLUTININ TITER	SURVIVAL	CAUSE OF DEATH
	ABO Types						
1	AB	→	A		1:4 (anti-B)	173 days	Sepsis
2	AB	→	A		1:32 (anti-B)	61 days	Sepsis Pulmonary emboli Liver failure
3	A	→	O		1:512 (anti-A)	41 days	Disseminated herpes and cytomegalovirus Pulmonary emboli Brain infarction

TABLE 35-3. ANTIGRAFT ISOAGGLUTININ TITERS IN THE THREE RECIPIENTS OF ABO INCOMPATIBLE LIVERS DESCRIBED IN TABLE 2

POST-OP DAY	CASE 1 (Anti-B)	CASE 2 (Anti-B)	CASE 3 (Anti-A)
0	1:4	1:32	1:512
1	1:4	1:16	
3	1:1	1:4	1:64
5	1:1	1:2	1:64
7	1:1	1:8	1:2048
9	1:4	1:64	1:8192
11	1:4	1:64	1:8192
13	1:4	1:32	1:4096
15	1:4	1:16	1:2048
17	—	1:8	1:1024
19	1:2	1:4	1:1024
21	1:1	1:4	1:512
28	1:1	1:2	1:256
35	1:2	1:2	1:128
42	1:2	1:2	
49	1:2	1:1	
56	1:2	1:8	
63	1:2		
70	1:2		
77	1:8		
84	1:4		

homograft seemed to have been severely damaged by ischemia, although its poor initial function could have been a manifestation of acute antibody-mediated injury. After 10 days, the organ was removed and replaced by a chimpanzee heterograft, against which the recipient cytotoxins also reacted. The chimpanzee liver functioned for most of the 14

subsequent days of the patient's life. Upon pathologic examination, the initial homograft had many focal areas of necrosis compatible with the diagnosis of ischemic injury. In contrast, the heterograft was well preserved. Centrilobular cholestasis was a prominent feature. Otherwise, there was little evidence of rejection.

TABLE 35-4. THREE CASES OF HEPATIC TRANSPLANTATION IN WHICH THE RECIPIENTS HAD ANTIDONOR CYTOTOXIC ANTIBODIES

CASE NUMBER	PRE-OP CYTOTOXICITY TITER	SURVIVAL	CAUSE OF DEATH
1	1:2	Alive	
2	1:64	26 days	Extra-hepatic biliary obstruction Peritonitis Bleeding diathesis
3	(Homograft) 1:16	(Removal of the graft at 10 days)	
	(Heterograft) 1:16	14 days after re-transplantation	Pulmonary edema Hemorrhage

It goes without saying that preformed antibody states should be avoided if at all possible. However, the experience cited both with the ABO red cell and cytotoxic antibodies makes it clear that this kind of positive cross-match is not an absolute contraindication to liver transplantation.

PREOPERATIVE PREPARATION

Prospective liver recipients are generally poor risks for a major operation. Those with hepatic failure from non-neoplastic disease may even appear at first evaluation to be hopeless. Paracentesis or thoracentesis may be required before anesthesia can be contemplated. Transfusions of blood or albumin may be useful for the correction of blood volume or other fluid space abnormalities. If fresh whole blood, fresh frozen plasma or platelets are judiciously given, some improvement in coagulation may be possible. Otherwise, there is usually little of real value that can be done to reduce the impending operative hazards.

Theoretically, one way of transiently increasing liver function before the definitive procedure would be with *ex vivo* hepatic support, using an extracorporeal heterologous liver by techniques adapted from Eiseman *et al.*⁶ Such an approach to resuscitation prior to transplantation has not yet been tried. One reason is that the resuscitation obtained by this method has been of borderline benefit when weighed against the potential complications. In addition, even patients near death from hepatic disease can be brought through the transplantation procedure with almost immediate improvement, providing the homograft functions properly and promptly.

The surprising ability of these moribund recipients to survive such major surgery may be related partly to the troublesome operative bleeding which is almost invariably encountered. The consequent necessity for major blood replacement frequently results in intraoperative exchange transfusions of at least the magnitude reported by Trey *et al.* to be of benefit in acute liver insufficiency.³⁰ The coincidental therapeutic effect of massive transfusion, as well as the immediate benefits of good hepatic function by the transplant, have usually resulted in patients returning to the

ward in better condition than at the time of their departure.

Secondary abnormalities of organs other than the liver can sometimes be effectively ameliorated. For example, the effects of renal failure secondary to the hepatorenal syndrome can be treated with the artificial kidney. Pulmonary manifestations may be improved by simple tracheobronchial toilet, particularly if aspiration has occurred.

The inability to be more specific in preparing patients for surgery means that most prospective recipients cannot be maintained for very long during a search for a suitable donor. At present, only a small fraction of patients who might be candidates for liver transplantation can actually be treated, since there are no means of providing therapy analogous to that utilizing the artificial kidney to tide over prospective recipients while an organ is being found. Until an artificial liver is developed which will provide some of the more crucial hepatic functions, liver transplantation will not be able to achieve anything like its true potential.

OPERATIVE PROCEDURES

DONOR HEPATECTOMY

In removing a liver for eventual transplantation, the essential steps are to incise the restraining ligaments that bind the organ to the diaphragm and body wall and to skeletonize the vessels and duct that must be anastomosed to the companion structures in the recipient. Figure 35-7 depicts the initial steps in this process. Then, the portal vein, hepatic artery, and common duct are dissected (Fig. 35-8). Details of the various surgical maneuvers are described elsewhere.¹⁹

THE RECIPIENT ORTHOTOPIC OPERATION

Most of the steps in the recipient are identical or similar to those described above for the donor, except that long cuffs of vessels and the duct are left with the patient rather than with the homograft. After removal of the liver, the residual anatomy consists of cuffs of four cut vessels, the common duct stump (except in biliary atresia), and the raw areas left by incision of the various hepatic

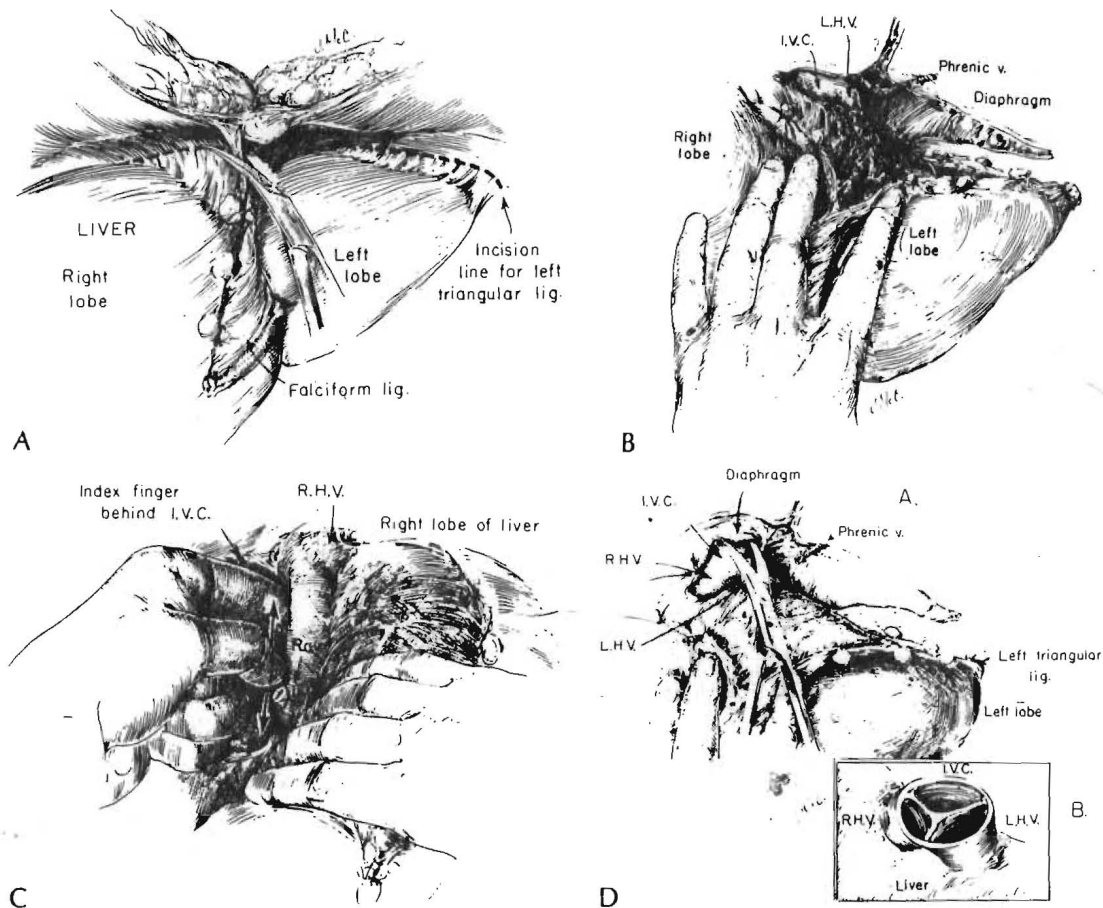


FIG. 35-7. Initial steps in hepatic homograft removal. A) The falciform and triangular ligaments are incised as far away from the liver as possible so that they can be resutured later to the companion structures in the recipient. B) Exposure and initial dissection of the suprahepatic vena cava and its tributaries. This is done by entering the raw area formed by divergence of the leaves of the falciform and triangular ligaments. A short segment of the left hepatic vein (L.H.V.) is usually seen first. C) After incising the right triangular ligament and the anterior leaf of the right coronary ligament, the liver is retracted to the left, exposing the bare area of the right lobe. The right adrenal vein, usually the only posterior tributary of the retrohepatic vena cava, is ligated and divided. It is then possible to sweep behind the vena cava from the diaphragm to the renal veins. If resistance is encountered, it usually indicates the presence of extra branches which must be ligated and divided. R.a.v.—ligated right adrenal vein. D) Development of suprahepatic vena caval cuff. At this stage it is desirable to ligate and divide one or more phrenic veins on each side. The latter step is not mandatory but it allows the mobilization of a longer segment for subsequent anastomosis. Each length can also be obtained by dissecting off the diaphragmatic reflection, as is being shown. *Inset.* Cross-sectional appearance of the venous confluence above the liver as it is seen from above. The cloaca is formed by the junction of the right and left hepatic veins with the inferior vena cava. (Starzl, T. E. and Putnam, C. W.¹⁰)

ligaments (Fig. 35-9). The reconstruction consists of anastomosing the individual vessels to the vessels of the homograft as quickly as feasible. The "standard" operation is shown in Fig. 35-10.

The most commonly employed biliary reconstruction has been with cholecystoduodenostomy (Fig. 35-10), connecting the gallbladder to the duodenum with an external layer of interrupted silk and a continuous in-

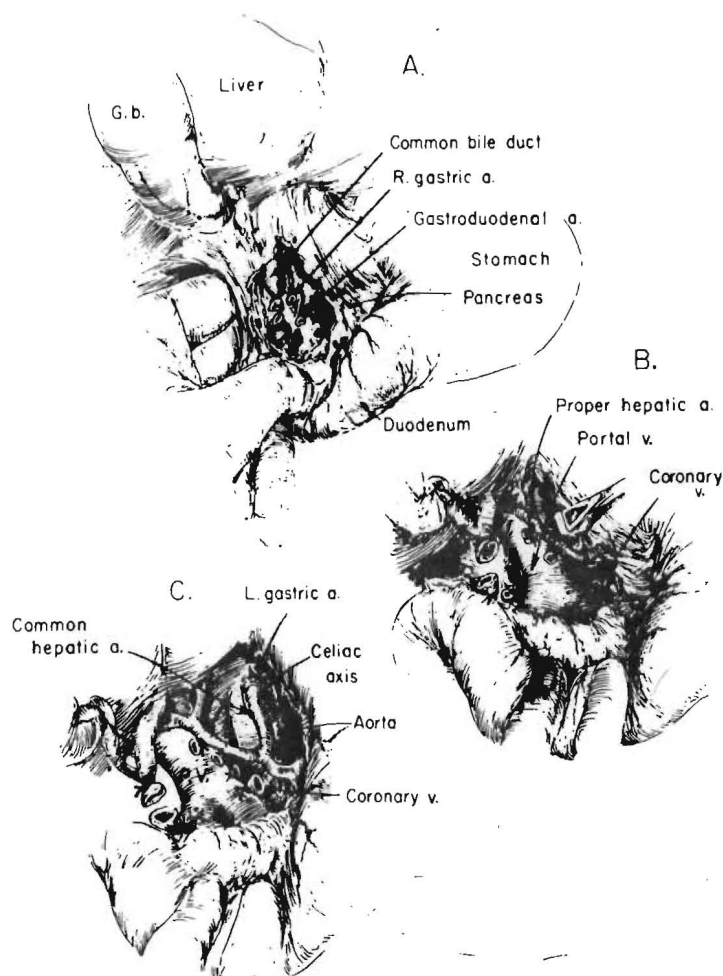


FIG. 35-8. Dissection of the portal triad. A) The common duct and the gastroduodenal and right gastric arteries are tied off and divided. Before ligation of the common duct, it should be determined that it communicates freely with the gallbladder via the cystic duct. If anomalies are present, failure to observe these precautions may lead to accidental bile duct obstruction. B) The hepatic artery has been mobilized far enough so that the anterior surface of the portal vein is uncovered. The coronary vein entering the left side of the portal trunk is almost always found; this tributary is ligated and divided. C) The portal vein has been freed and the celiac axis mobilized. The splenic artery has not yet been ligated and divided. When the liver is removed, all the celiac axis is usually retained with the specimen and in children, it may be advisable to include a segment of aorta as well. (Starzl, T. E. and Putnam, C. W.¹⁹)

ternal layer of catgut. More will be said later about alternative techniques.

INTRAOPERATIVE COMPLICATIONS

Anesthesia. Liver transplantation is an operation on the primary organ involved in the metabolism and detoxification of most common anesthetics. The challenge faced by the anesthesiologist is to administer correctly drugs that, first, are not hepatotoxic and second, do not depend primarily on the liver for their degradation. In most of our first cases, reliance was placed mainly on combinations of volatile agents such as fluoroxene and nitrous oxide-oxygen mixtures in nonexplosive concentrations. Such management, which was standardized by Aldrete,¹ permitted use of the electrocautery, gave flexibility in light-

ening or deepening anesthesia, and allowed anesthesia to be abruptly stopped if required by changing physiologic circumstances. More recently, the tendency has been to give anesthesia with less preoccupation about hepatic factors, but whether this approach will be satisfactory remains to be seen.

A number of swiftly changing metabolic conditions have to be carefully scrutinized during the anhepatic phase and immediately afterwards. Because the patient is at risk from acute hypoglycemia, a constant infusion of glucose is required. For proper control, frequent blood sugar determinations must be obtained. At the same time, the majority of recipients develop some element of acute metabolic acidosis, also requiring monitoring and correction. A third life-threatening complication which is frequently seen just after

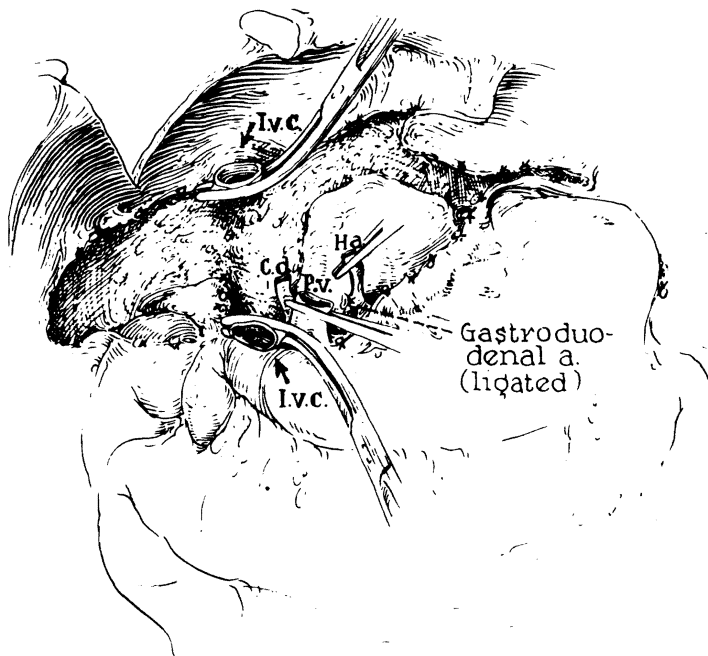


FIG. 35-9. The operative field after removal of the diseased recipient liver. In the illustration, an incision in the diaphragm is shown as part of a thoracoabdominal exposure. In all more recent cases, the chest has not been entered. C.d. = common duct; H.a. = hepatic artery; I.V.C. = inferior vena cava; P.v. = portal vein. (Starzl, T. E., et al ²⁴)

revascularization and lasts for several hours is hypokalemia. Apparently, the potassium is sequestered in the grafts to the extent that serum potassium concentrations may fall to as low as 1.5 mEq. per liter.

Hemorrhage. Liver transplantation is a long, difficult and bloody procedure. Acute bleeding can be particularly troublesome because of the mechanical factor of portal hypertension present in nearly every patient. In addition, many of the normal coagulation factors that might help control hemorrhage are dependent on the liver and are therefore defective to begin with in the diseased recipient. These coagulation deficiencies may become rapidly worse after revascularization of an organ which has suffered ischemic damage, apparently due to consumption of clotting factors by the injured graft.⁸

When hemorrhage occurs, all mechanical hemostatic tactics including ligation, suture, and cautery are used until the revascularized homograft can participate in what is hoped will be appropriate coagulation function. In our early patients, an attempt was made to treat such bleeding problems by administering thrombogenic agents such as epsilon amino caproic acid (EACA). However, for a number of years, we have studiously avoided such

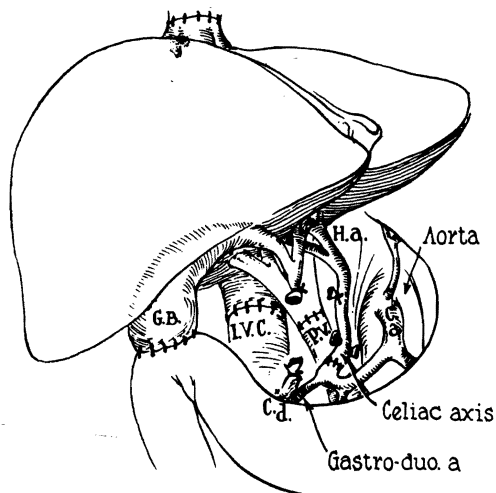


FIG. 35-10. Recipient operation. In most recent cases cholecystoduodenostomy has been performed for biliary drainage as shown. C.a. = celiac axis; C.d. = common duct; G.B. = gallbladder; H.a. = hepatic artery; I.V.C. = inferior vena cava; P.V. = portal vein; The kind of arterial anastomosis most commonly used. The homograft celiac axis or common hepatic artery is attached to the proper or common hepatic artery of the recipient. (Starzl, T. E., et al.: Orthotopic homotransplantation of the human liver. *Ann. Surg.*, 168:392, 1968.)

practices since they seemed to cause an increased incidence of thrombotic complications.

Bile Duct Reconstruction. An end-to-end anastomosis of the common duct, if it were feasible (an option not available in recipients with biliary atresia), would have the advantage of preserving the sphincter of Oddi, thus reducing the chances of reflux of food or bacteria. Because of the factor of immunosuppression, this anastomosis carries a high risk of leakage and infection whether or not T-tube stents and drains are employed. Consequently, the safer if less elegant technique is usually used of anastomosing the gallbladder directly to the duodenum and ligating the common duct (Fig. 35-10).

If there are unrecognized anomalies such as a septum between the cystic and common ducts, ligation of the transplant common duct in conjunction with cholecystoduodenostomy may lead to disaster. In two cases in our experience, biliary drainage was inadvertently obstructed when the common duct ligature closed both parallel passages (Fig. 35-11), a technical error that subsequent surgery failed to correct and that proved to be fatal.

While cholecystoduodenostomy remains the preferred primary operation, the slightest suspicion that it will not provide effective drainage for anatomic or other reasons should lead to a decision for choledochocholedochostomy or choledochoduodenostomy. With either procedure, the gallbladder should be removed.

Vascular. Multiple arteries of either the graft or host have been encountered in more than one-third of our cases, necessitating multiple anastomoses or other variant procedures which have had an increased risk of thrombosis.¹⁹

Other Complications. A homograft of exactly the right size may be difficult to find for any given recipient. Consequently, major size disparities often have had to be accepted. There have been few difficulties in using undersized organs. For example, it has been possible to carry out orthotopic transplantation of a five-year-old liver to a full-sized adult.

On the other hand, serious risks are borne when the donor organ is disproportionately large. Size disparities in this direction may lead to compression of the blood supply (Fig.

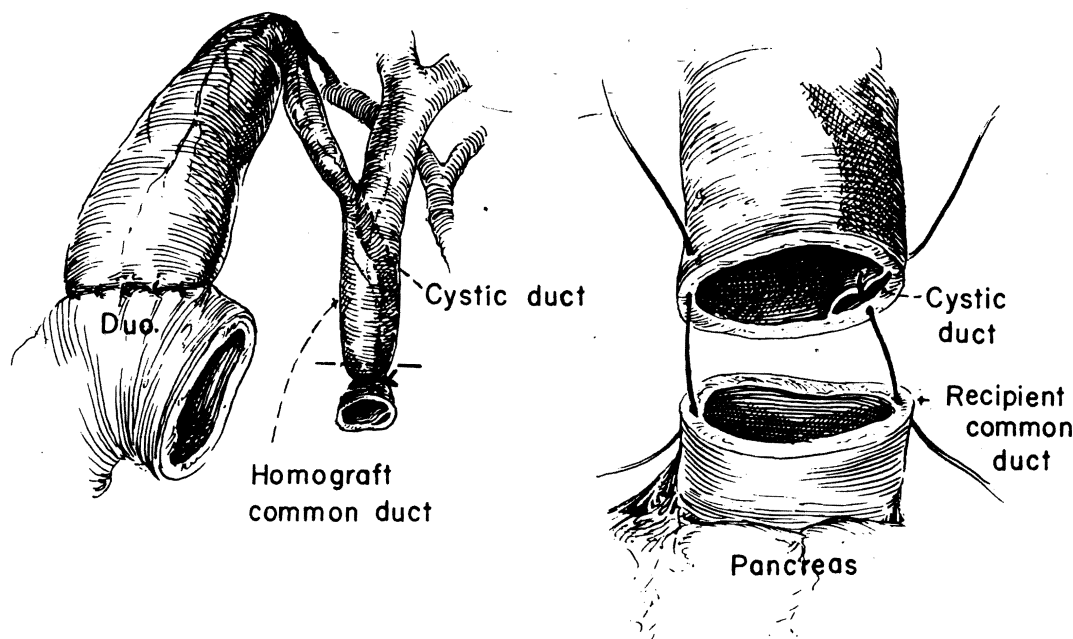


FIG. 35-11. The anatomical basis for a technical error which cost the lives of two patients. Distal ligation of the double-barreled extrahepatic duct system resulted in total biliary obstruction. Despite surgical correction of the obstruction by choledochocholedochostomy, both patients died of septic complications. (Starzl, T. E. and Putnam, C. W.¹⁹)

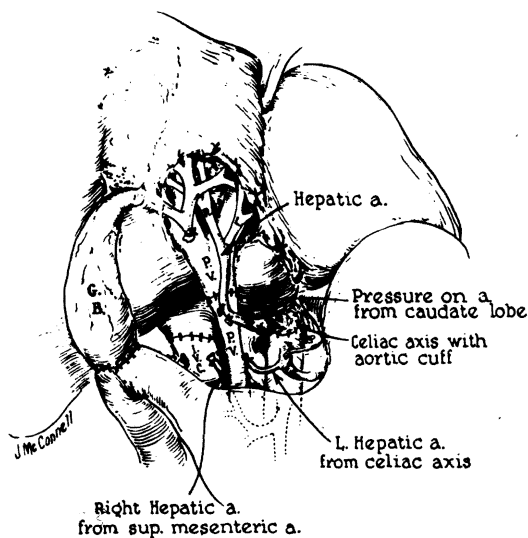
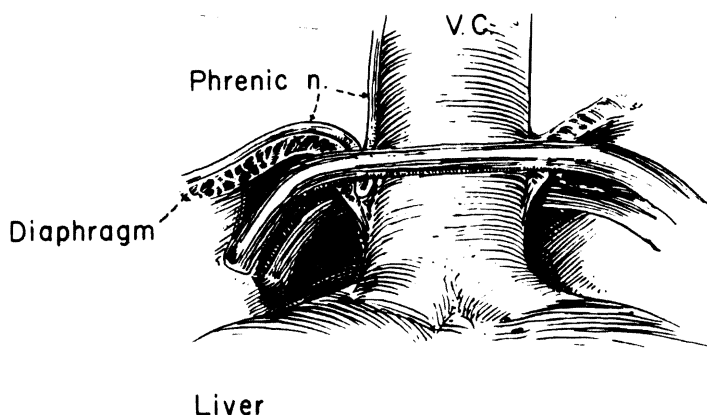


FIG. 35-12. Anomalous hepatic arterial supply encountered in a pediatric recipient of an orthotopic homograft. The larger right hepatic artery originated from the superior mesenteric artery; the small left branch came from the celiac axis. For this reason, the homograft celiac axis was anastomosed directly to the recipient aorta. Note the compression of the homograft arterial supply by the oversized homograft. This was not detected and resulted in death 15 hours later. (Starzl, T. E., et al.: *Transplantation of the Liver*. In *Progress in Liver Disease* (Popper, H. and Schaffner, F., Eds.). New York, Grune and Stratton, Inc., 1969.)

35-12). This kind of complication tends to occur just as the abdomen is being closed, in which case an adverse chain of events leading to death may be set in motion, but not appreciated until it is too late for correction.

FIG. 35-13. Probable mechanism of operative injury of the right phrenic nerve in four pediatric patients. Note the inclusion of the nerve in the bite of the vascular clamp, which has been placed across the suprahepatic vena cava and which has also included a piece of diaphragm. (Starzl, T. E. and Putnam, C. W.¹⁹)



A long list of other technical pitfalls includes venous infarction of the right adrenal gland secondary to the sacrifice of the adrenal vein during removal of the diseased native liver, air embolism during this time, and crushing of the right phrenic nerve by clamps placed too superiorly on the upper vena caval cuff (Fig. 35-13), to mention only three examples. A detailed discussion of these and other surgical problems has been published.¹⁹

NONIMMUNOLOGIC POSTOPERATIVE COMPLICATIONS

DELAYED BILIARY OBSTRUCTION

For reasons already described, the most commonly used method of biliary duct reconstruction has been with cholecystoduodenostomy. In more than a half-dozen patients who had satisfactory initial bile drainage with this reconstruction, delayed obstructive jaundice appeared which was diagnosed by the technique of cholangiography illustrated in Figure 35-14 or by transhepatic cholangiography (Fig. 35-15). The point of obstruction was at or near the junction of the cystic and common ducts. The first four patients with this complication died in spite of the fact that two of them had secondary conversion of the cholecystoduodenostomy to choledochoduodenostomy.

The pathological findings in the gallbladder and biliary ducts of these homografts were of great interest.¹³ The walls were infested with cytomegalovirus (CMV) which had caused swelling and shedding of the epithelial cells.

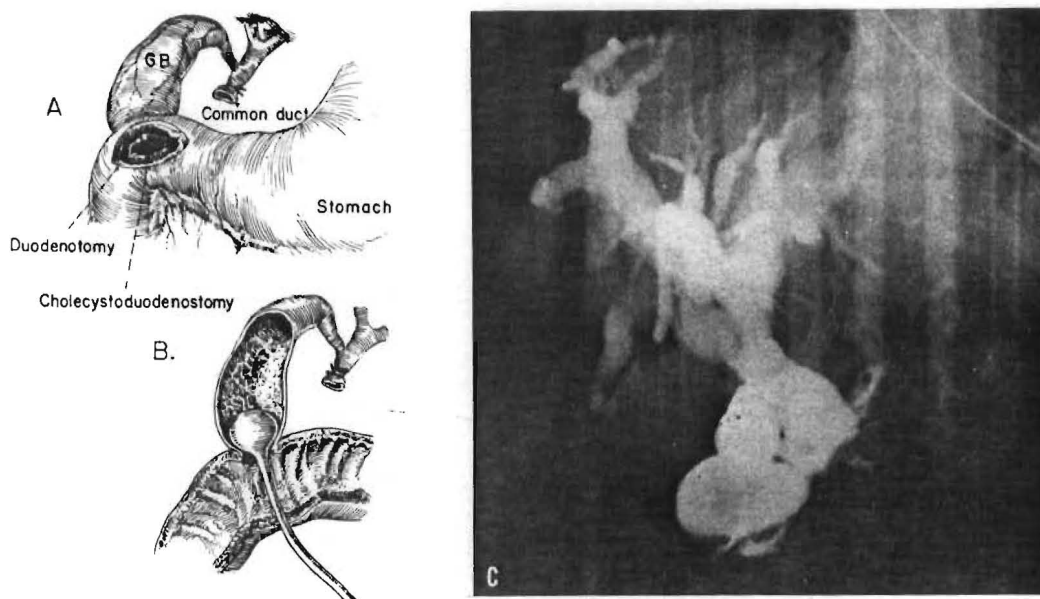


FIG. 35-14. Cholangiography of hepatic homografts. A) (Left) Technique of dye injection through a duodenotomy and the anastomosis. B) (Right) Obstructed duct system in a liver recipient whose primary biliary reconstruction was with cholecystoduodenostomy. (Martineau, G., et al.¹⁸)

Consequently, the etiology of this complication was at least partly infectious and presumably secondary to the immunosuppression required in all such cases.

Recently, secondary reconstruction has been successfully carried out for the first time in several patients who had the syndrome of cystic duct obstruction. When the diagnosis was suspected, transhepatic cholangiography was undertaken which permitted high-quality definition of the problem (Fig. 35-15). With this information, re-exploration was carried out, the cholecystoduodenostomy (Fig. 35-16A) was taken down, and the gallbladder removed. Then the dilated common duct was anastomosed to the hole in the duodenum which was the site of the previous anastomosis to the gallbladder (Fig. 35-16B). In most instances, the anastomosis was stented with a tube brought transhepatically through a stab wound (Fig. 35-16C) by the technique described by Smith.¹⁷

In these last cases, the secondary duct reconstruction was surprisingly well-tolerated, if this was done late after the first operation. The same thing was previously noted concerning secondary ureteral repair in kidney

transplantation recipients. In the latter patients, ureteral reconstruction six weeks or later after renal homotransplantation proved quite safe, whereas reintervention before this time carried a forbidding mortality.²²

Whether early or late after liver transplantation, the best hope of rectifying a biliary obstruction and potential cholangitis is prompt recognition of the problem with precise diagnostic techniques of which transhepatic cholangiography is without doubt the most important. Because of the background of immunosuppression, unrecognized cholangitis secondary to mechanical duct obstruction has extremely serious implications in liver recipients. In both experimental animals and man, homograft cholangitis may lead to multiple intrahepatic abscesses which cannot be effectively treated if permitted to exist for too long. Bacteremia results, usually with microorganisms that are indigenous to the intestinal tract (Fig. 35-17). All of the manifestations of gram-negative septicemia, including cardiovascular collapse, may follow.

In following patients with liver transplantation through the early postoperative period, blood cultures are frequently obtained. If these become positive, biliary duct obstruction

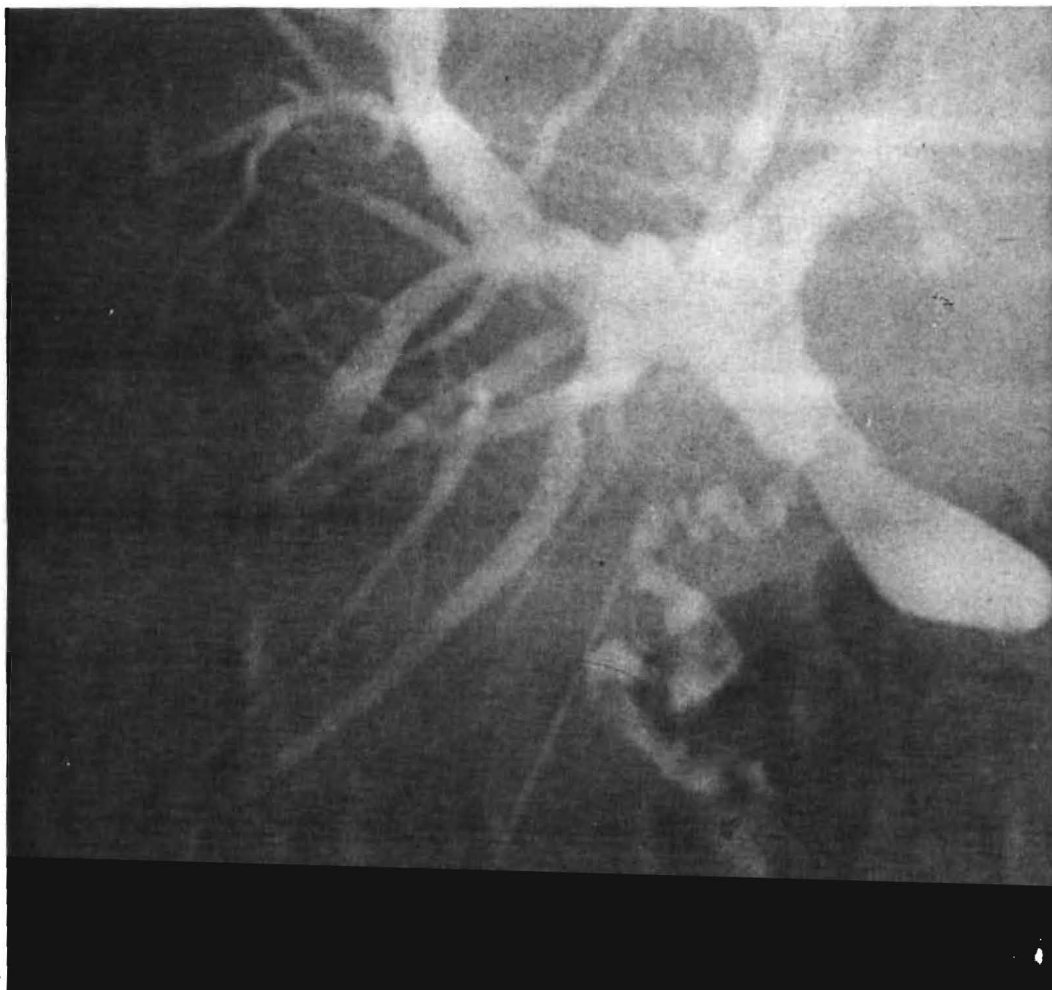


FIG. 35-15. Transhepatic cholangiogram of a liver recipient whose primary biliary reconstruction was with cholecystoduodenostomy. After the cholangiogram revealed obstruction at the level of the cystic duct, a choledochoduodenostomy was performed with relief of the obstruction.

or some other complication relating to the homograft itself, such as devascularization, should be suspected and very decisive diagnostic steps should then be taken.

OTHER GASTROINTESTINAL PROBLEMS

Gastrointestinal hemorrhage is a rather common complication of the steroid component of the immunosuppressive regimen that all such organ recipients require. This has been particularly well-documented in the renal transplant population,¹⁵ but the same thing has been reported in liver recipients.¹⁰ The

most common etiology of the hemorrhage is peptic disease of the duodenum or stomach, but fatal gastrointestinal bleeding has resulted from enteritis caused by *Candida albicans* infestation of the bowel wall.

The same kind of fungal infection has also been responsible for at least one example of post-transplantation pancreatitis. In addition, a number of liver recipients dying from a few days to more than a year after transplantation have had histopathologic findings of idiopathic acute, subacute or chronic pancreatitis.¹⁰ Pancreatitis is undoubtedly related at least in part to the need for chronic immunosuppression.¹⁵

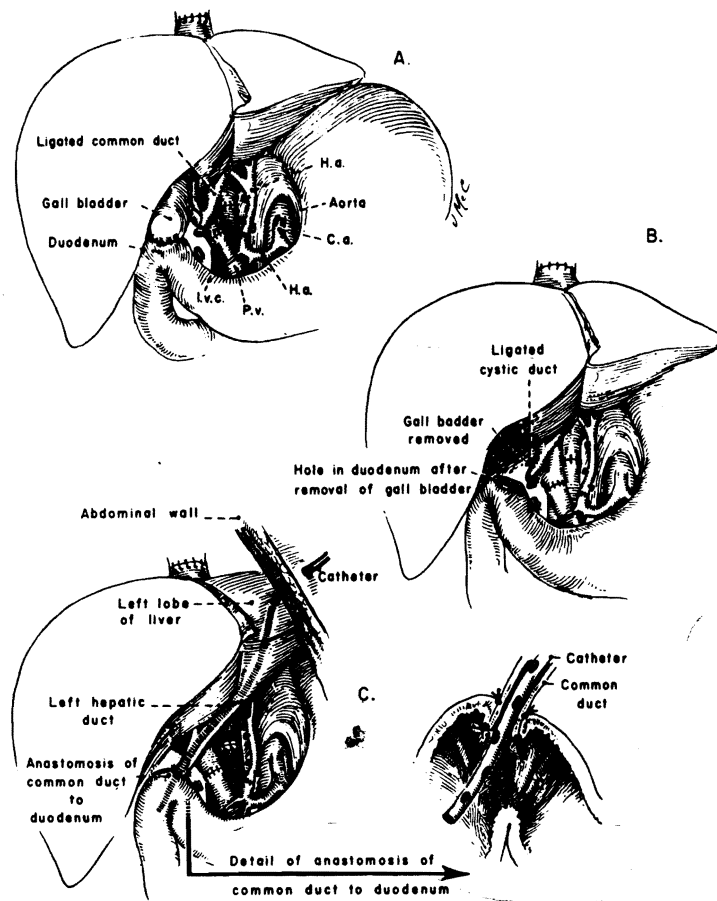


FIG. 35-16. Technique for conversion of cholecystoduodenostomy to choledochoduodenostomy. A) After transhepatic or operative cholangiography has demonstrated obstruction, the cholecystoduodenostomy is taken down and the gallbladder removed. B) The dilated common duct is then anastomosed to the hole in the duodenum at the site of the previous cholecystoduodenostomy. C) The anastomosis is stented with a tube brought out transhepatically and through the abdominal wall.

AN INTERESTING CARDIOCIRCULATORY COMPLICATION

After liver transplantation in children, arterial hypertension has been observed quite frequently. This has been attributed partly to the effects of steroid therapy but, in addition, the inability of the new liver to deal with pressor substrates may have been contributory. For example, evidence has been reported in pediatric liver recipients of defective tyramine degradation.¹⁹ Tyramine is an aromatic amine which is normally formed in the gastrointestinal tract by the decarboxylation of tyrosine which is then detoxified by hepatic monoamine oxidase. The sympathomimetic properties of tyramine are thought to be by its induction of norepinephrine release from adrenergic nerve endings. With defective early postoperative hepatic function, the tyramine and possibly other substances have apparently accumulated to physiologically significant levels.

IMMUNOSUPPRESSION

With the transplantation of any whole organ from other than an identical twin donor, the prevention of rejection is the unique problem which distinguishes this kind of surgery from all others. Control of rejection depends upon the systematic weakening of the host defenses which ordinarily provide resistance against invasion by a wide spectrum of microorganisms.

TECHNIQUES OF IMMUNOSUPPRESSION

The therapeutic regimens used for hepatic recipients were evolved and tested in patients treated by renal homotransplantation. These treatment programs have been used with very little modification in liver recipients.

Double Drug Therapy. The first protocol which was used for organ recipients in most transplantation centers throughout the world consisted of "double drug" treatment with

azathioprine and the synthetic adrenal corticosteroid, prednisone.^{10, 14, 25, 32} Evolution of the use of these two agents together, appreciation of their marked synergism, and demonstration that rejection could be easily reversed by increasing the steroid doses were among the advances which made clinical transplantation practical and which introduced what is known as "the modern era" of this clinical field.¹⁸ But, in spite of fair results with renal transplantation, double drug therapy either did not prevent rejection of hepatic homografts in the early trials or else it proved too toxic to permit host survival. All patients treated with liver transplantation from 1963 to 1966 under this kind of treatment died within a month or less.¹⁹

Triple Drug Therapy Including ALG. In 1966, heterologous antilymphocyte globulin (ALG) was introduced clinically at our center as a third immunosuppressive agent added to the drugs mentioned above.²⁷ Starting then and continuing until early 1971, this "triple drug" therapy was given to essentially all of our renal, hepatic and cardiac recipients. ALG is the globulin removed from the serum of an animal immunized against lymphoid tissue obtained from the species to be treated. Our greatest experience has been with ALG obtained from horses immunized against human lymphocytes (Fig. 35-18). It has seemed to us that rejection has been more easily and regularly controlled and the risks and morbidity imposed by the necessity for high-dose steroid therapy have been reduced with the use of the triple drug program.

More recently, cyclophosphamide, a well-known cancer chemotherapeutic agent with potent cytotoxic properties, has been used during the early postoperative period instead of azathioprine in the triple drug regimen (Fig. 35-19). There are potential advantages to the use of cyclophosphamide, including the fact that it apparently has somewhat less hepatotoxicity than azathioprine. In addition, it may retain its potency better than azathioprine under conditions of abnormal liver function.

MANIFESTATIONS OF REJECTION

In spite of immunosuppressive therapy, most liver recipients develop some signs of

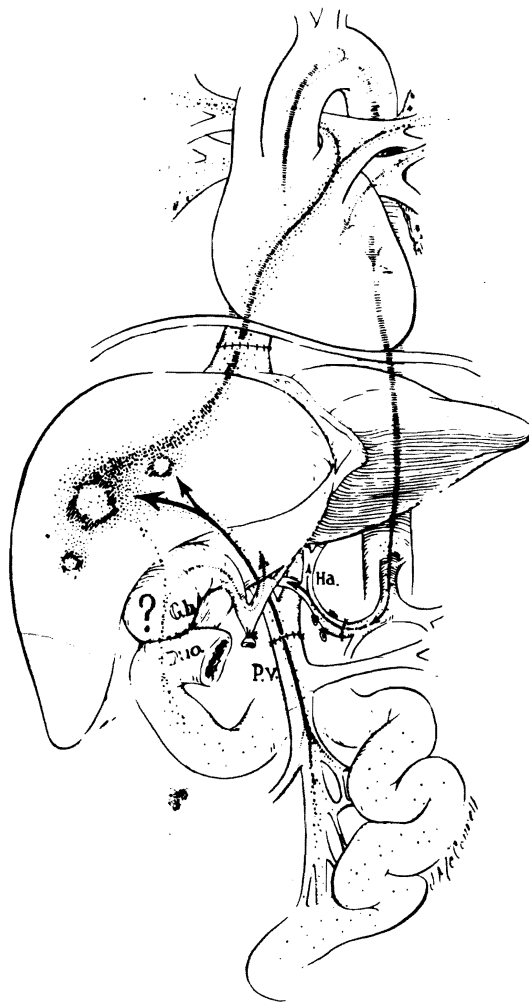


FIG. 35-17. An explanation of the predisposition of the liver to bacterial sepsis. Presumably the invading micro-organisms enter via the portal vein or through the reconstructed biliary tract. (Starzl, T. E., et al.: Orthotopic homotransplantation of the human liver. *Ann Surg.* 168:392, 1968.)

hepatic homograft rejection; usually these appear within the first few postoperative weeks. Jaundice occurs with increases in both the total and conjugated bilirubin, as might be expected with biliary duct obstruction. However, it has come to be recognized that these biochemical manifestations are a reflection of intrahepatic cholestasis. Consequently, it is not surprising that sharp rises in the alkaline phosphatase also occur. The fact that both rejection and biliary obstruction may lead to

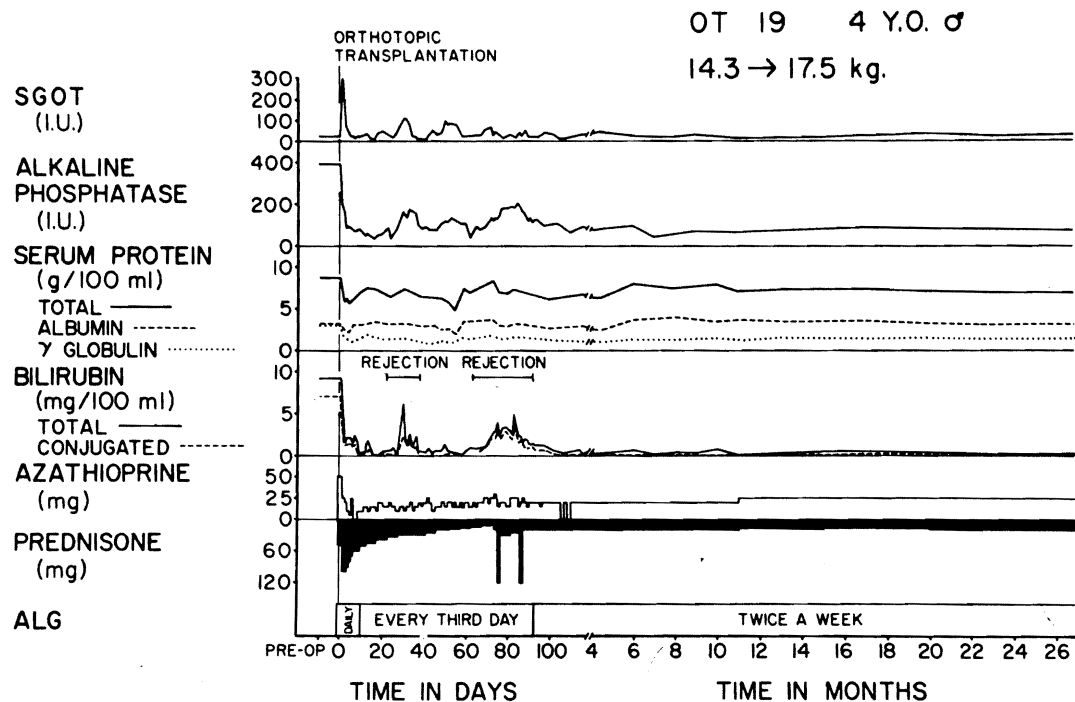


FIG. 35-18. A 4-year-old child with intrahepatic biliary atresia who was treated with orthotopic liver transplantation. A very transient rejection occurred after one month. This underwent almost immediate and complete remission. A late rejection which began on postoperative day 72 was also easily controlled. Note the change in time scale after four months. The child survived 3½ years post-transplantation, nearly all of that time in good health.²⁸ The normal enzyme values in international units at this age are: alkaline phosphatase, 57 to 151; SGOT 3 to 27; and SGPT, 2 to 30. (Starzl, T. E. and Putnam, C. W.¹⁹)

the same pattern of obstructive jaundice may make the differential diagnosis impossible without cholangiography, as described earlier.

With rejection, additional abnormalities in the liver function tests may indicate variable hepatic necrosis. There are increases in the SGOT, SGPT, and the liver specific enzyme, isocitric dehydrogenase. The synthetic functions of the liver are surprisingly well-maintained even with advanced degrees of rejection.

The manifestations of rejection occupy a wide spectrum. The process may be very indolent with obstructive jaundice being the main finding (Fig. 35-20), or it can even be so mild that clinically obvious icterus never appears. At the other extreme, rejection may occur as an acute crisis (Fig. 35-21) with evidence of massive tissue necrosis. Then, bacteremia can complicate matters, apparently as the result of seeding by bacteria from the in-

testinal tract of necrotic foci within the liver.

Fortunately, rejection is a highly reversible process with increased doses of steroids, or sometimes without any adjustment in therapy at all (Figs. 35-18 & 35-21). After rejection is controlled, it is often possible to ultimately reduce the amount of day-to-day immunosuppression required to prevent a recurrence.

PENALTIES OF IMMUNOSUPPRESSION

Risks with All Organs. Heightened susceptibility to infection is the most obvious penalty of a depressed immune system. In the early compilations of results in kidney transplant recipients, a repeated and often fatal chain of events was infection by bacteria, fungi, viruses, or even protozoa. When these infections were caused by pathogenic bacteria against which effective antibiotics were available, treatment was usually not difficult. How-

ever, infection with opportunistic fungi or other microorganisms for which antibiotics are not available emerged as the most serious late problem after transplantation.

It has also become obvious²⁶ that chronically immunosuppressed patients have an increased vulnerability to *de novo* malignancies. In our own series of chronic survivors after renal transplantation, more than 5 per cent have developed either mesenchymal or epithelial malignant tumors. Almost all other major transplantation centers have recorded the same complication which, as discussed earlier in this chapter, is presumably due to failure of the depressed immunologic surveillance mechanism to identify mutant neoplastic cells as alien and to eliminate them or to restrict their growth. Fortunately, these tumors can

usually be treated by conventional means, including surgical excision and radiotherapy.

To date, there has only been one example of *de novo* malignancy in a chronically surviving recipient of a hepatic homograft. This was in a patient treated by Calne and Williams in England. Some months after operation, a reticulum cell sarcoma developed which involved the new liver and which was a major factor in causing death.

Extra Risks for Liver Recipients. In addition to the foregoing general liabilities of immunosuppression, there are some special risks for the liver recipient. Of the chronic survivors after hepatic transplantation in our center, about one-third have developed some serologic evidence of serum hepatitis by tests for Australia antigen (Fig. 35-19). In other liver

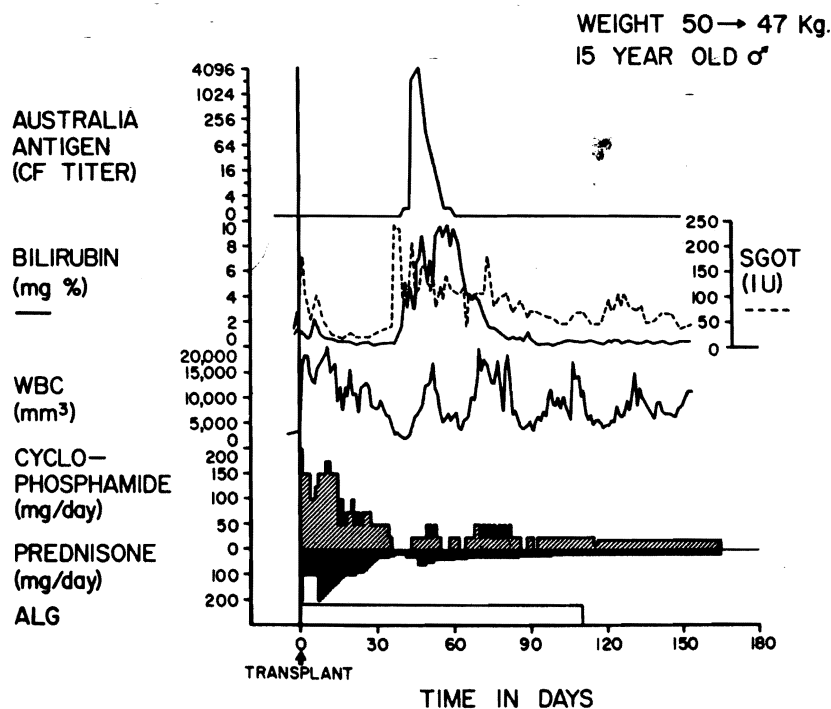


FIG. 35-19. The course of a patient who had triple drug therapy with cyclophosphamide (instead of azathioprine), prednisone and horse ALG. Note that there was excellent liver function except during the second and third post-operative months, when the patient developed jaundice and rises in the levels of the serum transaminases. These abnormalities were coincidental with the appearance of Australia antigen in the serum and consequently were probably reflections of serum hepatitis rather than rejection. The recipient's original diagnosis was Wilson's disease. He is well 2½ years after transplantation. (Starzl, T. E. and Putnam, C. W. In *Abdominal Operations* (Maingot, R., Ed.), 6th Edition. New York, Appleton-Century-Crofts, 1974, pp. 1247-1271.)

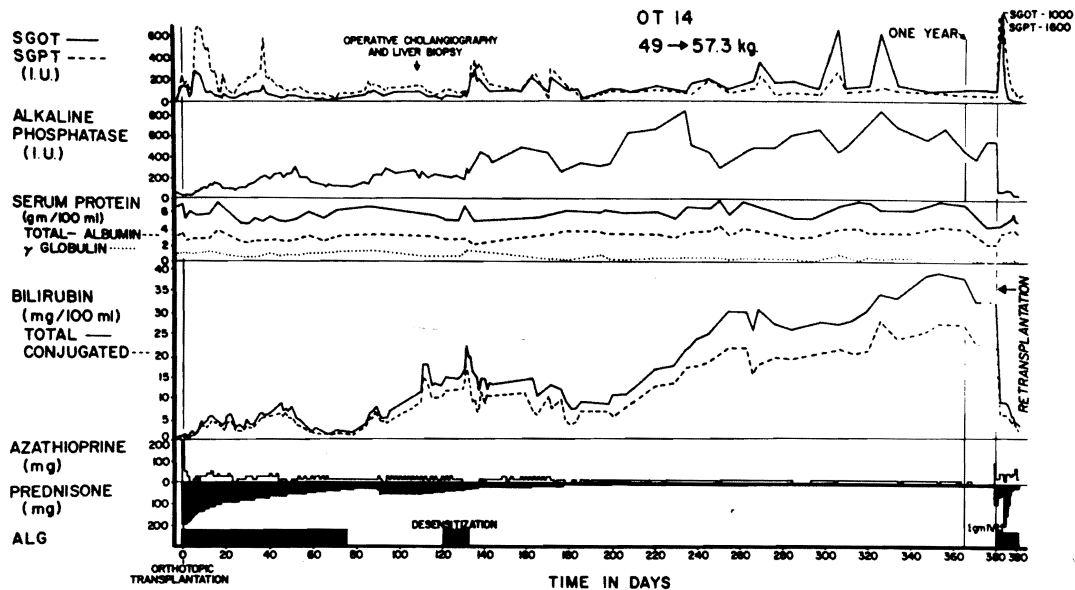


FIG. 35-20. The course of a patient after two orthotopic liver transplantations. The second liver replacement was 380 days after the first. At the time of retransplantation, local recurrence of the neoplasm was demonstrated, but there was very little tumor in the liver to account for its functional deterioration. Throughout the period of follow-up very small doses of azathioprine were given, usually 12.5 mg. per day. Shortly after the discontinuance of the first course of ALG, a chronic rejection developed. An effort at desensitization to the horse globulin was not successful. Despite the deepening jaundice, the synthetic functions of the liver were well-maintained for a long time. Note the low gamma globulins late in the course. The liver function tests were performed with microchemical techniques. With these methods, the normal ranges in International Units (I.U.) of alkaline phosphatase, SGOT and SGPT, respectively, are 60 to 260, 0 to 65, and 0 to 55. (Starzl, T. E. and Putnam, C. W.¹⁹)

recipients, hepatotoxicity of the immunosuppressive drugs rather than uncontrolled rejection may have been responsible for deterioration of graft function, although this possibility has been difficult to prove. With liver malfunction, whatever its cause, dose control of some of the immunosuppressive agents may become difficult since the liver participates in their pathways of activation and/or degradation.

Postoperative sepsis of the graft itself has proven to be a special problem, as alluded to earlier, no doubt partly because of the anatomic location of the orthotopically placed organ, interposed between the intestinal tract and the heart. Bacteria from the bowel, particularly of the gram-negative variety, can thus be brought into contact with the transplanted liver via the intestinal veins draining into the portal vein or alternatively by retrograde spread up the duct system after passage

through the biliary anastomosis. In either event, the presence of nonviable or obstructed hepatic tissue provides a perfect medium for bacteriologic growth and then systemic dissemination (Fig. 35-17).

CLINICAL RESULTS

Our own experience, including all patients treated with orthotopic liver transplantation, has consisted of 56 cases. Survival of at least one year was obtained in 16 (29%) of the 56 recipients.

The life survival curve of these patients (Fig. 35-22) has a familiar appearance to students of renal transplantation except that the immediate mortality was so much higher than with kidneys. The vast majority of the deaths occurred before the end of the second month. Technical problems of one kind or another made a major contribution to this

mortality. By six months, the attrition was stabilized at a low rate which would have been even more impressive except that three deaths occurred in the twelfth to fifteenth months from recurrences of the hepatomas for which the transplantations had been performed in the first place. This subject was covered earlier in the chapter.

After one year, 8 of 16 twelve-month survivors were lost for the reasons and at the times shown in Table 35-5. The causes of late failure included the three examples of carcinomatosis just alluded to, late chronic homograft rejection (three examples) and se-

rum hepatitis (two examples). Deaths have occurred as long as 3½ years after operation.²⁸ The eight patients still living have been followed for 48, 42, 28, 24, 17, 16, 15 and 14 months post-transplantation.

So far, with one possible exception, no disease has been identified with a highly favorable prognosis after transplantation (Table 35-6). The possible exception is Wilson's disease. This disorder is an inborn error of metabolism characterized by the progressive accumulation of copper in tissues with subsequent degenerative changes that affect the brain and liver among other organs. Discolor-

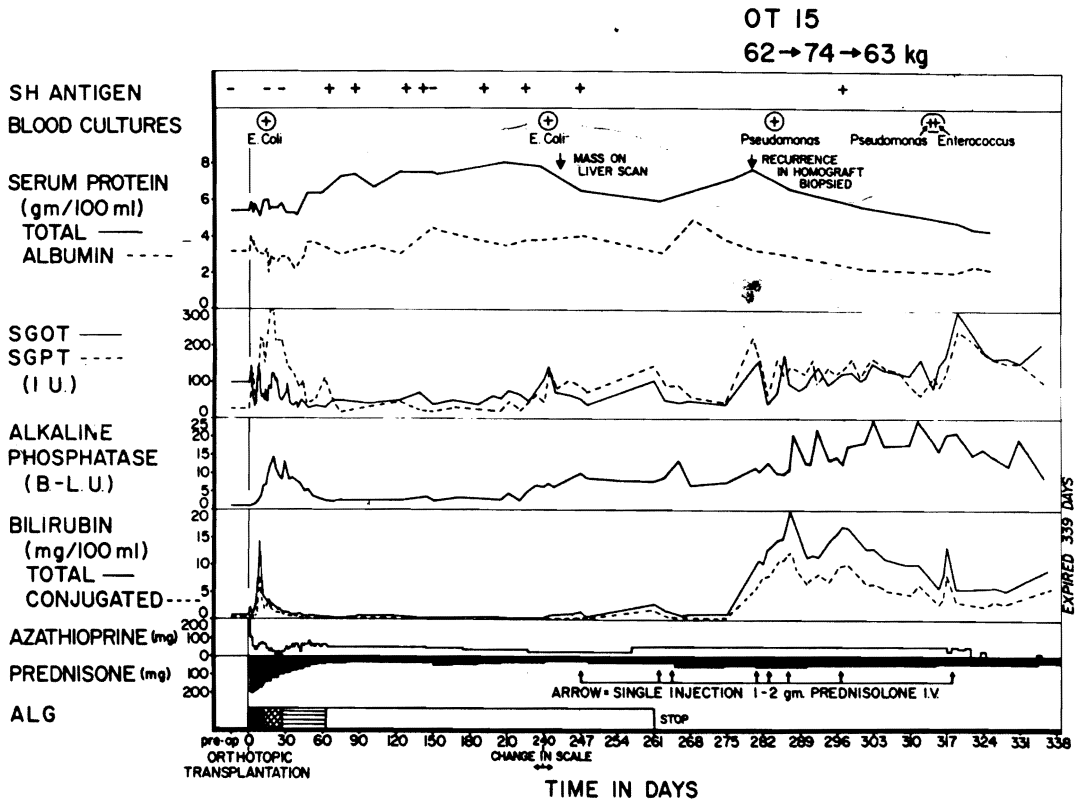


FIG. 35-21. The course of a patient who died of recurrent hepatoma despite total hepatectomy and orthotopic liver transplantation. He passed through an early and vigorous rejection crisis, but then had normal liver function for many months. The recurrent tumor was first diagnosed with the liver scan about eight months after transplantation, and biopsy confirmation was obtained more than a month later. The episodic septicemia and deterioration of liver function were probably the consequences of invasion by tumor of the extrahepatic ducts. The intermittent large steroid doses were given on the chance that rejection was also occurring. From left to right, the different shadings in the ALG bar indicate that the injections were daily, every other day, every three days and twice a week. The normal alkaline phosphatase range in Bessey-Lowry units is 1 to 3. For the SGOT and SGPT, the normal ranges are 60 to 100 and 5 to 35 units, respectively. SH Antigen represents positive tests for Australia antigen. (Starzl, T. E., and Putnam, C. W.¹⁹)

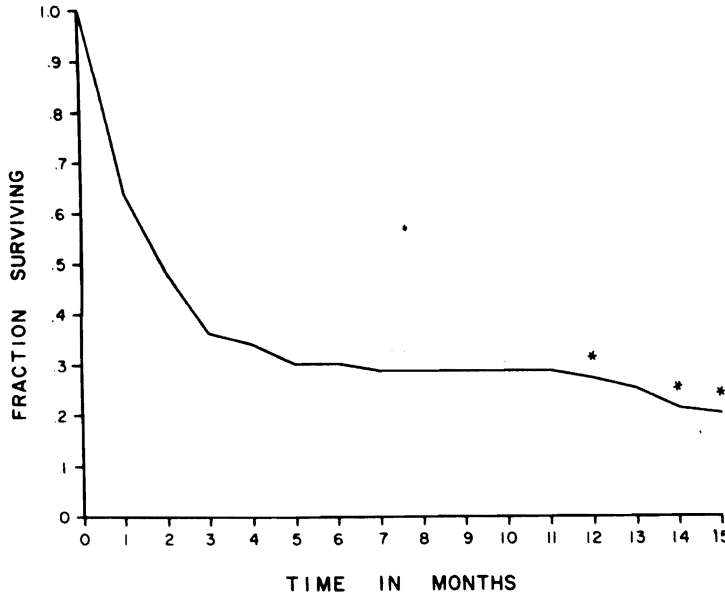


FIG. 35-22. Life survival curve for 56 recipients of orthotopic hepatic homografts. A minimum follow-up of 15 months is available for each case. Note that the majority of deaths occurred in the first two months post-transplantation, after which the curve achieves a much more gentle slope. The asterisks indicate late death from recurrent cancer; 3 of the 4 patients lost after 6 months died of carcinomatosis.

ation of the cornea by copper is seen as the Kayser-Fleischer ring with slit lamp examination. Abnormal biochemical findings may include elevated albumin-bound serum copper, increased urinary excretion of copper, low levels of the copper-containing serum protein ceruloplasmin and low total serum copper. The nature of the primary metabolic defect remains obscure (see also Chapter 30):

At our institution, two boys with Wilson's disease had liver replacement 4 and 2½

TABLE 35-5. 16 ONE-YEAR SURVIVORS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

STATUS	NO. OF PATIENTS	TIME SURVIVED
ALIVE	8/16	1½ TO 4 YEARS
DIED	8/16	1 TO 3½ YEARS
12 months—Cancer *		
12 months—Serum hepatitis, liver failure		
14 months—Cancer		
15 months—Cancer		
15 months—Rejection, liver failure		
20 months—Chronic aggressive hepatitis and disseminated Nocardia infection †		
30 months—Rejection, liver failure		
42 months—? Rejection, liver failure		

* This patient actually died a few days short of one year.

† The homograft showed severe chronic aggressive hepatitis, just as in her previously removed native liver.

TABLE 35-6. INDICATIONS FOR AND RESULTS OF ALL ORTHOTOPIC LIVER TRANSPLANTATIONS AT THE UNIVERSITY OF COLORADO TO JULY, 1973

INDICATION	NO. PATIENTS	ALIVE 1 YR.	ALIVE NOW
Biliary atresia	27	7	3
Hepatic malignancy	13	3	0
Chronic aggressive hepatitis			
Au negative	7	2	2
Au positive	1	1	0
Laënnec's cirrhosis	4	0	0
Wilson's disease	2	2	2
Juvenile hepatitis	1	0	0
Congenital biliary cirrhosis	1	1	1
Total	56	16	8

years ago for terminal hepatic failure and moderate cirrhosis plus severe neurologic involvement, respectively. Both patients had a high liver copper value. The second boy had low ceruloplasmin and total serum copper and increased urinary copper excretion. In this second case, the patient apparently went through a bout of serum hepatitis associated with Australia antigenemia early in the post-operative course (Fig. 35-19) and from which

there was complete recovery. The 100 per cent good results in these two cases is probably only a coincidence, but the observations, including analyses from liver biopsies, have suggested that liver replacement is a curative procedure for Wilson's disease. As a corollary, the findings are consistent with, although they do not absolutely prove, the statement that the metabolic perturbation of Wilson's disease is liver-based, as recently reviewed by Groth *et al.*⁹

The single largest group of recipients in our series (27 in all) has comprised extrahepatic (24 examples) or intrahepatic (3 examples) biliary atresia. The one-year survival was a disappointing 26 per cent (7 of 27).

The second largest category of recipients in our experience was primary hepatic malignancy, containing 13 patients. Because these recipients did not have such severe portal hypertension, the procedures were technically less difficult, less time-consuming and less bloody. Unfortunately, this advantage was more than outweighed by the high incidence of recurrent tumor (see above) which accounted for a half-dozen deaths, before or after the first year.

The other miscellaneous contributions to the case material are listed in Table 35-6. So far, we have had no long-term survivors among patients with alcoholic cirrhosis. Three patients with chronic aggressive hepatitis have lived for a long time, including one whose serum contained Australia antigen.

This last recipient had liver transplantation in the summer of 1970. The Australia antigen became negative by all tests except radioimmunoassay (RIA) for almost two months, although trace quantities could still be detected by RIA. After about two months, all tests returned to positive at the same time as a clinically obvious bout of acute serum hepa-

titis appeared. She recovered from this, but her Australia antigen remained positive until she died of recurrent chronic aggressive hepatitis 20 months later. Nevertheless, her health was satisfactory for all but the last month or so of her survival. Even though her original disease obviously affected the ultimate outcome, we will probably do more such cases in the future in view of the fact that the patient had substantial prolongation of meaningful life.

CAUSES OF PAST FAILURES

The operation of liver transplantation is an extraordinarily difficult undertaking, exceeding in complexity any other ever undertaken by the authors. Furthermore, the procedure must usually be done on patients who, under any other conceivable circumstance, would categorically be considered inoperable. Under these conditions, it is not surprising that technical complications have been responsible for much of the exceedingly heavy mortality of the first two or three months (Fig. 35-22).

Even if the operation has been a perfect one, the depleted state of the patient may make it difficult to be out of bed and active during the critical early phase of convalescence. The consequences may be disastrous, particularly since immunosuppression is required at the highest doses in the first few weeks or months in order to prevent rejection.

For those patients who succeed in running the fearful gauntlet of the first half-year, the chances become bright of living on for prolonged periods if the original diagnosis was not cancer. As a consequence, there are now several patients alive in the third, fourth and fifth years after hepatic transplantation who are living proof that the feasibility stage of liver transplantation has been passed.

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