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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. In the subsequent 18 years, more than 400 attempts have been made throughout the world, 212 of these by us. The historic 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.[3] The last complete summary of clinical experience was published in 1979.[4]

KINDS OF OPERATIONS

Auxiliary Transplantation

Liver transplantation was first performed and recorded by C. S. Welch of Albany, New York, in 1955. 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 in dogs, 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 anastomosis of the distal inferior vena cava or a distal iliac vein to the homograft portal vein. Outflow was into the inferior vena cava.

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. Adherents to 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, because the synthesizing functions of the liver are often retained until the terminal stages of this disease. Furthermore, 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.

The results in animals with auxiliary transplantation have been inferior to those with liver replacement, partly because coexisting 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 atrophy. More recently, evidence has been acquired to explain the beneficial effect of perfusing the portal vein with splanchnic venous blood. It has been shown that the "hepatotrophic factors" in this kind of venous blood emanate from the pancreas and that the most important constituent is apparently endogenous insulin.[6] Because 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 liver replacement.

But early in 1973, Fortner of New York City lightened the pessimism about auxiliary transplantation by revascularizing a homograft, as shown in Figure 35-1, whereby the splanchnic blood was directed through the heterotopically located liver. Fortner's patient suffered from biliary atresia. After operation, the bilirubin level fell to

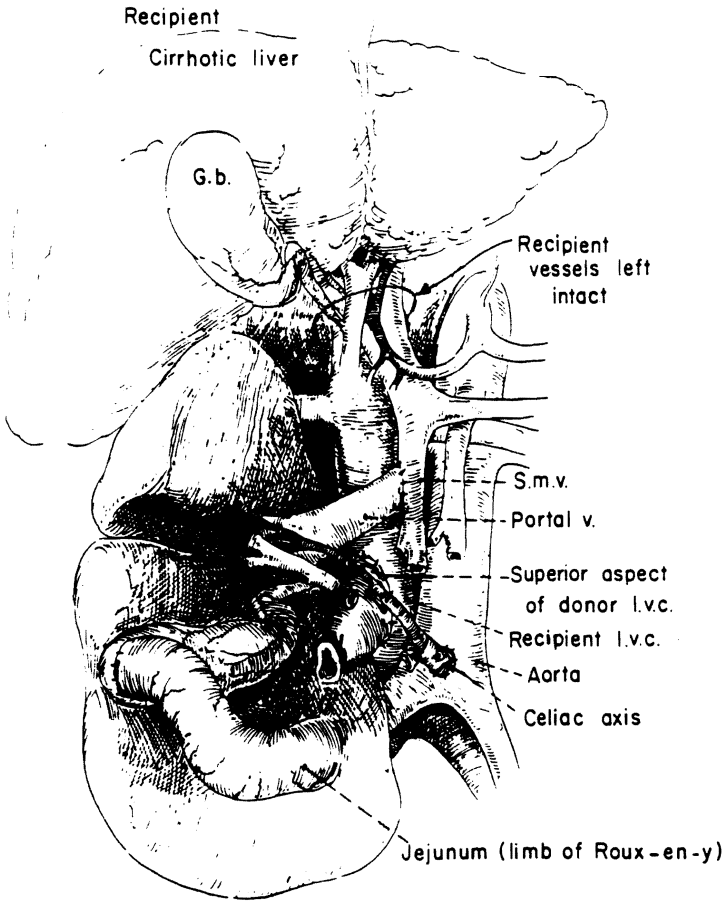


FIG. 35-1. A technique of auxiliary liver transplantation in which the homograft receives through its portal vein venous blood derived from the splanchnic bed. (Starzl, T. E., and Putnam, C. W.: Experience in Hepatic Transplantation, pp. 1–553. Philadelphia, W. B. Saunders, 1969)

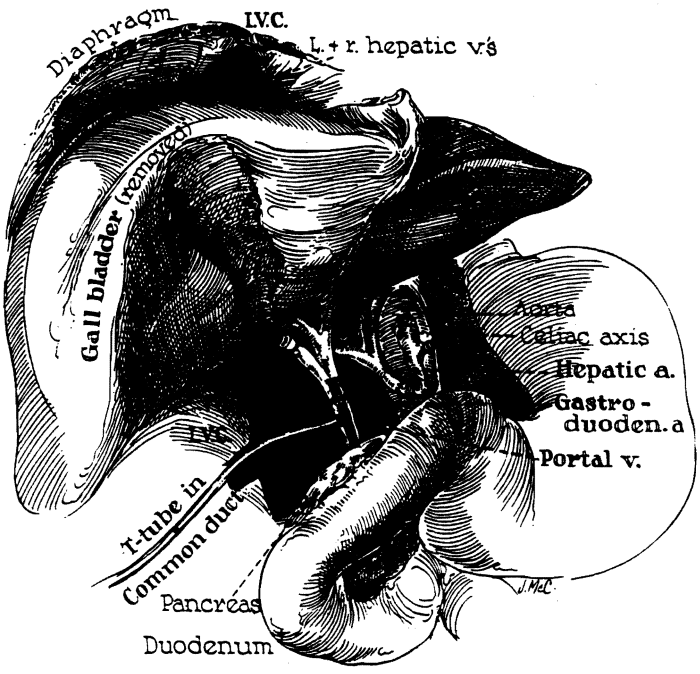


FIG. 35-2. Completed orthotopic liver transplantation. (Starzl, T. E., and Putnam, C. W.: Experience in Hepatic Transplantation, pp. 1–553. Philadelphia, W. B. Saunders, 1969)

normal, the native liver underwent marked shrinkage, and the splenomegaly and hypersplenism were relieved. The follow-up time in the case is now more than 8 years. In view of this encouraging experience, additional clinical trials of auxiliary transplantation will probably be forthcoming. By September, 1978, Fortner and his associates had information on 43 cases, including seven of their own. Besides their one unqualified success, another of Fortner's patients with biliary obstruction from an intrahepatic cancer had temporary clearing of jaundice but died eight months later. The other 41 patients died in less than two months from a variety of complications.[2]

Our own view is that auxiliary transplantation should be reserved for patients with acute hepatic disease, in which the objective is temporary life-support during which recovery of the native liver can be obtained. The feasibility of this approach has been proved in several animal studies but not yet in humans.

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 (Fig. 35-2). Survival exceeding 10 years has been achieved in both dogs and humans. The remarks in succeeding sections pertain to the more promising orthotopic transplantation as opposed to the auxiliary operation discussed above.

INDICATIONS FOR HEPATIC REPLACEMENT

No matter what the underlying disease, certain criteria should be met before patients are accepted 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 or organs other than the liver, such as coexisting 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 high incidence of a

variety of gastrointestinal complications, including gastroduodenal hemorrhage and colonic problems.

From March, 1963, to December, 1977, 141 consecutive patients were treated with orthotopic liver transplantation. The propriety of the various indications for operation has been reviewed on several occasions.[3,4]

Benign Disease

Among the first 141 recipients were 74 infants and children (Table 35-1). The most common diagnosis in this pediatric group was biliary atresia. Chronic aggressive hepatitis was a distant second. Eight patients had the inborn errors of metabolism summarized in the footnote to Table 35-1. It has been established that liver-based inborn errors are permanently rectified by providing livers of normal phenotypes.[4] An example is shown in Figure 35-3 of a boy with Wilson's disease. After liver replacement, his serum ceruloplasm rose from undetectable to normal levels. For many months, he underwent a massive cupruresis, which caused corneal copper deposits (Kayser/Fleischer rings) to disappear. Pre-existing serious neurologic abnormalities were reversed. The patient is still alive with normal liver function ten years after transplantation.

There were 67 adults among the first 141 liver recipients. The reasons for proceeding are listed in Table 35-2. With the exception of primary hepatic malignancies, these indications are all still considered valid. Excluding hepatic malignancies, the most common indications for operation were chronic aggressive hepatitis and alcoholic cirrhosis.

In the future, the leading indications for transplantation in adults undoubtedly will be chronic aggressive hepatitis and Laennec's cirrhosis. The presence of HB_sAg viremia is not a contraindication, because effective postoperative treatment can be given with hyperimmune serum.[1] Cases of cirrhosis pose a supreme technical challenge. If results are to be improved, candidates need to be selected at an earlier time. Too often in the past, recipients have been moribund by the time of operation.

TABLE 35-1. Indications for Transplantation (1963–1977) in Patients < 18 Years of Age

Biliary Atresia	48
Chronic Aggressive hepatitis	12
Inborn metabolic errors	8*
Hepatoma	3
Neonatal Hepatitis	2
Congenital biliary cirrhosis	1
Total	74

*Inborn errors:

$Alpha_1$-antitrypsin deficiency	4
Wilson's disease	2
Tyrosinemia	1
Type IV glycogen storage disease	1

TABLE 35-2. Indications for Transplantation (1963–1977) in Patients 19 to 70 Years of Age

Chronic aggressive hepatitis	23
Primary liver malignancy	16
Alcoholic cirrhosis	15
Primary biliary cirrhosis	5
Sclerosing cholangitis	4
Secondary biliary cirrhosis	2
Massive hepatic necrosis (B virus)	1
Budd–Chiari syndrome	1
Total	67

Hepatic Tumors

Three of our early liver transplantations in children and 16 in adults were carried out to treat nonresectable hepatomas, duct-cell carcinomas, angiosarcomas, and cholangiocarcinomas. Ten of these patients lived beyond three months, but nine of them later developed metastases, which usually contributed to or were primarily responsible for their deaths after a few months to several years. Similarly, the recurrence rate in the Cambridge–King's College series in England has been 70%.[1] As more and more such cases have been documented, we have had less and less enthusiasm for and, indeed, usually avoid transplantation for malignancy.

In spite of this pessimism, there is no denying that some patients with malignancy have benefitted from liver replacement. Our longest survivor, who has now lived almost 12 years postoperatively, was cured of an incidental hepatoma in her excised biliary atretic liver. Three of our patients lived for more than two years in spite of recurrences, and one of the three is still alive after more than five years.

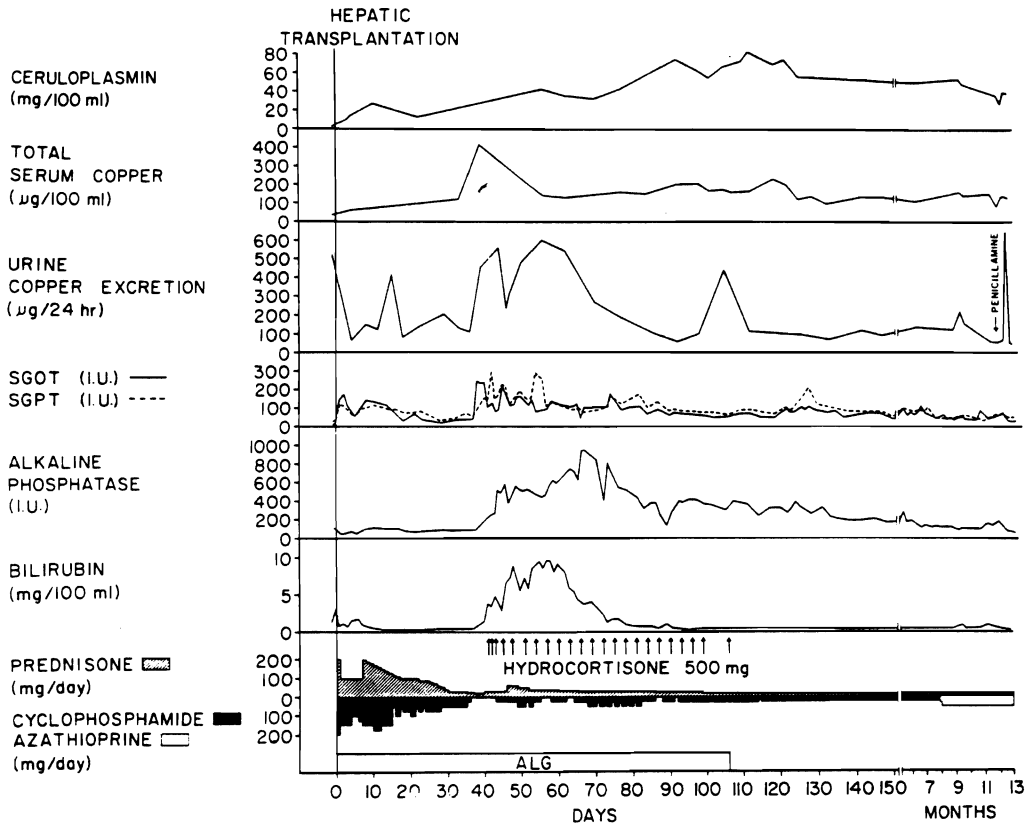


FIG. 35-3. The course of a patient with Wilson's disease who received an orthotopic liver homograft. Note that the ceruloplasmin rose from undetectable to normal levels and that there was a heightened urinary copper excretion for almost a year. In this patient, cyclophosphamide and azathioprine were used interchangeably. The deterioration in liver function, which started just a month after onset of Wilson's disease, was caused by serum hepatitis (HB_sAg). (Groth, C. G., *et al.*: Transplant. Proc., 5(1):829–833, 1973. Reproduced by permission)

DONORS

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 dissection prior to 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.

Recipient Matching

With the exception of patients with 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 is conducted. The consequence has been that the HLA antigen matches in our series have not been good. In 100 consecutive Colorado cases, only two patients received livers with three or four antigen matches. One of these recipients of a well matched organ died of technical

complications 62 days after operation. The other died after 11½ months. His graft contained chronic rejection.

Because of urgent need, a number of liver transplantations have been performed despite the presence in the recipients of cytotoxic antibodies that were anti-donor-specific. We have carried out more than a dozen liver transplantations under these circumstances. There were no examples of hyperacute rejection, which almost invariably destroys renal homografts under these conditions; and, in fact, no unequivocal harmful effects were seen later, in contrast with patients without cytotoxic antibodies.[4] We and Calne and Williams[1] have concluded that the liver is highly privileged in confrontations with preformed cytotoxic antibodies.

Renal homografts are also hyperacutely rejected if there is a breach of blood-group barriers. We proceeded in spite of this adverse factor in 11 liver recipients who could not wait for blood group-compatible organs. The livers did not function well in two of the recipients, leading to attempted retransplantation and eventual death. The blood violations in these cases were B to O and B to A. The excised primary livers had superficial infarcts and focal necrosis, but, histopathologically, there was nothing to suggest damage by antiblood group isoagglutinins. Thus, we will still perform transplantation despite blood group incompatibility, although we avoid the condition, if possible. Except in the two exceptional cases, the other patients did not behave differently than those given blood group-compatible livers.[4]

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

OPERATIVE PROCEDURES

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.

The surprising ability of these moribund recipients to survive such major surgery may be related partly to the troublesome operative bleeding that is almost invariably encountered. The consequent necessity for major blood replacement frequently results in intraoperative exchange transfusions of at least the magnitude reported to be of benefit in acute liver insufficiency. 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 an 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, because there are no means of providing therapy analogous to that of the artificial kidney to tide over prospective recipients while an organ is being found. Until an artificial liver is developed that provides some of the crucial hepatic functions, liver transplantation will not be able to achieve anything close to its true potential.

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 35-4 depicts the initial steps in this process. Then the portal vein, hepatic artery, and common duct are dissected (Figure 35-5). Details of the various surgical maneuvers are described elsewhere.[3,4]

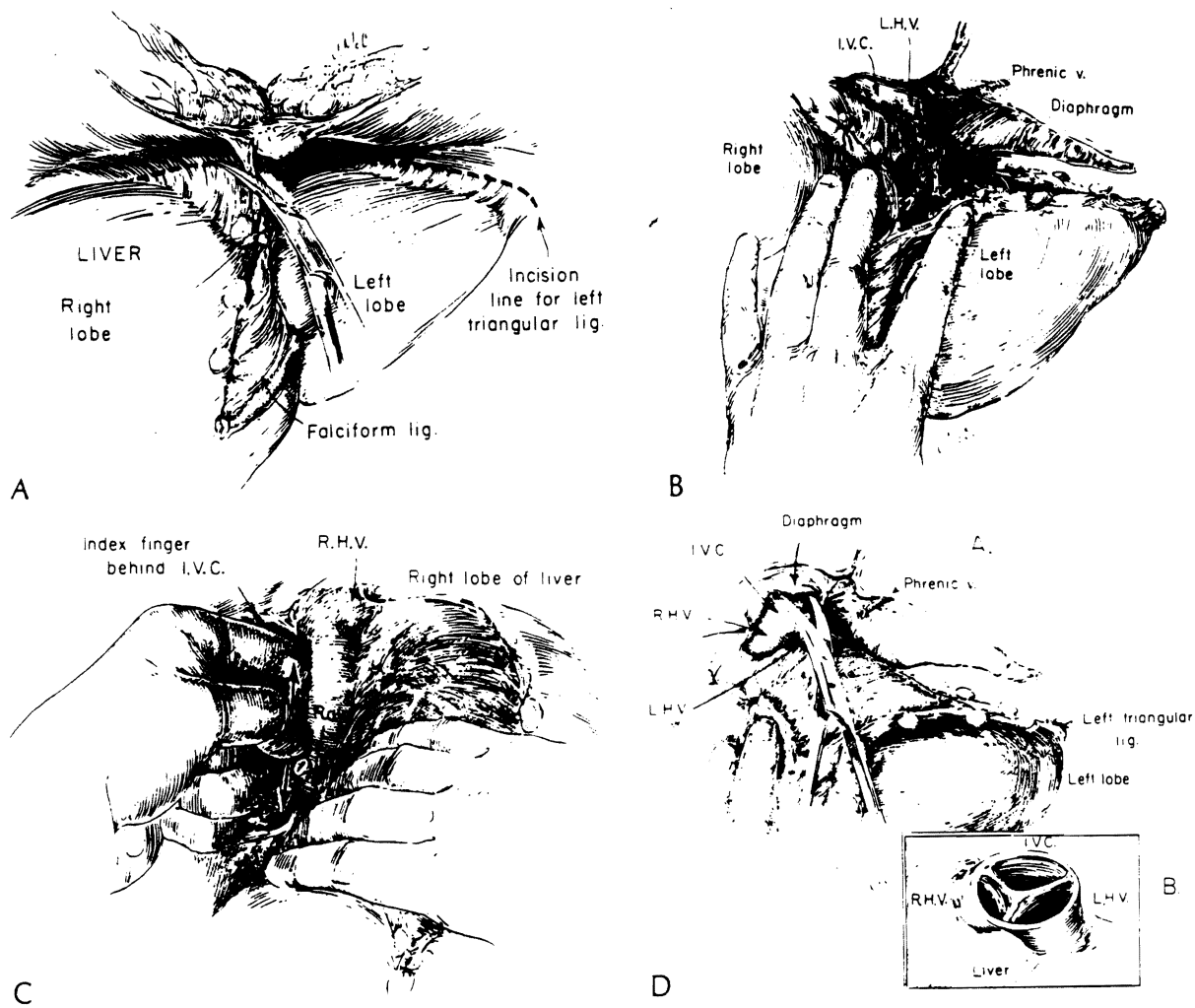


FIG. 35-4. Initial steps in hepatic homograft removal. **(A)** The falciform and triangular ligaments are incised. **(B)** The suprahepatic vena cava and its tributaries are exposed and initially dissected. This is done by entering the raw area formed by divergence of the leaves of the falciform and 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 shown. *Inset.* Cross-sectional appearance of the venous confluence above the liver as 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.: Experience in Hepatic Transplantation, pp. 1–553. Philadelphia, W. B. Saunders, 1969)

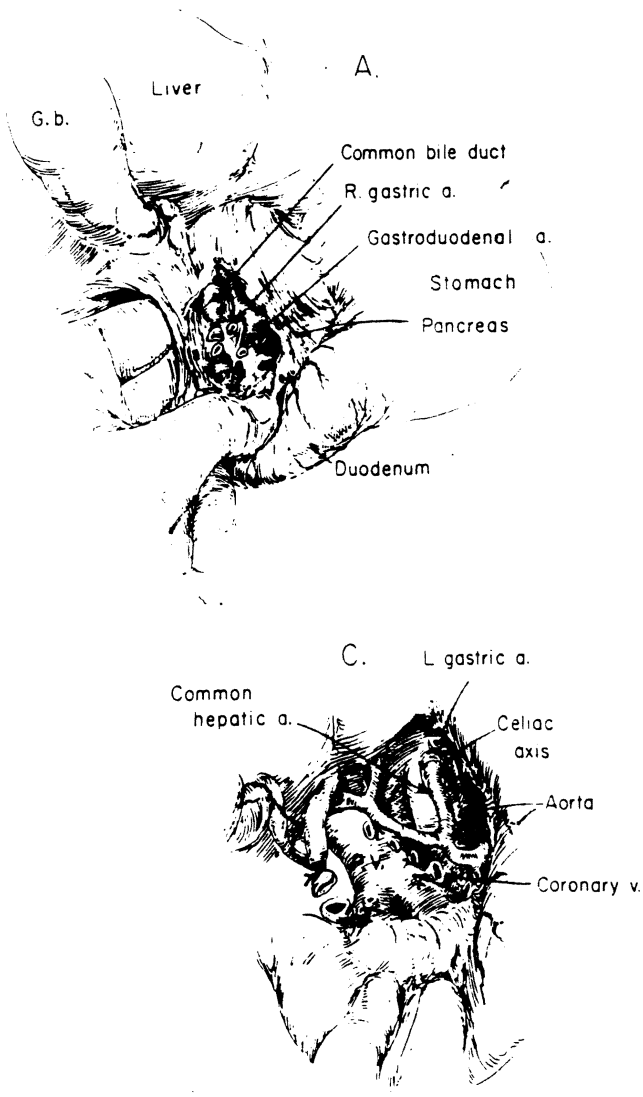


FIG. 35-5. Dissection of the portal triad. **(A)** The common duct and the gastroduodenal and right gastric arteries are tied off and divided. Before ligation, it should be determined that the common duct communicates freely with the gallbladder by way of the cystic duct. If anomalies are present, failure 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; in children, it may be advisable to include a segment of aorta as well. (Starzl, T. E., and Putnam, C. W.: Experience in Hepatic Transplantation, pp. 1–553. Philadelphia, W. B. Saunders, 1969)

Preservation Techniques

The subsequent preservation of the liver is also of vital importance and has been accomplished by one or more preservation modalities, depending on circumstances, always including organ hypothermia.[3] After removal, quick cooling may be accomplished by running a chilled electrolyte solution through the portal vein, thus lowering the donor organ temperature to about 10 or 15°C, which is sufficient for adequate preservation during the hour or two required for the vascular anastomoses in the recipient.

Since 1976, methods have been available that permit relatively safe and simple storage for longer periods. The Cambridge–King's College team has used a plasma solution for cold infusion of the homografts,[1] and we have employed an electrolyte (Collins) solution with a composition similar to that found in cells.[4] In dogs, the two approaches yield comparable results and permit safe preservation for up to 12 hours. The same applies in humans and has permitted the shipment of livers from city to city. The Cambridge surgeons have cautioned that ischemia or bile left within the ducts of such livers may cause autolysis and set the stage for delayed mucosal sloughing and cast formation.[1]

Despite the advantages afforded by brain-dead donors and the improvements in preservation, hopelessly damaged organs are still occasionally transplanted. There is at present no reliable way to prevent such tragedies by any practical test for homograft viability.

Recipient Orthotopic Operation

Most of the steps in the recipient are identical or similar to those described above for the donor; however, 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 ligaments (Fig. 35-6). Reconstruction consists of anastomosing the individual vessels to the vessels of the homograft as quickly as possible. A completed operation is shown in Figure 35-2.

The first anastomosis performed is of the suprahepatic vena cava. As the vena caval anastomoses are constructed, slow infusion of electrolyte solution is continued through the portal vein. Air bubbles can be seen floating out of the graft (Fig. 35-7). If infusion is not provided during this time, the air bubbles in the homograft may be flushed into the circulation after revascularization. They may then pass through abnormal right-to-left venous communications (secondary to liver disease) and on to the brain. A high incidence of cerebral air embolus was encountered in our early experience. This was eliminated with the infusion technique.

The hilar structures have smaller calibers. Increasingly in infants and young recipients, we have used microvascular techniques, particularly for reconstruction of the hepatic artery and portal vein. If such techniques are not used, pediatric recipients have a high incidence of thrombosis in these vessels.

Biliary tract reconstruction has caused more complications than any other part of the operation.[1,3,4] In our early experience, one of every three recipients subsequently had biliary duct obstruction or biliary fistula. Even without obstruction or fistula, there was a high incidence of bacteremia, probably because of constant contamination of the biliary ducts through the cholecystoduodenostomies (Fig. 35-8A) that were being used in those days.

Since 1974, we have not used cholecystoduodenostomy. We think that duct-to-duct reconstruction (choledochocholedochostomy) is the best method (Figs. 35-2 and 35-8D). If this is not feasible (as, for example, in patients with biliary atresia), we use cholecystojejunostomy to a Roux-en-Y limb (Fig. 35-8B) or choledochojejunostomy (Fig. 35-8C).

It is now realized that biliary tract complications (especially obstruction) were frequently the cause of postoperative jaundice that developed after an initial period of bilirubin clearing. When obstruc-

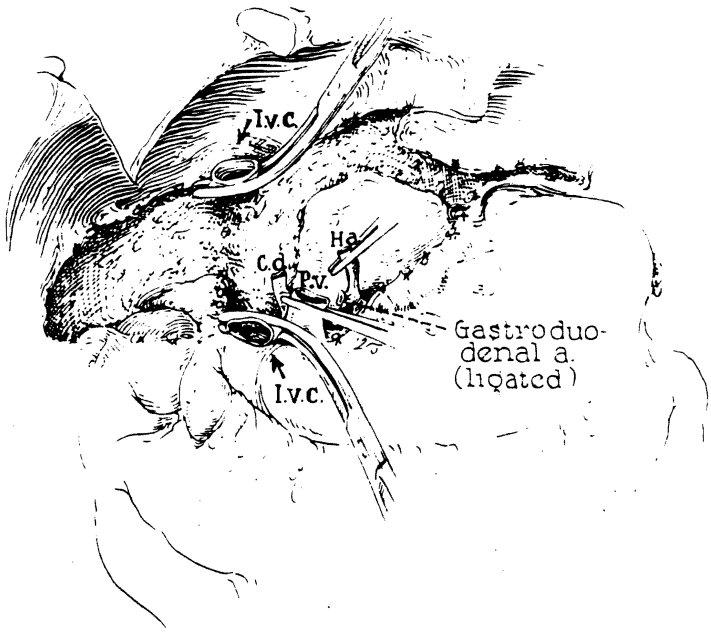


FIG. 35-6. The operative field after removal of the diseased recipient liver. In the illustration, an incision in the diaphragm is shown as part of a thoracoabdominal exposure. In more recent cases, the chest has not been entered. C.d., common duct; H.a., hepatic artery; I.V.C., inferior vena cava; P.v., portal vein. (Starzl, T. E., *et al.*: Surg. Gynecol. Obstet., *117*:659, 1963)

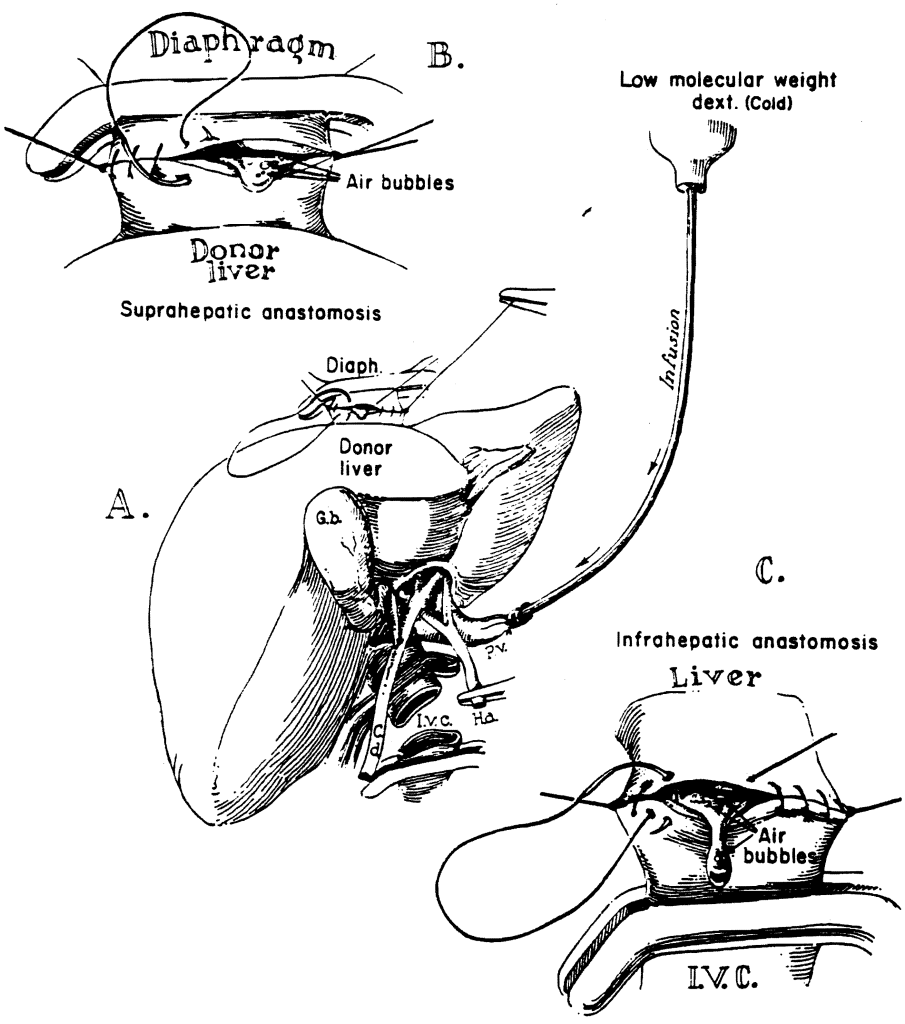


FIG. 35-7. Technique to prevent air embolism from orthotopic liver homografts. (A) Continuous perfusion of solution through the portal vein as vena caval anastomoses are constructed. (B), (C) Escape of air bubbles as the anastomoses are completed. (Starzl, T. E., *et al.*: Ann. Surg., *187*:236–240, 1978)

tion occurred, it usually was at the narrowed cystic duct after cholecystojejunostomy (Fig. 35-8B). Once the problem was appreciated, it was found safe to secondarily operate, to remove the homograft gallbladder, and to make a conversion to choledochojejunostomy (Fig. 35-8C).

Calne and associates of England have also modified their practices of biliary reconstruction.[1] Their presently preferred method is the creation of a cloaca between the homograft gallbladder and common duct, with anastomosis of the common chamber to the recipient common duct. The complexity of this procedure compared to more standard biliary reconstruction militates against its widespread acceptance.

Splenectomy is usually performed at the time of transplantation. The majority of liver recipients have greatly enlarged spleens and such serious hypersplenism that treatment with azathioprine and prednisone would be jeopardized without elimination of this factor.

MANAGEMENT

Nonimmunologic Complications

In view of the enormous difficulty of performing liver transplantation, it is not surprising that the procedure has been followed by a long list of technical complications. Such complications have been responsible for more than half of all deaths within the first year.[3,4] Included have been vascular thrombosis, hemorrhage, the unknowing use of

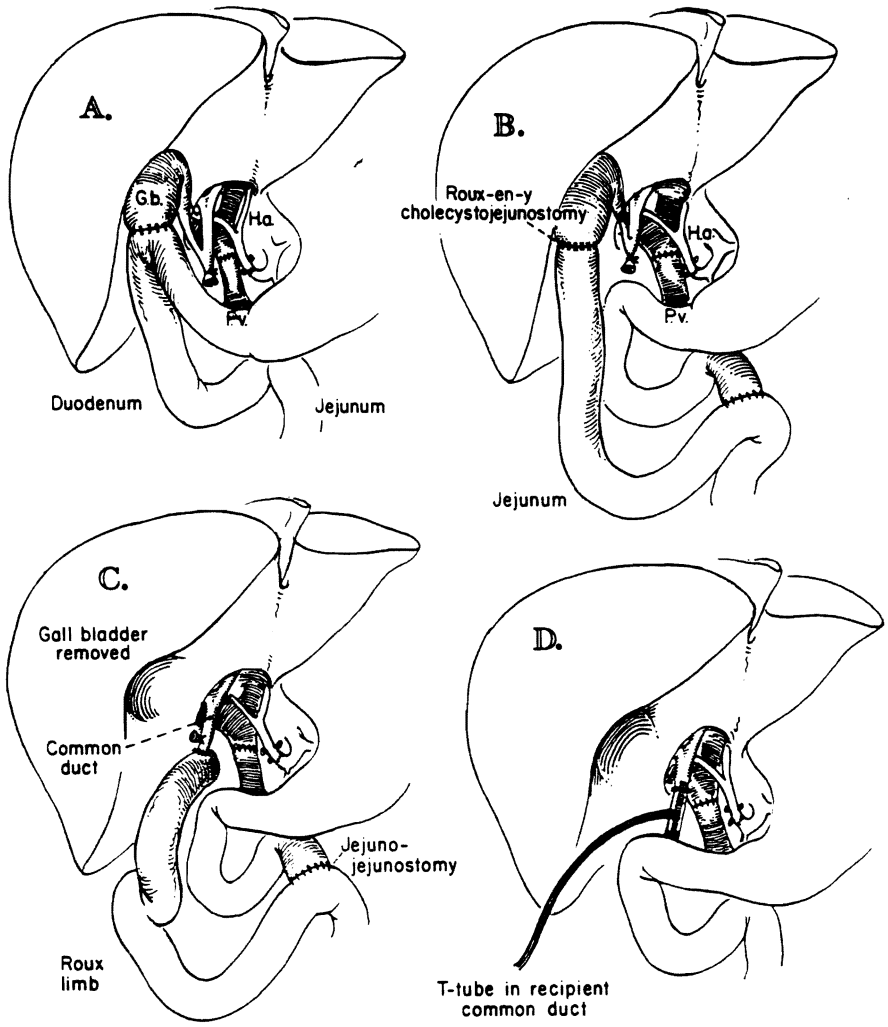


FIG. 35-8. Techniques of biliary-duct reconstruction used for most of the transplantation recipients treated in Colorado. (A) Cholecystoduodenostomy. This operation is no longer performed. (B) Cholecystojejunostomy. (C) Choledochojejunostomy after removal of the gallbladder. (D) Choledochocholedochostomy. Note that, if possible, the T-tube is placed in the recipient common duct. (Starzl, T. E., *et al.*: Surg. Gynecol. Obstet., *142*:487, 1976)

ischemically damaged grafts, and biliary tract obstruction or fistulization, to provide a very incomplete accounting. These complications have influenced postoperative immunosuppressive management. For example, better diagnosis and management of biliary complications were made feasible by an increase in the use of cholangiography (percutaneous, retrograde endoscopic, or T-tube).

Another recent change in policy has been the more frequent use of needle biopsy. Evidence of viral hepatitis has thereby been obtained in a surprising number of cases. Severe or lethal homograft hepatitis has been caused by HB_sAg virus, herpes, chicken pox, and adenovirus. An example of HB_sAg hepatitis is shown in Figure 35-3. Correct diagnosis helped avoid the lethal error of intensifying immunosuppression at the very moment when the opposite change might have been in order.

The infectious consequences of other major, nonimmunologic complications such as vascular thromboses and enteric fistulas have been difficult to manage under the influence of immunosuppression.[3,4]

Immunosuppression

The unique requirement after transplantation of any organ is immunosuppression. All of our liver recipients have had double drug therapy with a cytotoxic agent, azathioprine (which can be used interchangeably with cyclophosphamide), and prednisone (Figs. 35-3 and 35-9). To the double

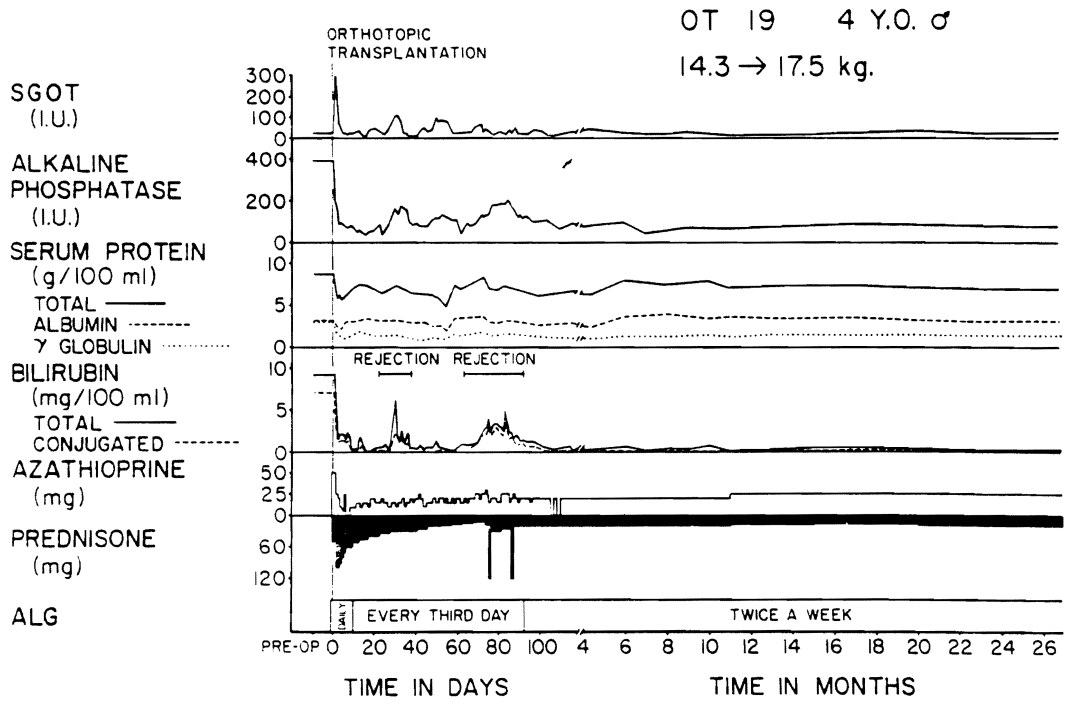


FIG. 35-9. Data on a 4-year-old child with intrahepatic biliary atresia who was treated with orthotopic liver transplantation. A very transient rejection occurred after one month. The patient underwent almost immediate and complete remission. A late rejection that began on postoperative day 72 was also easily controlled. Note the change in time scale after four months. The child survived for 3½ years post-transplantation, nearly all of that time in good health. 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.: Experience in Hepatic Transplantation, pp. 1–553. Philadelphia, W. B. Saunders, 1969)

TABLE 35-3. Cases of Liver Replacement at the University of Colorado*

	TOTAL	LIVED 1 YEAR†	ALIVE NOW
SERIES 1 (March, 1963–July, 1976)	111	31 (28%)	13 (5½ to 12 years)
SERIES 2 (July, 1976–January, 1978)	30	15 (50%)	13 (4–5½ years)
SERIES 3 (March, 1978–April, 1979)	30	10 (33%)	9 (2½–3½ years)

* Follow-up is to November, 1981.

† Deaths between one and six years postoperatively are considered "late deaths."

drug regimen, we have often added heterologous antilymphocyte globulin (ALG) (Figs. 35-3 and 35-9). Irreversible hepatic rejection can usually be prevented with these techniques. Because of this, there was speculation for a long time that overimmunosuppression was being systematically practiced.

This view undoubtedly requires some revision in light of our recent experience with patients submitted to frequent homograft biopsy.[4,5] As in earlier cases, irreversible rejection was not common, but definite rejection was frequently seen in biopsies and was highly variable in degree, according to the timing of the biopsy. Yet, at autopsy, many of these homografts were free of rejection. Evidently, intensification of immunosuppression was a justified action to save these livers but

lethal one if there were any other kind of problem, including a technical or mechanical one.

Thus, the tendency to ascribe most of the high mortality after liver transplantation to factors other than rejection is probably not completely correct. The possibilities for more effective immunosuppression are discussed below, and it is upon such advances that the next major jump in survival has depended. The most important development has been the use of the new immunosuppressive agent, cyclosporin A.

RESULTS

Conventional Immunosuppression

The demonstration of its feasibility did not make orthotopic liver transplantation a widely used clinical procedure; in fact, only we and Calne and Williams of England have persisted in large-scale trials. By early summer of 1976, we had treated 111 consecutive patients. Of these recipients, 31 (28%) had survived for at least 1 year (Table 35-3). Now, with follow-ups of 5.5 to 12 years, 13 patients are still living. The flatness of the late-life survival curve has been an important stimulus for us to persist in these efforts, as has the very acceptable quality of life of these chronic survivors. Chronic graft rejection has been the single most common cause of late death.

A second Colorado series of 30 patients was compiled in the subsequent 18 months, ending in early 1978. Of these patients, 50% survived for at least 1 year, and today, after 4 to almost 6 years, 13 (43%) are still living (Table 35-3). It was thought that improvements in surgical technique (especially biliary tract reconstruction), better diagnosis of postoperative hepatic dysfunction, and refinements in immunosuppression were responsible for the better results.

It is distressing to report that we were unable to maintain these gains in a further series of 30 patients. Many of these last 30 patients, instead of ALG, had lymphoid depletion with thoracic duct drainage[7] or lymphaphoresis. All 30 were given azathioprine and prednisone. The one-year survival rate was only 33% (Table 35-3). Many of the early deaths in the last series were attributable to technical or management errors, as in the past. These misadventures often were not intrinsically lethal but became so because of the need for high-dose steroid therapy.

Cyclosporin–Steroid

Cyclosporin A is a new immunosuppressive agent that was first used clinically by Calne of Cambridge. We have used this agent in combination with low-dose steroid therapy for all liver recipients treated since March of 1980.

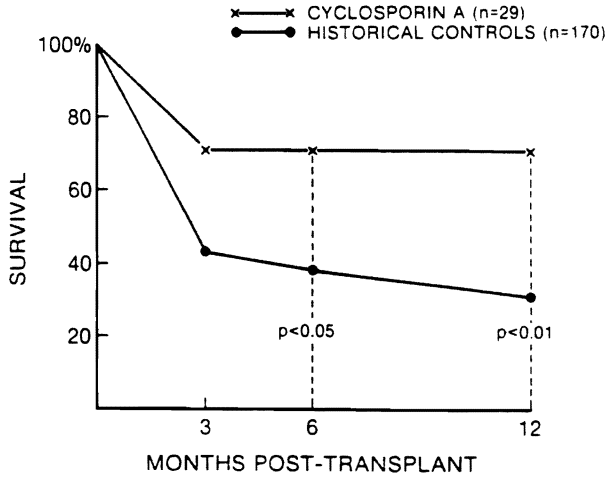
At the University of Colorado, 14 patients were planned for such therapy. Two died during operation. Of the other 12, 11 lived for at least 1 year.[8] Two died subsequently, one of a recurrent malignancy and the other of recurrent Budd–Chiari syndrome.

Twenty-three more patients have had similar therapy at the University of Pittsburgh. The first 4 recipients were given poorly preserved livers and died. Of the next 19, 17 have survived with follow-ups of ½ to 6 months.

The actuarial life survival curve of the combined Colorado and initial Pittsburgh experience is shown in Figure 35-10. There has been a striking improvement over our cumulative historical record.

This great advance in immunosuppression should make feasible the much wider use of liver transplantation.

FIG. 35-10. Data on the survival of liver transplant patients. Recipients included 14 patients treated at the University of Colorado[8] and 15 treated at the University of Pittsburgh. Immunosuppression was with cyclosporin A and steroids. Note the marked improvement of results in the group that received cyclosporin A over historical controls, in whom conventional immunosuppression was used.



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