

to the ensiform process. The routine radiological tests, liver function tests, blood examinations, etc., were all negative. At exploratory operation through a midline epigastric incision, a small cystic oval tumour was found in the attachment of the falciform ligament to the liver. The pathologist's report was benign fibrolipoma: cystic degeneration, with elements of liver tissue in the walls of the cyst.

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TRANSPLANTATION OF THE HUMAN LIVER

THOMAS E. STARZL
LAWRENCE J. KOEP,

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In this chapter, the usual practice has been omitted of devoting a section to historical background. The reason is that the first report by Welch¹ of whole-organ hepatic transplantation in animals was only 23 years ago. Furthermore, the first clinical attempts at liver transplantation were not made until 1963.² Consequently, these as well as most of the other early articles on liver transplantation are still of current interest. A complete bibliography of this subject through early 1969 is available in a recently published text, with ~~an~~ later update³ through 1975.³ and 1984⁴.

KINDS OF OPERATIONS

Auxiliary Transplantation

There are two general approaches to transplantation of the liver. With one method, an extra liver is inserted at an ectopic site without removal of the diseased native organ. This was the procedure that Welch¹ developed in dogs with the ultimate objective of treating patients

who were dying of cirrhosis or other nonneoplastic hepatic diseases.

One technique used for auxiliary hepatic transplantation as adapted to human subjects is depicted in Figure 1. Here, the extra liver is placed in the right paravertebral gutter or right pelvis. Its hepatic arterial supply is derived from the aorta or an iliac branch. Venous inflow is reconstituted by anastomosing the host superior mesenteric vein to the homograft portal vein. Outflow is into the inferior vena cava.

At first thought, the use of auxiliary homografts for the treatment of benign hepatic disease has a special appeal. First, sacrifice of the remaining, albeit limited, function of the failing recipient liver can be avoided. Thus, in the event of poor initial performance by the homograft due to ischemia or to a severe but reversible rejection, it might be hoped that some assistance would be provided by the diseased host liver during a transition recovery period. This would be predicted to 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 dis-

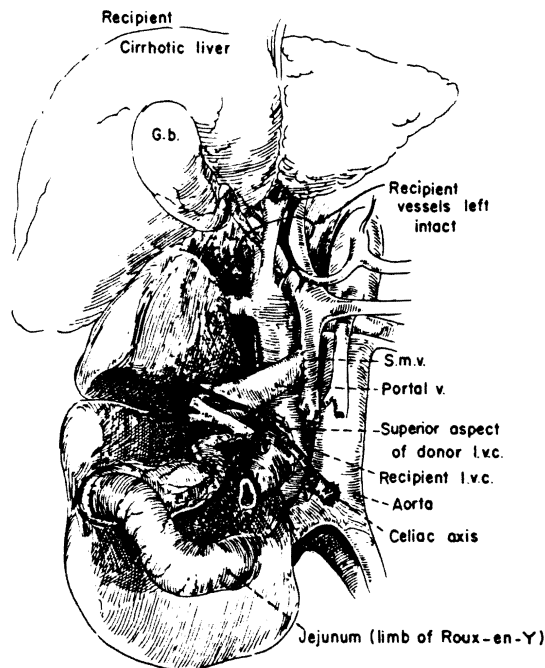


FIG. 1. Technique of auxiliary liver transplantation that provides splanchnic venous flow for the homograft. Because of portal hypertension caused by the diseased native liver, splanchnic flow will pass preferentially through the homograft. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969, p. 503.)

ease. Second, it was assumed initially that the placement of an extra liver would be safer and technically less demanding than the orthotopic procedure.

In actual practice, auxiliary transplantation has lost much favor. The results in animals 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 by mechanisms that have been ascribed to "interliver competition." A detailed discussion of this fascinating topic has been published,⁴ and the broader implications of splanchnic blood factors in controlling hepatic physiology and function has been the subject of a recent Ciba Foundation Symposium.⁵

Here, it will only be noted that most patients who would be candidates for liver transplantation do not have adequately functioning livers, so that the concept of competition may not be a critical one in clinical practice. Nevertheless, auxiliary liver transplantation for the indica-

tion of hepatic failure has resulted in the significant prolongation of life for only one patient. This was a child with biliary atresia who is still well as of April 1978, more than 6 years after auxiliary transplantation by Fortner,⁶ using a technique similar to that shown in Figure 1.

The reasons for failure have been several. In many cases good initial homograft function was not obtained due to an ischemic injury during and after donor death. In others, the presence of an extra organ within the abdomen was not well tolerated with restriction of diaphragmatic movement and consequent lethal pulmonary complications. Finally, the expectation that the placement of an extra organ would be technically simpler than with liver replacement has not been borne out by actual experience, as evidenced by an extremely high incidence of mechanical complications. Because of the poor clinical results, the number of attempts at human auxiliary transplantation has declined to the point that this kind of operation will not be considered further in the rest of the chapter.

Orthotopic Transplantation

In contrast, there is mounting evidence that the operation of orthotopic hepatic transplantation (liver replacement) will play an increasing role

in the future treatment of liver disorders. With this procedure, the diseased host liver is removed, creating a space into which a graft is transplanted with as normal an anatomic reconstruction as possible. Survival in dogs and human subjects has been achieved exceeding 12 and 8½ years, respectively. The remarks in succeeding sections will pertain to orthotopic transplantation.

PREOPERATIVE PREPARATION

Virtually all prospective liver recipients are poor risks for a major operation, and many of those with hepatic failure from nonneoplastic diseases appear at first evaluation to be hopeless. Symptomatic relief may be obtained by the performance of procedures such as paracentesis or thoracocentesis. But, unfortunately, there is probably little of real value that can be done to reduce the consequent operative hazards short of providing liver tissue. Nevertheless, even patients near death from complications of hepatic disease can be brought through the transplantation procedure with almost immediate improvement providing the homograft functions properly and promptly.

Although little can be done for the preexisting liver failure, secondary abnormalities of other organs 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. 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.

CASE SELECTION

According to Underlying Disease

Hepatic Malignancy. When orthotopic liver transplantation was first attempted in humans, primary liver malignancy was considered to be an outstanding indication for proceeding. Liver replacement was conceived of as a means of extending the limits of resectability in patients who did not have extrahepatic spread of their tumors.

In actual experience, our results have been discouraging. About 80 percent of our patients who were treated in this way for hepatomas, intrahepatic duct cell carcinomas, cholangiocarcinomas, and sarcomas and who lived through the early postoperative interval developed tumor recurrence.^{3,4} Most commonly, the posttransplantation metastases involved the new liver (Fig. 2). Deaths from recurrence have occurred as early as 143 days (Fig. 2) and as long as 2 years after transplantation.³

It is a bit too early to conclude once and for all that liver replacement in the face of hepatic malignancy is a futile 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 dl of alpha fetoprotein. After operation in January 1970, the fetoprotein disappeared from the serum (Fig. 3) and has not recurred in the 8½ years of posttransplantation life. Apparently, this child has achieved a cure from her hepatoma. Another of our patients, a 45-year-old man, is free of tumor 3½ years after liver replacement for a small intrahepatic duct cell carcinoma. Finally, a 28-year-old woman is well but with very slowly growing pulmonary metastases 1½ years after transplantation for sclerosing cholangiocarcinoma. Palliation or even cure of primary hepatic malignancies has also been reported by Calne et al.⁷

Biliary Atresia. Nevertheless, the prime indications for orthotopic liver transplantation have come to be terminal liver diseases of nonneoplastic origin. Of these, 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. With intrahepatic biliary atresia, more conservatism is exercised, as some of these children can survive for many years.

Other Benign Diseases. The problem of the proper time for liver transplantation may be a difficult one for almost all other kinds of nonneoplastic liver disease. This is particularly so if alcoholism is a significant etiologic factor that could be eliminated by abstinence. Other common diseases in our series have been chronic aggressive hepatitis, inborn errors of metabolism (Wilson's disease, alpha₁-antitrypsin deficiency, Type 4 glycogen storage disease), sclerosing cholangitis, and primary biliary cir-

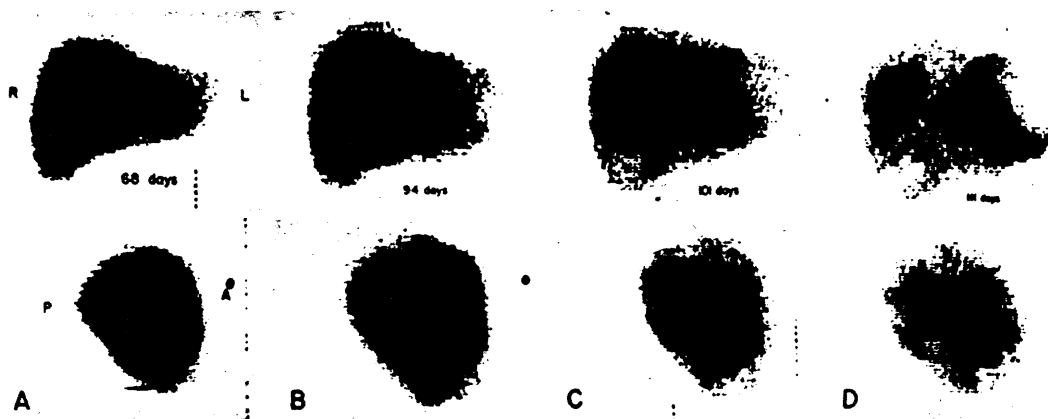


FIG. 2. ^{99m}Tc liver scans in a patient whose indication for transplantation was hepatoma. Note progressive invasion of liver homograft by tumor beginning at 94 days. The patient died of carcinomatosis 143 days posttransplantation. At autopsy, the homograft was almost completely replaced with carcinoma. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969.)

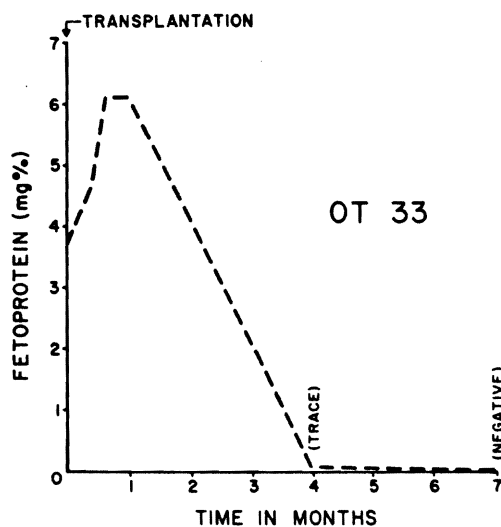


FIG. 3. Alpha-fetoprotein determinations in a 3-year-old child who underwent transplantation for biliary atresia. A small hepatoma was discovered within the operative specimen. The child is now 3½ years after transplantation. Alpha-fetoprotein determinations continue to be negative and she remains free of tumor.

rhosis. The time to proceed is when the patient is socially and vocationally invalidated, or cannot live longer outside the hospital. Patients with acute liver disease are usually not considered since they have the capacity to recover spontaneously. Contraindications would include advanced age (probably above 50 years), a history of sociopathic behavior that would prevent post-operative management, preexisting and untreatable systemic or local infections, or serious disease of organs other than the liver, as, for example, with coexisting severe heart disease.

According to Immunologic Criteria

ABO Matching and Cytotoxic Antibodies. When possible, the rules of tissue transfer are followed (Table 1). These are designed to avoid the transplantation of an organ into a recipient who possesses preformed antidonor isoagglutinins. Violation of these guidelines in kidney transplantation can lead to immediate graft destruction by hyperacute rejection. The liver has proved resistant to this complication, meaning that blood group barriers can be breached in

TABLE 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.

the case of desperate need.⁴ Even more surprisingly, the presence of preformed cytotoxic antibodies against donor tissues does not usually cause hyperacute liver rejection.⁴

HL-A Matching. The poor correlation in renal, cardiac, and liver transplantation between HL-A matching and clinical outcome has led us to ignore the question to HL-A matching for liver transplantation. Nor do we even use the most favorable matching as an instrument of selection amongst a given group of candidates for transplantation. At the present, our major criterion concerns who has the most pressing need.

DONOR PROCUREMENT

One of the important advances in transplantation has been social in nature, consisting of acceptance by the public of the concept of cadaveric organ removal. In the United States and many other countries, this acceptance has led to a sharpening and liberalization of the criteria of death in accordance with the concept of irreversible brain injury. If brain death is accepted, one of the most serious problems in organ transplantation is virtually eliminated, since the interval of normothermic ischemic injury subsequent to cardiac arrest 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.

With the advantages conferred by the acceptance of brain death, it is possible to maintain a well perfused liver in situ up to the moment of its excision. After removal, human livers can be preserved for as long as 12 hours by infusing them with specially prepared cold solutions.^{8,9} These recent developments have permitted the

shipment of preserved livers from city to city and have relieved some of the problems of organ supply.

OPERATIVE PROCEDURES

Donor Hepatectomy

The essential feature of liver removal is extremely straightforward and consists of skeletonization of the structures entering and leaving the liver. Frequently, the first step upon entering the abdomen and after examining the liver is incision of the restraining ligaments of the liver. The falciform ligament is divided down to or near the entry of the hepatic veins (Fig. 4). The left triangular ligament is incised (Fig. 5), as well as the right triangular and coronary ligaments (Fig. 6).

It is particularly important in freeing the right lobe of the liver from the bare area that the dissection be carried out sharply. Otherwise, subcapsular hematomas or capsular tears may be caused inadvertently. As the right lobe of the liver is rotated into the wound with exposure of the bare area, the right adrenal vein is readily identified entering the vena cava behind the liver (Fig. 7); this vessel is ligated and divided. After clearing loose areolar tissue away, it is usually possible to sweep behind the vena cava from the diaphragm to the entry of the renal veins without resistance (Fig. 8).

The rest of the dissection of the donor liver consists in isolating the structures below the liver as depicted in Figure 9. Usually the hepatic artery is dissected back to its origin from the celiac axis, ligating its gastroduodenal and right gastric branches (Fig. 9A and B). A long segment of the portal vein is similarly freed inferiorly to at least the entrance of the splenic vein (Fig. 9C). In many cases, the biliary drainage procedure of cholecystoenterostomy is planned. If this is contemplated, the common duct is ligated below the entrance of the cystic duct and an incision into the gallbladder is made so that the bile may be washed out. In experimental animals, failure to observe this precaution may lead to autolysis of the extrahepatic biliary duct system during the time when the organ is without a circulation.

The final step in the removal of the liver is further development of the cuff of vena cava above the liver into which empty the main he-

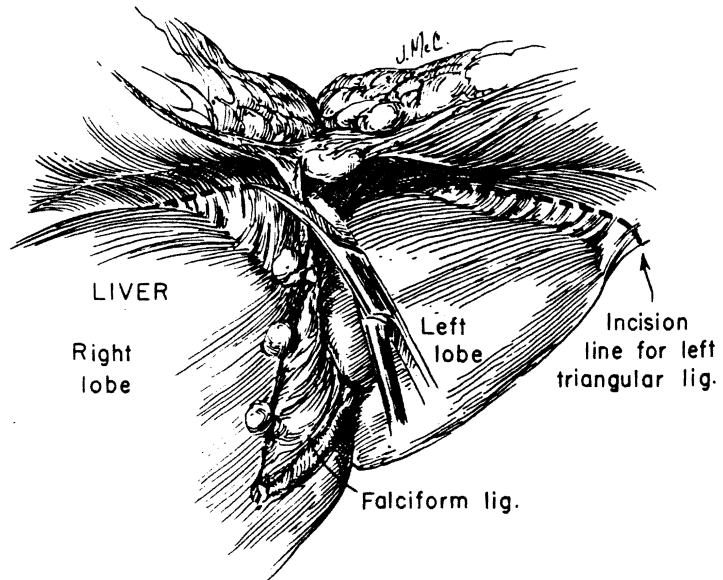


FIG. 4. Initial steps in donor hepatectomy. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969.)

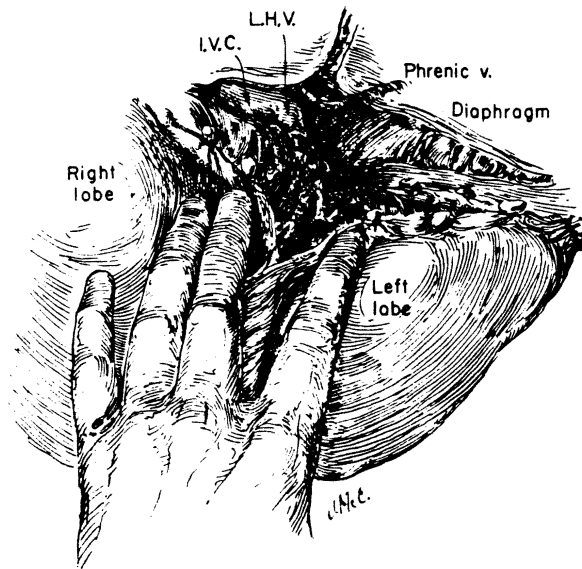


FIG. 5. Donor hepatectomy (continued). Exposure and the initial dissection of the suprahepatic vena cava and its tributaries. After entering the raw area formed by divergence of the leaves of the falciform and triangular ligaments, a short segment of the left hepatic vein (L.H.V.) is usually seen first. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969.)

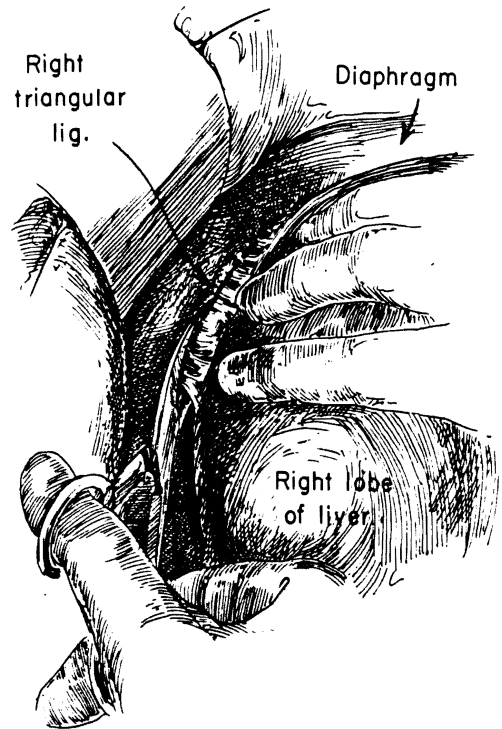


FIG. 6. Donor hepatectomy (continued). Incision of the right triangular ligament and the anterior leaf of the right coronary ligament. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969.)

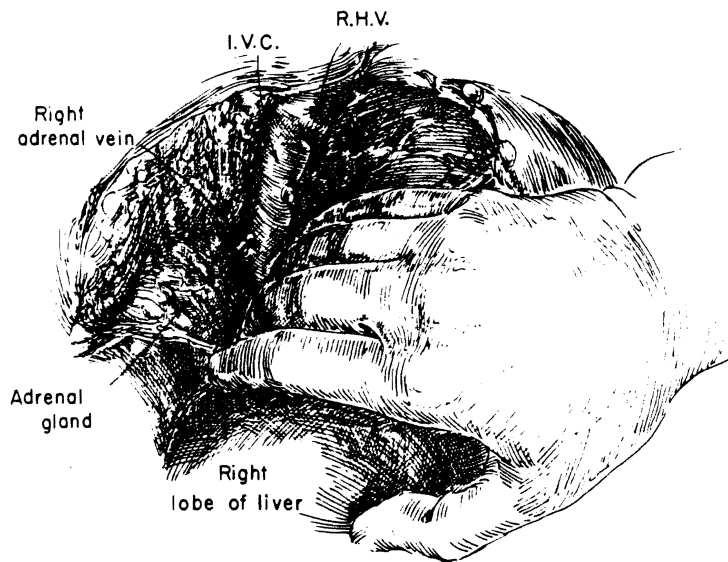


FIG. 7. Donor hepatectomy (continued). The liver is retracted to the left, opening the bare area of the right hepatic lobe and exposing the adrenal gland. The right adrenal vein is ligated and divided. This is usually the only posterior tributary to the retrohepatic vena cava. At this stage, the right hepatic vein (R.H.V.) can be identified. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969.)

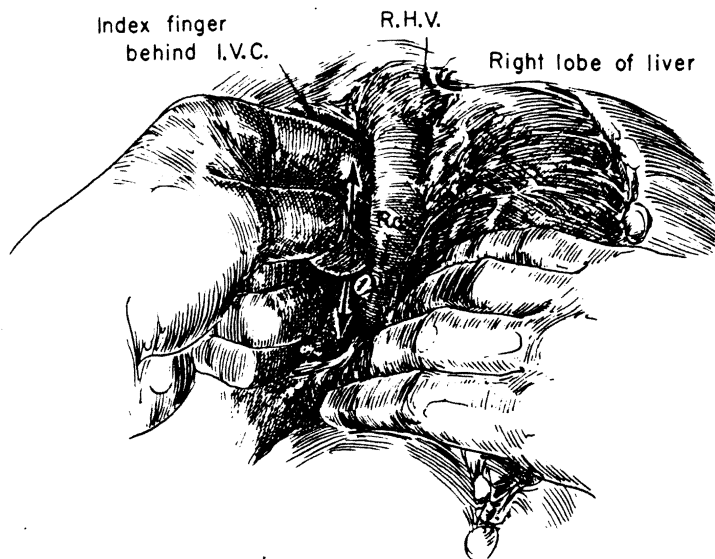


FIG. 8. Donor hepatectomy (continued). After ligating the right adrenal vein (R.a.v.), it should be possible to sweep the finger behind the retrohepatic vena cava from the diaphragm to the renal veins. If resistance is encountered, it usually indicates the presence of extra branches which must be ligated and divided. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969.)

patic veins (Fig. 10). This segment of vena cava is extremely short and is actually a confluence of vessels to form a venous cloaca. When the vena cava is finally transected and one peers into the liver side of this cloaca, the view is as shown in Figure 10 (inset).

With removal of the liver, infusion with a chilled solution is carried out via the portal vein (Fig. 11). In addition to cooling the organ, blood is washed out, thereby facilitating the anastomoses which can be performed in a clean field. There have been a number of infusion fluids recommended ranging from simple electrolyte solutions to the elaborate concoctions that have allowed longer preservation.^{8,9}

The Recipient Operation

Most of the steps in the recipient are identical or similar to those described above under the donor except that the long cuffs are left with the patient rather than with the homograft. After removal of the liver, the usual anatomy consists of cuffs of four vessels, the common duct stump (except in biliary atresia), and the raw areas left by incision of the various hepatic ligaments (Fig. 12). The reconstruction consists of anastomosing the individual vessels to the com-

panion vessels of the homograft as quickly as feasible. The "standard" operation is shown in Figure 13.

One feature of the vascular reconstruction that is a special one in liver transplantation is the necessity to perform some of the vascular anastomoses in cramped quarters and with short vessel lengths. To permit this kind of anastomosis, intraluminal suturing techniques have been developed (Fig. 14), in which the principle is the formation of shoulders of venous wall posteriorly with systematic eversion.³ This has sometimes been done with a double posterior layer (Fig. 14) or more recently a single everting layer has been employed.

Various biliary reconstructions that we have used are shown in Figure 15. If possible, choledochocholedochostomy is performed (Fig. 15D). The first alternative is cholecystojejunostomy to a Roux limb, realizing that conversion to choledochojejunostomy may be necessary at a secondary operation. If the gallbladder is not in perfect condition or if the cystic duct enters the common duct at an anomalously low level, the gallbladder is removed and primary choledochojejunostomy is performed. We no longer do cholecystoduodenostomy (Fig. 15A) because of a high incidence of cholangitis and because there

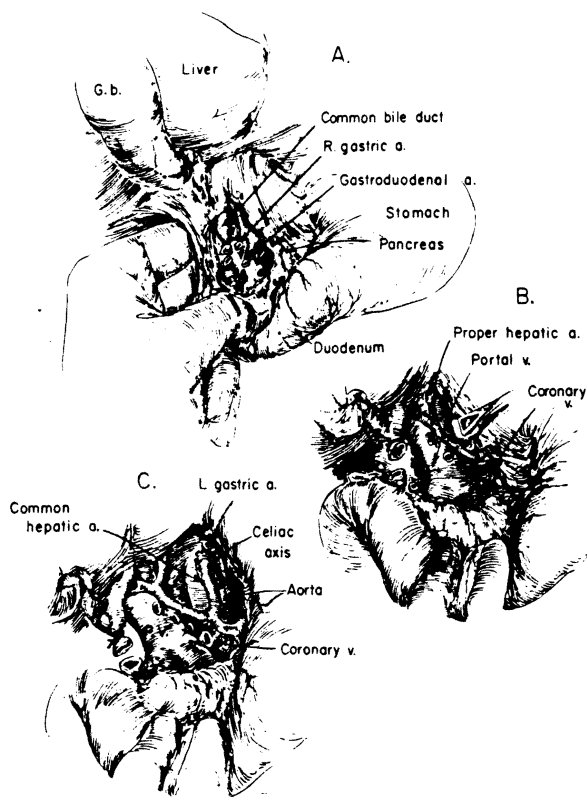


FIG. 9. Donor hepatectomy (continued). Dissection of the portal triad. **A.** The gastrooduodenal and right gastric arteries are tied off and divided. Before ligating the common duct, it should be determined that it communicates freely with the gallbladder via the cystic duct. **B.** The hepatic artery is mobilized, uncovering the anterior surface of the portal vein. The coronary vein entering the left side of the portal trunk is almost always found; this tributary is ligated and divided. **C.** Mobilization of the celiac axis. The splenic artery has not yet been ligated and divided. The entire celiac axis is usually retained with the homograft. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969.)

have been too many problems with the duodenum when secondary conversion to choledochoenterostomy became necessary.

Technical Difficulties and Dangers

Hemorrhage. Acute bleeding can be particularly troublesome during the actual liver transplantation because of the portal hypertension that is present in nearly every patient. During the operation, the usual sequence is mechanical bleeding that can rapidly assume nightmare proportions if a severe coagulation disorder supervenes. Many of the normal coagulation factors that might help control hemorrhage are dependent on the liver and are, therefore, defec-

tive 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 because of consumption of clotting factors by the injured graft.⁴

When hemorrhage occurs, all mechanical hemostatic tactics including ligature, 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). Lately, we have studiously avoided such practices for reasons to be discussed later.

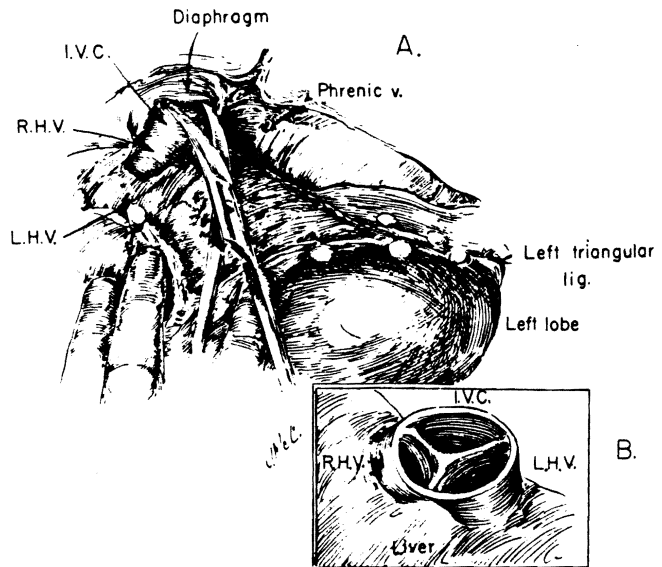


FIG. 10. Donor hepatectomy (continued). Dissection above the liver. **A.** Development of suprahepatic vena caval cuff. A longer caval segment for subsequent anastomosis may be obtained by ligating and dividing one or more phrenic veins on each side and by dissecting off the diaphragmatic reflection, as shown. **B. (Inset)** The cross-sectional appearance of the venous confluence above the liver, as seen from above. The venous cloaca is formed by the junction of the right and left hepatic veins with the inferior vena cava. (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders, 1969.)

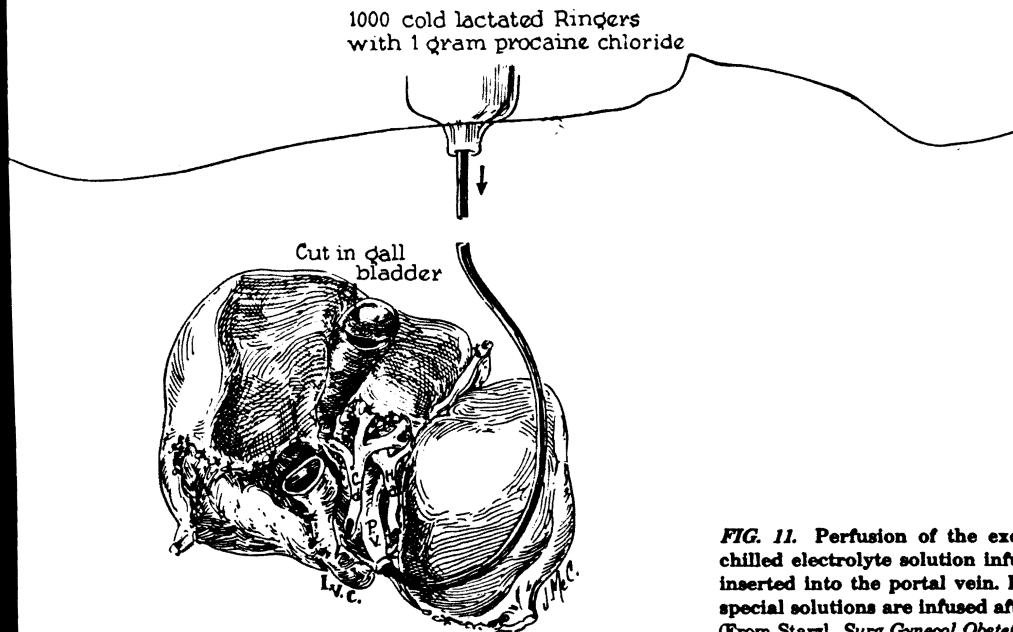


FIG. 11. Perfusion of the excised homograft with a chilled electrolyte solution infused through a catheter inserted into the portal vein. For longer preservation, special solutions are infused after the initial flushing.^{4,5} (From Starzl. *Surg Gynecol Obstet* 117:659, 1963.)

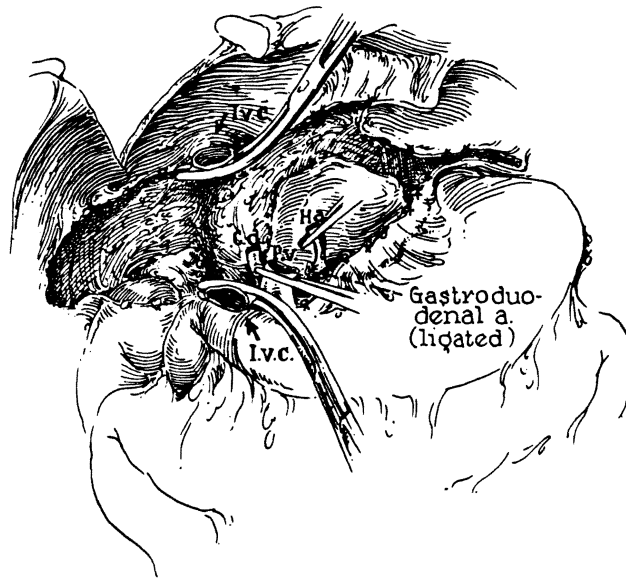


FIG. 12. Recipient operation. The operative field after removal of the diseased host liver. A bilateral subcostal incision is usually used with a right thoracic or xiphoid extension if required (see Fig. 16).

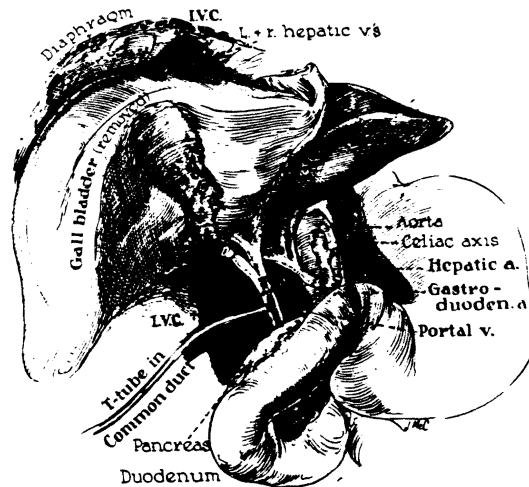


FIG. 13. Standard operation. In children with biliary atresia, and often in adults whose common duct will not reach the proper position at the homograft, biliary reconstruction is to an 18-inch Roux-en-Y limb of jejunum (see Fig. 15). (From Starzl. *Experience in Hepatic Transplantation*. Philadelphia, Saunders 1969, p 138.)

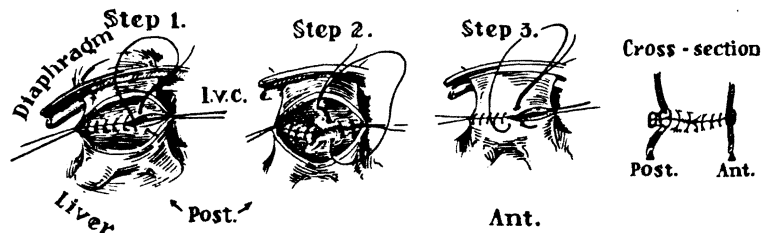


FIG. 14. Intraluminal suturing technique for the performance of the suprahepatic vena caval anastomosis. The posterior row may be fashioned in two layers from within the lumen, but recently a single layer everting technique has been employed. (From Starzl. *Surg Gynecol Obstet* 117:659, 1963.)

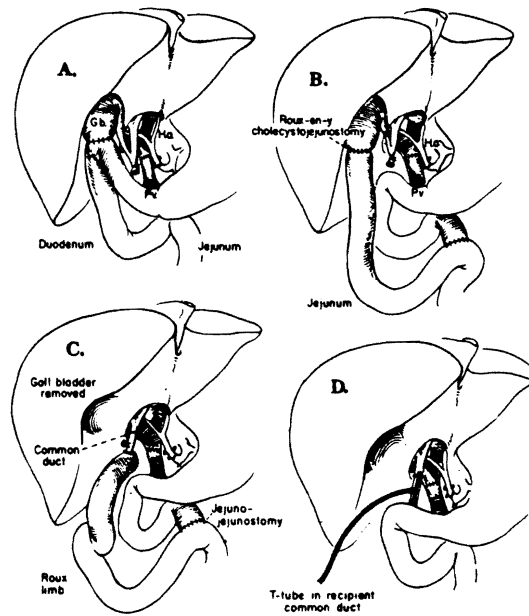


FIG. 15. Techniques of biliary reconstruction. Cholecystoduodenostomy (A) is no longer used (see text). (From Starzl. *Surg Gynecol Obstet* 142:487, 1976.)

Instead, complete dependence is placed on natural processes for correction of the abnormalities.

In adults with cirrhosis, it has been possible to reduce hemorrhage by avoiding dissection in the bare area or above the liver until the hilar structures are divided. When everything is ready, the inferior vena cava is transected. Then by pulling on clamps that are placed on the hepatic side of these structures, the liver is dissected free from below to above, ligating all cut tissues on the way (Figs. 16, 17). The suprahepatic inferior vena cava remains intact as the stalk of the specimen until it is clamped just before the liver is removed. This variation in operation has been particularly useful in developing a reasonably long suprahepatic cuff of the inferior vena cava in adults. The vena cava or

main hepatic veins may be dissected free from within the cirrhotic liver in a bloodless field (Fig. 17B).

Anesthesia Problems. The complexity of anesthetic management during liver transplantation is increased by the fact that the procedure is long, difficult, and often bloody. Even more importantly, it is an operation on the primary organ involved in the metabolism and detoxification of most common anesthetics. The task of 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 our cases, reliance has been placed mainly on combinations of volatile agents in nonexplosive concentrations. Such

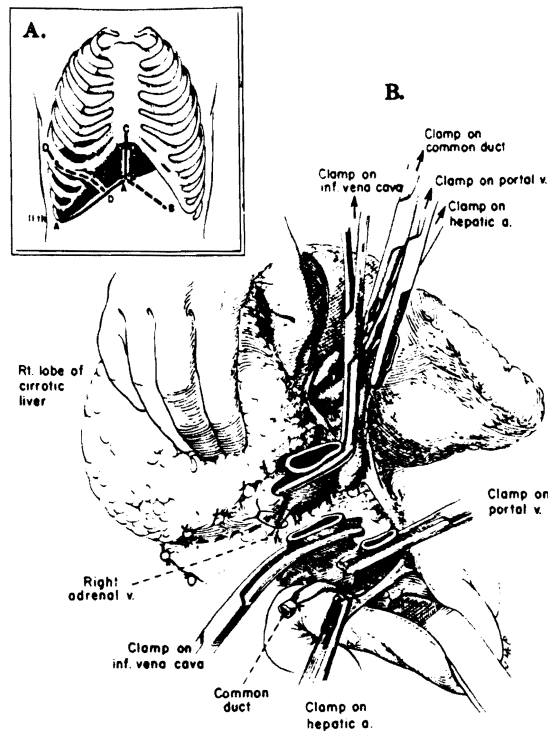


FIG. 16. Technique of retrograde removal of liver. *A.* Incisions. *AA.* Subcostal incision used for all orthotopic liver transplantations. *BB, CC, DD.* Frequently used extensions from the *AA* incision. *B.* Beginning retrograde removal after transection of inferior vena cava and hilar structures. All posterior tissue that is cut should be ligated, although the named vessels encountered, such as the right adrenal vein, are few in number. (From Starzl. *Surg Gynecol Obstet* 142:487, 1976.)

management permits use of the electrocautery, gives flexibility in lightening or deepening anesthesia, and allows anesthesia to be abruptly stopped if required by changing physiologic circumstances.

A number of swiftly changing metabolic conditions have to be carefully scrutinized during the anhepatic phase and immediately afterward. Since the patient is at risk from acute hypoglycemia, a constant infusion of glucose is required, and for proper control of the situation 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 that has been frequently seen just after revascularization and lasting for several hours

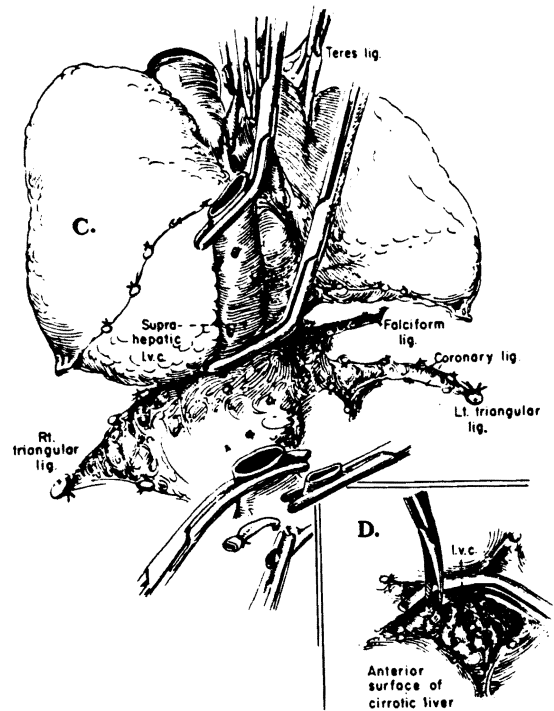


FIG. 17. *A.* Operative field after retrograde liver mobilization. The last remaining structure, the suprahepatic inferior vena cava, has been clamped above the liver. *B.* Technique for mobilizing a suitable length of suprahepatic vena cava after placement of clamp. In adults, this usually involves cutting away cirrhotic liver tissue over the frequently distorted and foreshortened right and left hepatic veins. (From Starzl. *Surg Gynecol Obstet* 142:487, 1976.)

is hypokalemia. Apparently, the potassium is sequestered in the grafts to the extent that serum potassium concentrations as low as 1.5 mEq per liter have been observed.

Spatial Problems. Not surprisingly, 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 5-year-old liver to a full-sized adult. Other size mismatches nearly as extreme have been safe.

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. 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.

Vascular Anomalies. Anatomic variations of either the graft or host arteries have been encountered in almost 40 percent of our cases. Multiple arteries have been the most frequent anomalies. When these have been found in the recipient, most commonly the graft celiac axis has been connected to the host celiac axis. When the multiplicity has been of the transplant vessels, multiple arterial anastomoses or other variant procedures have been used. Unquestionably, the need to improvise in these situations imposes an extra risk, particularly in the very young recipients whose arteries are quite small and thin-walled. In patients with biliary atresia, anomalies may be encountered of which the complexity may be so great as to make it virtually impossible to succeed.

Other Operative Problems. A long list of other technical pitfalls aside from biliary duct problems has been accumulated.^{3,4} These include vascular thrombosis, crushing of the phrenic nerve(s) at the diaphragm, adrenal infarction secondary to sacrifice of the right adrenal vein, and air embolism. Early in our experience, air emboli caused crippling neurologic injury in about 20 percent of our adult recipients. The

best evidence is that the air came from the homograft itself, passed around the lungs via large right to left collaterals that are well developed in chronic liver disease, and passed to the brain.¹⁰ The complication has been eliminated with the flush-out technique shown in Figure 18.

NONIMMUNOLOGIC POSTOPERATIVE COMPLICATIONS

In 1975 and 1976, complete clinicopathologic correlations were made in the first 100 cases of orthotopic liver transplantation. The objective was to determine the reasons for success or failure in every case. The perspective that emerged was different from that generally held, in that the most important lethal problems were nonimmunologic in nature. The main reasons for death were technical and mechanical and were responsible for about half of the ultimate mortality.

The inception of fatal complications was often traceable to some of the intraoperative complications mentioned earlier. The starting point of recovery was flawed in other instances by the use of severely damaged organs, suboptimal vascularization procedures leading to later portal vein or hepatic artery thrombosis, and leaving a nidus for subsequent intraabdominal infection. There was also a high incidence of gastrointestinal hemorrhage and perforation of

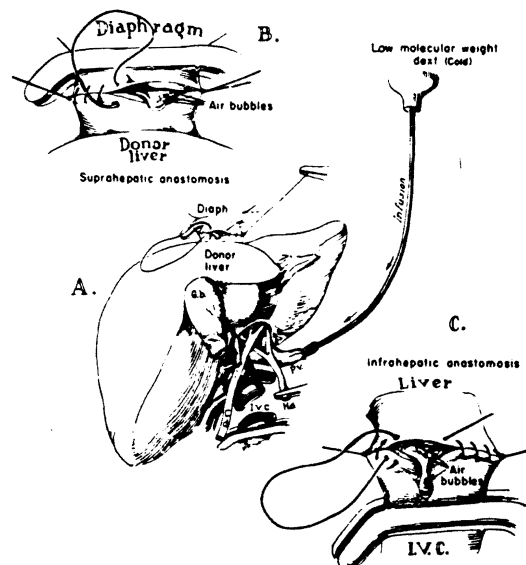


FIG. 18. Technique to prevent air embolism from orthotopic liver homografts. **A.** Continuous perfusion of solution through portal vein as vena caval anastomoses are constructed. **B, C.** Escape of air bubbles as the anastomoses are completed. (From Starzl. *Ann Surg* 187:236, 1978.)

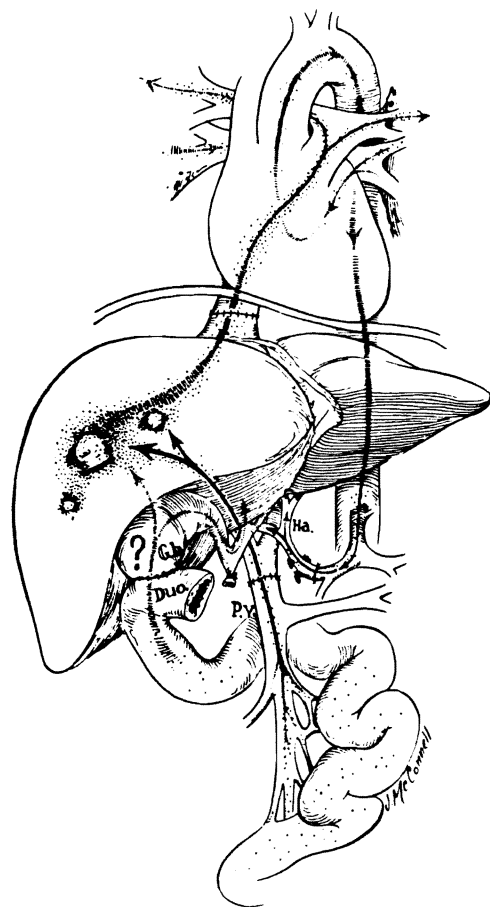


FIG. 19. An explanation for the predisposition of the liver to bacterial and fungal sepsis. Presumably the invading microorganisms enter through the reconstructed biliary tract. (From Starzl. *Ann Surg* 168:392, 1968.)

viscera (especially the colon). Analyses of these calamities have been published.^{3,4}

The Special Role of Biliary Complications

However, the leading cause of delayed death stemmed from faulty biliary tract reconstruction.^{3,11} For example, in the first 93 consecutive cases there were 24 examples of biliary obstruction and 8 of bile fistula formation. Reoperation was attempted in only half of these patients and even then, attempts were almost uniformly unsuccessful. In most of these early patients, the method of biliary reconstruction had been with cholecystoduodenostomy (Fig. 15A) from which stemmed a very high incidence of cholangitis. Conversion of cholecystoduode-

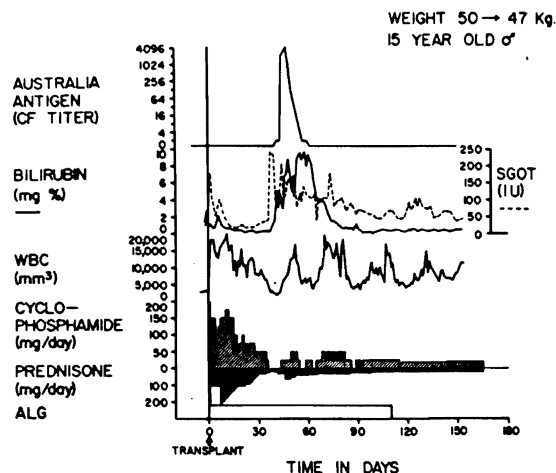


FIG. 20. The course of a patient who had triple drug therapy with cyclophosphamide (instead of azathioprine), prednisone, and horse ALG. Note that there was excellent liver function except during the second and third postoperative months, when the patient developed jaundice and rises in the levels of the serum transaminases. These abnormalities were coincidental with the appearance of the 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 7 years after transplantation.

nostomy to choledochoduodenostomy proved unsatisfactory since it carried a high incidence of duodenal fistula, and did not uniformly relieve the cholangitis. The contamination of the liver became the starting event of systemic sepsis in which organisms indigenous to the gastrointestinal tract (including *Candida albicans*) lodged in other locations (Fig. 19). In addition, there were multiple other causes of hepatic dysfunction such as serum hepatitis (Fig. 20), cytomegalovirus (CMV) infection, and possibly azathioprine toxicity.

In retrospect, the mistake that had been systematically made was to ascribe postoperative homograft dysfunction invariably to rejection and to respond therapeutically by intensifying immunosuppression. Therefore, reforms were instituted of two kinds. First, cholecystoduodenostomy was abandoned as a primary procedure in favor of choledochocholedochostomy, cholecystojejunostomy, and choledochojejunostomy (Fig. 15 BCD).

Equally important was a vigorous diagnostic postoperative approach whereby repeated biopsies and intrahepatic cholangiography were performed. Immunosuppression was then planned on the basis of the findings. The greatest divi-

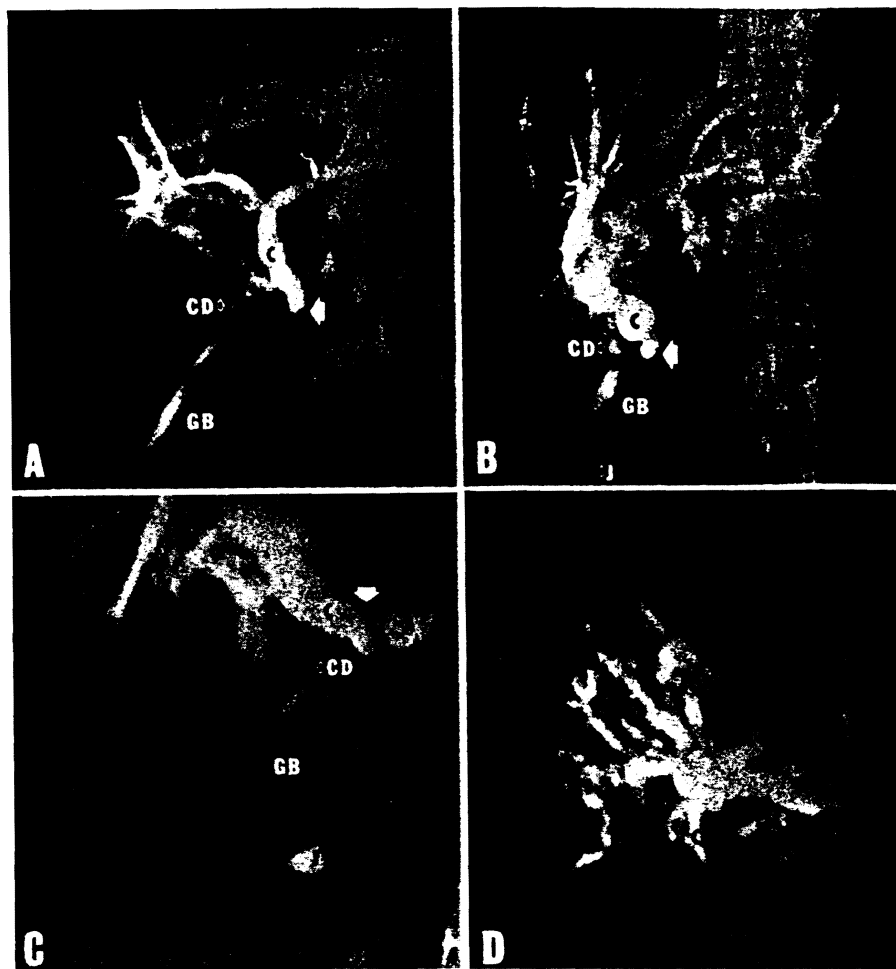


FIG. 21. Transhepatic cholangiograms in four patients whose original biliary reconstructions were with Roux-en-Y cholecystojejunostomy. As depicted in (A), minimal obstruction; (B), moderate obstruction; (C), severe obstruction with leak and abscess formation; (D), very severe obstruction. At reoperation the common duct was necrotic. (Key to abbreviations: A = leak and abscess formation; C = common duct; CD = cystic duct; GB = gallbladder; J = jejunum; large arrow = site of common duct ligation. (From Starzl. *Surgery* 81:212, 1977.)

dend has been the detection of biliary duct complications. In Figure 21 are shown examples of obstructed duct systems after cholecystojejunostomy. Stenosis was almost always found at or near the cystic duct. This complication has been easy to manage by converting cholecystojejunostomy (Fig. 15B) to choledochojejunostomy (Fig. 15C) by the technique shown in Figure 22. At reoperation, the gallbladder is removed, the end of the jejunal loop is closed, and the now dilated common duct is sutured to the side of the Roux limb. Stents are usually not necessary. After this reoperation, the wounds are broadly drained by leaving the central portion of the incision open.

The reintervention is life saving (Fig. 23). With relief of partial obstruction bacteremia, fever and jaundice are relieved promptly and most such patients have recovered rapidly with appropriate antibiotics. An argument could be made to avoid this two-stage approach by performing primary choledochojejunostomy and this has, in fact, been done on a number of occasions. However, the anastomosis of the small, normal duct of the homograft to a jejunal loop may be difficult, especially in children. As a consequence, primary choledochojejunostomy has been reserved for cases in which the gallbladder is unsatisfactory.

Most of the biliary fistulas we have seen have

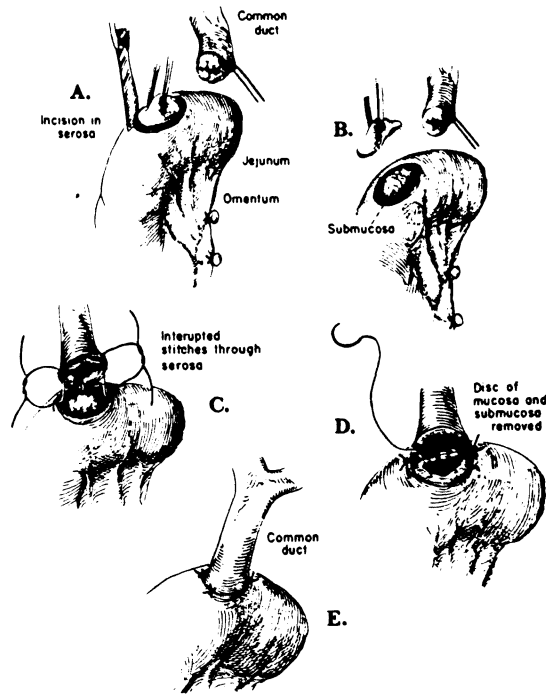


FIG. 22. Technique of choledochojejunostomy. (From Starzl. *Surgery* 81:212, 1977.)

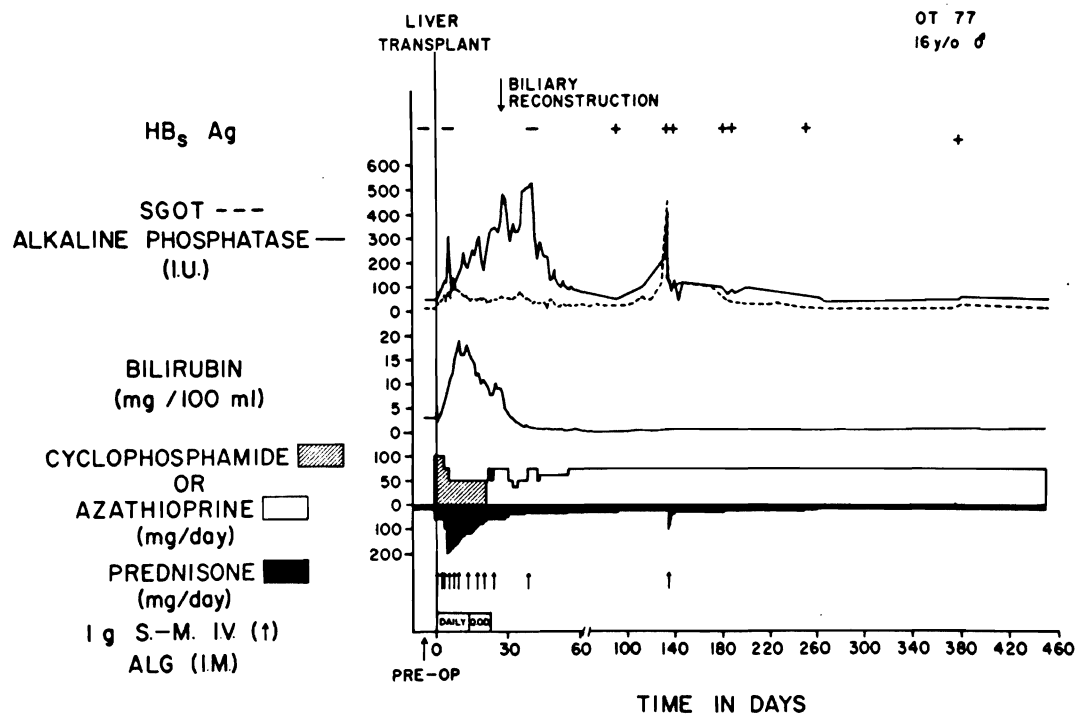


FIG. 23. Recovery after liver replacement for the indication of chronic aggressive hepatitis. The patient's postoperative transhepatic cholangiogram is shown in Figure 21(B). Jaundice persisted until the duct system was relieved of its obstruction by converting the initial Roux-en-Y cholecystojejunostomy to a choledochojejunostomy at the time indicated by the arrow. Note also that a bout of serum hepatitis complicated the recovery after about 2½ months. The patient recovered but became an HB_sAg carrier. He is well 4 years posttransplantation.

been after choledochocholedochostomy.¹¹ These can be managed effectively by wide drainage of the wound. T tubes have been left in place for as long as two years and as short as one month. It is probable that endoscopic retrograde cholangiography should be routinely used in the postoperative evaluation after the T tube has been removed. With the foregoing diagnostic and technical changes, deaths from biliary tract complications have been almost eliminated.

IMMUNOSUPPRESSION

The therapeutic regimens used in liver recipients have been the same as those evolved in kidney transplantation recipients.

Double Drug Therapy

Azathioprine and the synthetic adrenal corticosteroid, prednisone, are used together from the day of operation. This treatment protocol is preferred by Calne⁷ and has been used by us on a number of occasions.

Triple Drug Therapy Including ALG

In our center, most patients have had antilymphocyte globulin (ALG) as an adjunct to azathioprine and prednisone. Antilymphocyte glob-

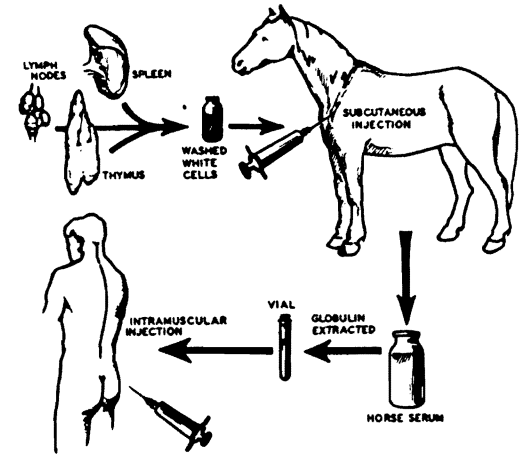


FIG. 24. The preparation of horse heterologous anti-lymphocyte globulin for use in patients. (From Starzl. *Christopher's Textbook of Surgery*. Philadelphia, Saunders, 1968.)

ulin (ALG) is purified from the serum of horses or rabbits that have been immunized against human lymphoid tissue (Fig. 24). When injected intravenously the ALG inactivates or kills recipient lymphocytes. The way in which the three agents are used together is shown in Figures 23 and 25. If azathioprine toxicity is suspected, cyclophosphamide can be substituted (Fig. 20).

The manifestations of rejection consist of the

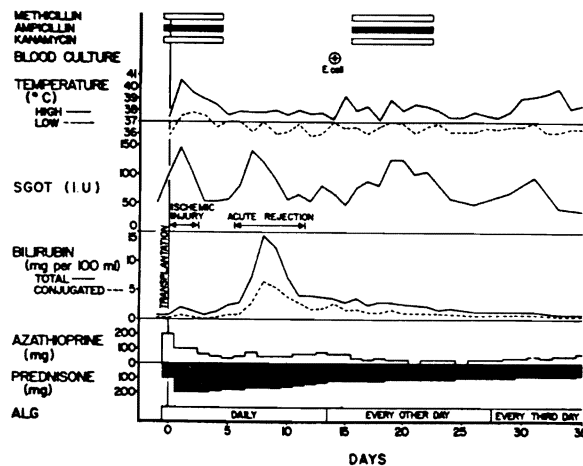


FIG. 25. The course of a patient who underwent a rejection crisis while under treatment with a triple drug program that included azathioprine, prednisone, and ALG. The rejection began on the sixth day, reached a peak within 2 days, and receded promptly. Gram-negative bacteremia was diagnosed from a blood specimen obtained on posttransplantation day 14. Note that the immunosuppressive therapy was actually lightened with the development and evolution of the rejection crisis.

TABLE 2. Fifty Adult Patients Treated by Liver Transplantation from March 1963 to July 1976 (Follow-up to April 15, 1978)

DIAGNOSIS	No. OF EXAMPLES	SURVIVAL (1 yr)		ALIVE NOW*
		No.	(%)	
Malignant tumor†	13	2	(15)	1 (42 mo)
Chronic aggressive hepatitis	17	5	(30)	1 (30 mo)
Alcoholic cirrhosis	11	1	(9)	1 (48 mo)
Primary biliary cirrhosis	4	0	(0)	0
Secondary biliary cirrhosis	1	0	(0)	0
Sclerosing cholangitis with ulcerative colitis	1	0	(0)	0
Massive hepatic necrosis due to hepatitis B virus	1	0	(0)	0
Budd-Chiari syndrome	1	1	(100)	1 (41 mo)
Congenital biliary hypoplasia	1	1	(100)	1 (26 mo)
Total	50	10	(20)	5

* The 5 deaths after one year occurred after 13½, 15½, 19, 20½, and 25 months.

† These include 7 hepatomas, 4 duct cell carcinomas, 1 cholangiocarcinoma, and 1 hemangioendothelial sarcoma. The patient who is still alive had a small obstructing duct cell carcinoma.

full range of liver malfunction (Fig. 25), including jaundice, elevations of serum transaminase (indicating necrosis), and failure of synthetic functions. However, as pointed out earlier, these perturbations are not pathognomonic. Consequently, the diagnosis of rejection must be one of exclusion. Once all other possibilities have been ruled out, rejection is usually treated by intensification of steroid therapy. In a few recent cases, thoracic duct drainage has been instituted for lymphocyte depletion at the time of unmanageable rejection.

Calne⁷ and we³ have found uncontrolled rejection to be less of a problem than was originally anticipated, possibly because the liver is less vulnerable than other organs to immunologic attack.⁴ Nevertheless, inadequate control of rejection remains a significant problem and has directly accounted for the death of about a quarter of our recipients.

RESULTS

Early Cases

Between March, 1963, through July, 1976, 111 consecutive patients were treated by liver replacement. Thirty-one (28 percent) lived for as long as a year, and as of April 15, 1978, 15 are still alive after 26 to 99 months. Of the 111 patients, 50 were more than 18 years old; 10 of the 15 lived for at least a year (Table 2), and 5 are still alive after 26 to 48 months. The 5 late deaths occurred after 13½ to 25 months (Table 2).

The other 61 patients in the original series of 111 were 18 years of age or younger with the most common diagnosis being congenital biliary atresia (Table 3). Twenty-one (34 percent) of these patients lived for a year and 10 are still alive after 41 to 99 months. In this group, 7 patients have lived more than 5 years and all but one are still alive.

In the original combined adult/pediatric series, 10 patients have lived more than 4 years and 9 are still alive.

Recent Cases

After the improvements in technique and management were instituted that were described earlier, an additional 30 consecutive patients were treated with liver replacement (Table 4). Fifteen of the 30 are alive with follow-ups of 3 to 20 months; 14 of the 15 survivors are already more than 6 months postoperative and 9 have passed the one-year mark. All of the 15 survivors are living outside the hospital. From this latest series it appears that the survival of both adult and pediatric recipients will be doubled compared to the results achieved before 1976. Calne and Williams⁷ and their associates from England have noted a similar, recent encouraging trend.

FUTURE PROSPECTS

It is probable that the one-year survival after liver transplantation cannot be brought much

TABLE 3. Sixty-one Pediatric Patients Treated by Liver Transplantation from March 1963 to July 1976 (Follow-up to April 15, 1978)

DIAGNOSIS	TOTAL No.	SURVIVAL (1 yr)		FOLLOW-UP PRESENT SURVIVORS*	
		No.	(%)	No.	Months
Congenital biliary atresia	42	12	(29)	6	41,54,62,74,81,99
Chronic aggressive hepatitis	10	3	(30)	2	41,50
Hepatoma	3	2	(67)	0	—
Wilson's disease	2	2	(100)	1	85
Congenital biliary cirrhosis	1	1	(100)	1	70
Alpha ₁ -antitrypsin deficiency	1	1	(100)	0	—
Tyrosinemia	1	0	(0)	—	—
Giant cell hepatitis	1	0	(0)	—	—

* Eleven other patients died after 12½, 13, 13½, 14, 17, 20, 26, 28, 30, 41, and 72 months

TABLE 4. Adult/Pediatric Division of 30 Cases August 1976 to December 1977 (Follow-up to April 15, 1978)

	No. OF EXAMPLES	6 MO ALIVE	1 YEAR POSTOP
Adults	18	8 (44%)	
Pediatric (<18 yr)	12	7 (58%)	

over 50 to 60 percent without major advances in immunosuppression. Even though rejection has been uncontrollable in only about one-fourth of our patients, the need for long-term high dose steroid therapy imposes life threats. How to achieve less toxic immunosuppression and earlier graft acceptance is still an unresolved dilemma. Wider use of thoracic duct drainage instituted at an earlier time may prove to be useful.

Even with the present limitations of immunosuppression, liver transplantation has slowly evolved in the last 15 years to a position of limited therapeutic value as opposed to an experimental undertaking. The achievement of 7 survivors beyond the 5-year mark in our own series

and the high quality of life being pursued by 6 of these patients constitute proof of the potential of both the present value and future potential of liver replacement.

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