plantation will probably occur after intermediate-term preservation has been successfully accomplished, as only then will the more time-consuming methods of donor-recipient matching, such as mixed lymphocyte culture, be practical. In addition, it would be an enormous advantage if kidneys could be stored for the same period of time that blood is stored now.

Long-Term Preservation

Long-term preservation awaits a breakthrough in freezing of whole organs at temperatures below $-79°$ C. The problems involved in freezing large organs, such as the human or dog kidney, are enormous. So far, there have been no published reports that such organs have been actually frozen for any length of time, thawed, and successfully implanted. Although this may become the procedure of choice in the distant future, this method probably depends upon the development of a nontoxic cryoprotective agent that will remain in liquid form at much lower temperatures than are currently possible. If such a cryoprotective agent can be found, the problems of uneven freezing and thawing of large organs could be solved.

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VI

LIVER HOMOTRANSPLANTATION

Thomas E. Starzl, M.D., Ph.D., and Lawrence Koep, M.D.   459

The liver has far more complicated metabolism than other transplanted organs, and its malfunction leads to vastly more complex physiologic derangements. Patients with liver disease are further handicapped by the lack of a satisfactory means of artificial support comparable to renal dialysis. The transplanted liver must function efficiently practically from the moment of anastomosis or the patient is lost. Despite these and other difficulties, there has been enough progress to state that liver transplantation may in certain cases be considered the treatment of choice. Human survivals of up to 9 2/3 years have been achieved.

KINDS OF LIVER TRANSPLANTATION

There are two general approaches to transplantation of the liver. With the first method, the host liver is removed and replaced with a homograft (orthotopic homotransplantation) (Fig. 1). The alternative technique is the insertion of an extra liver (auxiliary homotransplantation) at an ectopic site (Fig. 2). Both procedures were developed in dogs and later studied in other species, including rats, pigs, monkeys, and humans. The most encouraging results have been with orthotopic transplantation, for which reason this chapter will be concerned primarily with this replacement operation. However, in a special section near the end of the chapter, auxiliary hepatic transplantation will be briefly considered.

IMMUNOLOGIC CONSIDERATIONS

Is the Liver a Privileged Graft?

When liver replacement was first successfully performed in dogs, immunosuppression was stopped after 4 months. A surprising number of animals continued to thrive either with no signs of rejection or with rejection episodes that waxed and waned remittently.[3] One such dog lived in our laboratory for more than 11 years after transplantation. This phenomenon of "graft acceptance" has been noted in dogs with renal transplants, although less frequently. The seeming immunologic

Figure 1. Completed orthotopic liver transplantation (liver replacement).

advantage of the liver has been even more clearly seen in pigs, some of which can survive chronically with no immunosuppressive therapy at all[1, 3] in spite of the fact that pigs regularly reject skin and kidney grafts. The

Figure 2. Auxiliary liver transplantation with a technique that provides an adequate blood supply for the homograft. Note that the transplant is given a double blood supply and that the venous component is from the nonhepatic splanchnic bed. Biliary drainage can be with a Roux-en-Y cholecystojejunostomy.

reason for easier liver graft acceptance is not known. Whatever the explanation, overstatement of the case for the liver's privileged status could lead to erroneous conclusions about the practical requirements for immunosuppressive therapy following hepatic transplantation in man. In humans, control of hepatic rejection may be difficult or impossible in spite of very heavy immunosuppressive therapy.

Rejection Reversal

Rather than being unique, it is probable that liver homografts differ from other organs only by the degree of host immunologic response they evoke in all species, including the pig. In this context, two key observations initially made with kidneys have been extended to the liver. The first is the reversibility of rejection. Reversal usually requires intensification of treatment, but it has sometimes been noted without any change in the preexisting therapy, suggesting that such recoveries had an element of spontaneity.

Graft Acceptance

The second observation of overriding practical and theoretical interest concerns what has already been referred to as graft acceptance. In many of the human kidney and liver recipients treated years ago,[3, 4] it was shown that a melting away of host resistance to the homograft occurred surprisingly early after transplantation, sometimes following an acute rejection crisis. This was manifested by eventual declines in the doses of immunosuppressive agents necessary to retain stable graft function. In many patients, the level of chronic immunosuppression has proved to be less than that which at the outset failed to prevent the onset of a severe rejection. The ultimate step of cessation of all treatment has been too dangerous to attempt.

Explanations for Graft Acceptance

The degree to which graft acceptance develops is a prime determinant of the long-term prognosis. Unfortunately, the reason for the change in the host-graft relationship is not known. More than one immunologic pathway may be involved.

IMMUNOLOGIC TOLERANCE.   One possibility is that there is a selective loss of responsiveness to antigens. It might be envisioned that specific lymphocyte clones, induced to replicate by the graft antigens, are thereby rendered more vulnerable to the killing effect of immunosuppressive agents than the rest of the lymphocyte population (Fig. 3). Inasmuch as the maintenance of such activated cell lines appears to be thymus-dependent even in adult life, at least in some experimental animals, it is reasonable to be curious about the effect of thymectomy as an adjuvant immunosuppressive measure. The results of thymectomy in a series of our human renal transplants were inconclusive.[3]

The concept of specific, differential tolerance through "clone stripping" can partly explain the characteristic cycle of rejection and reversal occurring after whole-organ transplantation both in treated animals and in man as well as in the weak and self-resolving crises in the untreated pig. Moreover, it is consistent with the fact that a wide variety of agents that are capable of general immunologic crippling can also provide speci-

Figure 3. Hypothetical mechanisms by which nonspecific immunosuppression may lead to selective abrogation of the host immune response. Special susceptibility to these agents of a fraction of the lymphoid population could lead to exhaustion of a clone, and hence, tolerance. Since maintenance of such cell lines even in adult life is apparently thymic-dependent in experimental animals, thymectomy would be expected to aid the process; this appears to be true in rodents, but such an effect of thymus removal has not been proved in dogs or humans. A possible protective role of immunoglobulins elaborated by the replicating cells is also shown.
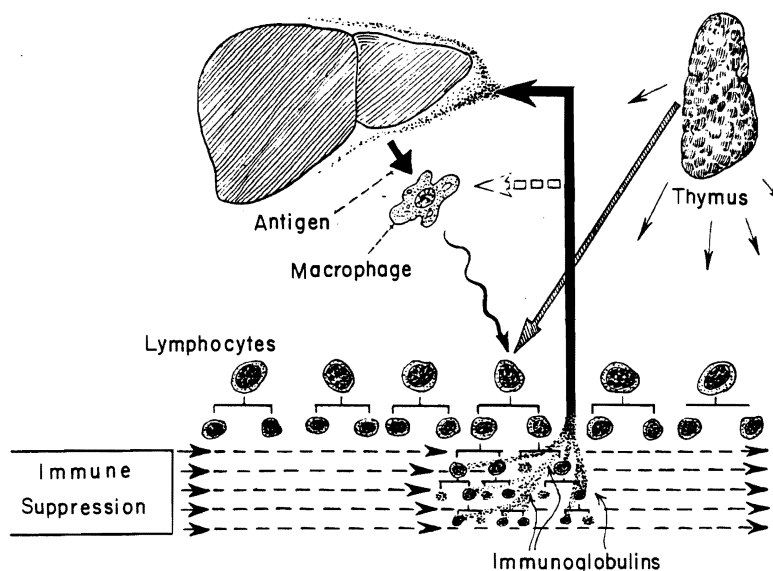
ficity of action under the stipulated conditions of immunosuppressive treatment during presence of the antigen. However, classic immunologic tolerance cannot be demonstrated in most patients who have chronically functioning whole-organ grafts.

ENHANCEMENT. These ambivalent findings do not disprove tolerance through "clone stripping" so much as they suggest that at least another mechanism of graft acceptance may be involved. One such mechanism, termed "enhancement," has been envisioned as a process in which immunoglobulins synthesized by the activated lymphoid tissues circulate to the target tissue and coat it or protect it in some way that is not yet understood (see Fig. 3).

The two foregoing mechanisms of graft acceptance by tolerance induction and enhancement are not mutually exclusive. Using immunologic monitoring tests, a number of investigators have demonstrated changing host-graft relationships in kidney recipients that are consistent with a multifactorial graft acceptance hypothesis.

TISSUE TYPING

In kidney transplantation, standard HL-A typing has not been a precise method of selecting biologically suitable donors. Even if these techniques were more reliable, it is unlikely that seeking well-matched livers would be possible. The need for transplantation has been so pressing in appropriate candidates that it often has been obligatory to proceed with the first available organ. Thus, almost all of the matches in our series have been bad ones.[4]

Because of urgent needs, ten liver transplantations have been performed despite the presence in the recipients of cytotoxic antibodies that were antidonor-specific. In addition, we have proceeded in 11 liver recipients who could not wait for blood group–compatible organs. There were no unequivocal examples of the hyperacute rejection that almost invariably destroys

renal homografts under these adverse immunologic circumstances. We[4] as well as Calne and Williams[1] have concluded that the liver is highly privileged, at least in confrontations with a preformed antibody environment. Nevertheless, transplantation into a hostile antibody environment is a violation of such an important biologic principle that it will require constant reassessment as more experience is acquired.

THE PROCUREMENT OF ORGANS

In contrast to typing, the procurement of a fresh, functioning, nonischemic liver is of paramount advantage.

The Source of Donors

Unquestionably, one of the most important advances that has been made in transplantation has been social in nature, namely acceptance by the public of the concept of cadaveric organ removal. The interval of normothermic ischemic injury was virtually eliminated, since the organ usually could be dissected free in the presence of an intact and effective circulation. Suitable donors usually are victims of head trauma or of asphyxia that has caused irreversible brain damage.

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 and 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 to humans and has permitted the shipment of livers from city to city. The Cambridge surgeons[1] have cautioned that ischemia or bile left within the ducts or both within such livers may cause autolysis and set the stage for delayed mucosal sloughing and cast formation.

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.

SURGICAL TECHNIQUES OF ORTHOTOPIC TRANSPLANTATION

A Species Difference

With removal of the host liver it is necessary to cross-clamp temporarily the great veins draining the intestines (portal vein) and the lower half of the body (inferior vena cava). Dogs die promptly if the distal venous pools are not decompressed.[3] In contrast, humans with liver disease have tolerated this venous obstruction surprisingly well. Although a slight duskiness of the intestine developed in some recipients, it immediately disappeared when blood flow was restored through the reconstructed venous channels. The ease with which portal and vena caval cross-clamping was tolerated can be explained by man's inherently richer network of potential collateral channels for the return of blood to the right heart, and by the presumed increase in their size and ramifications in consequence of the underlying liver disease.[3]

Hemorrhage

Other problems during and after operation may be caused by derangements in the coagulation mechanism which may result in either hemorrhage or thrombosis.[3] The nature of the underlying hepatic pathologic process produces portal hypertension in nearly every patient, and the nature of the operation tends to exaggerate it. The usual consequence is mechanical bleeding that can rapidly assume nightmare proportions during the procedure. Many of the normal coagulation factors that might help control hemorrhage are dependent on the liver and are therefore defective. If the homograft does not function properly, hemostasis may be impossible to achieve.

When hemorrhage occurs, the surgeon's challenge is to use all available hemostatic tactics — ligatures, sutures, and cautery — until the revascularized homograft can participate in what is hoped will be appropriate coagulation function. With our earlier patients, whose homografts were often of less than optimal quality, an attempt was made to treat bleeding problems by administering thrombogenic agents. However,

hypercoagulability was caused in some instances. The unacceptable incidence of pulmonary embolism in these patients led us to abandon this approach. Later, the bleeding may be succeeded by complications of heightened clotting. Ironically, the better the condition of the transplant, the greater the risk of unwanted coagulation. Almost every series of liver transplants, including our own, has had examples of thrombosis.

In general, it is now considered best to avoid iatrogenic manipulation of the clotting process with either thrombogenic or anticoagulant agents. Instead, our current approach is to leave correction of coagulation abnormalities to natural processes, intervening only under special circumstances and for very specific indications.

Air Emboli

Eventually lethal neurologic invalidism was seen in 9 of the first 48 adult patients undergoing liver replacement. The complications occurred during or shortly after operation. Several of these patients awakened from anesthesia but then had a secondary decrease in consciousness, seizures, and other crippling abnormalities. They died within a few days to 2 months. It ultimately was realized that air emboli from the homografts were responsible for some, if not all, of the focal infarctions.[4] The ease with which air passed to the systemic circulation was explicable by the right-to-left venous-arterial shunts that are common in chronic liver disease. Air released into the pulmonary circulation apparently passed through these collaterals to the systemic circulation, including the arterial supply to the brain.
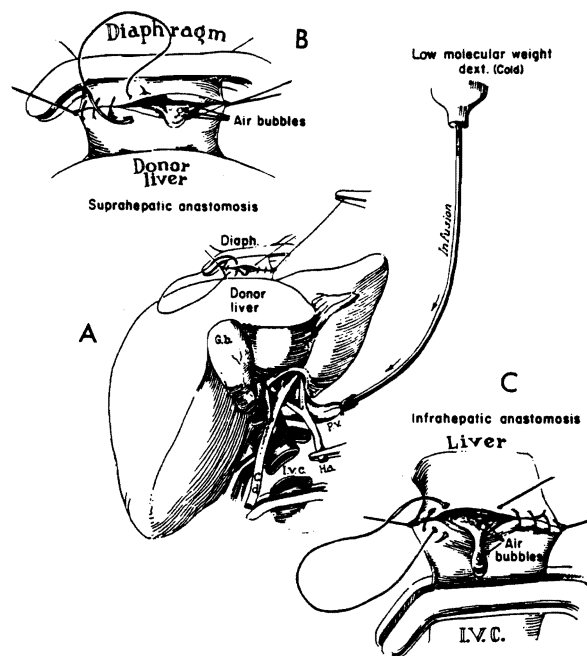

Figure 4. Technique to prevent air embolism from orthotopic liver homografts. A, Continuous perfusion of solution through the portal vein as vena caval anastomoses are constructed. B and C, Escape of air bubbles as the anastomoses are completed. (From Starzl, T.E. et al.: Ann. Surg., 187:236–240, 1978.)

With the delineation of this cause for the neurologic complications, measures were instituted to prevent it. During revascularization of the liver, electrolyte solution was slowly infused through a portal vein cannula. While the vena caval anastomoses were carried out, air bubbles could escape from the graft vessels before a blood supply was restored (Fig. 4). Since the institution of this simple preventive measure no further such difficulty has been encountered.

Vascular Anomalies

In planning a liver transplantation, the surgeon must be prepared for a high incidence of anatomic variations in either the graft or the host structures.[3] These have been encountered in almost 40 per cent of our cases. Multiple arteries have been the most frequent anomalies. When these have been in the recipient, most commonly the graft celiac axis has been connected to the host celiac axis. When the multiplicity has occurred in the transplant vessels, it usually has been possible to trace these back to their celiac axis origin and to perform a single anastomosis of the graft celiac axis to the recipient proper or to a common hepatic artery. However, multiple arterial anastomoses or other variant procedures have been used. The need to improvise in these situations imposes an extra risk, particularly in very young recipients whose arteries are quite small and thin-walled even under the best technical circumstances.

Biliary Tract Problems

Realization that the biliary tract was of prime importance in liver transplantation prompted major reforms both at our center and in England. Until 1976, we commonly performed cholecystoduodenostomy (Fig. 5A). Although the operation was simple, obstruction or bile fistula formation occurred in 30 percent of the patients, almost always leading to death.[4] Furthermore, homografts seemingly were subjected to repeated bacterial contamination, with resulting cholangitis and consequent systemic infection. We now believe that the ideal method of biliary reconstruction is choledochocholedochostomy, using a T-tube stent (Fig. 5D) which is left in place for many months. After the T-tube is removed, periodic retrograde cholangiography via the duodenum can be performed in such recipients. Choledochocholedochostomy often is not feasible, as, for example, in children with biliary atresia. As alternatives we perform cholecystojejunostomy (Fig. 5B) or choledochojejunostomy (Fig. 5C) to a Roux limb of jejunum. In immunosuppressed patients the initial construction of the Roux limb has carried an intrinsic risk, in that perforations of the Roux limb itself or the jejunojejunostomy below it occurred in 8 patients among the first 141. Seven of the eight patients died from this complication.

The advantage of cholecystojejunostomy is that a large-caliber anastomosis is possible, even with the use of pediatric livers. No stenting or draining is necessary. The disadvantage is that obstruction of the cystic duct (Fig. 6) has necessitated reoperation and conversion to choledochojejunostomy (see Fig. 5B and C) in almost one third of the cases. However, the secondary procedure has been safe. Calne and Williams have advocated
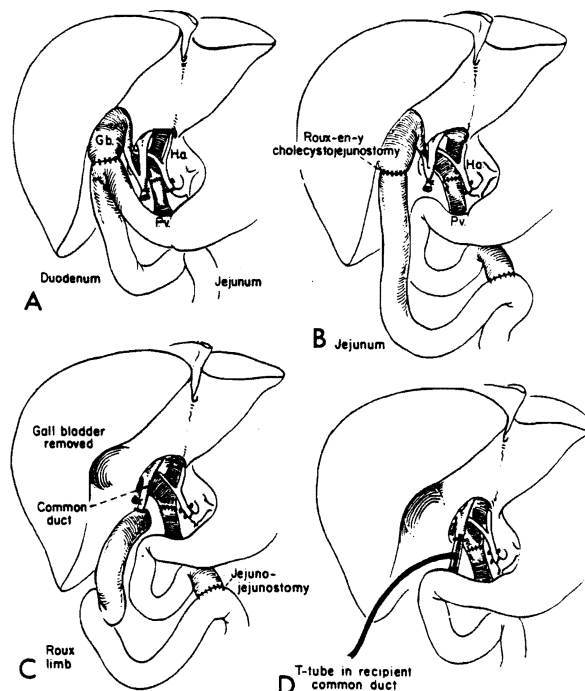

Figure 5. Techniques of biliary duct reconstruction used for most liver transplant recipients. A, Cholecystoduodenostomy. B, Cholecystojejunostomy. C, Choledochojejunostomy after removal of gallbladder. D, Choledochocholedochostomy. Note that T-tube is placed if possible in the recipient common duct. (From Starzl, T.E. et al.: Surg. Gynecol. Obstet., 142:487, 1976.)

a different surgical approach.[1] With Calne's technique, the common duct and gallbladder are connected into a common chamber, and a second anastomosis of the gallbladder fundus is made to the recipient common duct (or sometimes to a Roux limb). The cholecystocholedochostomy is stented with a T-tube, enabling the biliary system to be frequently studied or irrigated. Experience alone will tell if Calne's more complicated reconstruction is necessary or desirable.

In the postoperative management of liver transplantation, the possibility of duct obstruction must be entertained no matter what the method of reconstruction. Until the last few years, postoperative hepatic dysfunction was too readily ascribed to rejection, when, in fact, obstruction or cholangitis or both were frequently responsible. Even in the absence of a biliary tract problem, rejection may not be responsible. Hepatitis caused by $HB_S Ag$, CMV, and other viruses has been observed as well as drug toxicity. At the present time, the development of jaundice after transplantation is a signal for cholangiography and usually for liver biopsy. The histopathologic findings in the biopsy tissue may not provide an unequivocal answer. Then, the diagnosis of rejection must be made by exclusion.

Anesthesia

During operation, there are metabolic abnormalities other than those concerned with coagulation. These contribute to the complexity of anesthetic management. Not only is the procedure long and difficult, but

even more important, it is an operation on the primary organ involved in the metabolism and detoxification of most common anesthetics. At any point during the operation, the liver is either inherently impaired, absent, or untried in its new setting. Hence, 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 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. Further
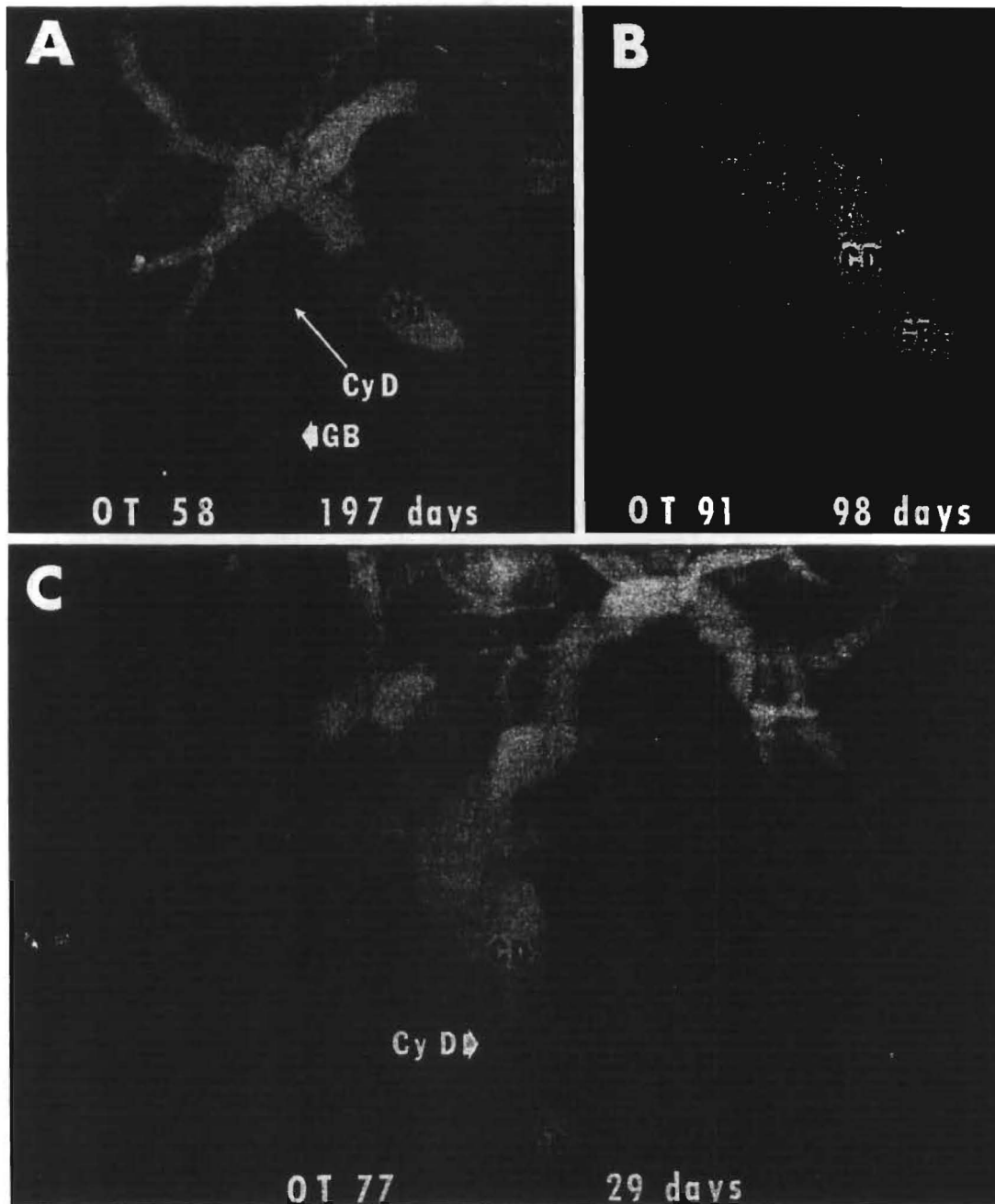
Figure 6. Examples revealed by transhepatic cholangiography of homograft cystic duct obstruction after biliary reconstruction with cholecystoenterostomy. *A,* Original procedure was cholecystoduodenostomy. After this transhepatic cholangiogram, conversion was made to choledochoduodenostomy. At operation, the filling defect near the exit of the cystic duct was found to consist of a chalk-like sludge. There was not complete relief of jaundice. When the patient died 13 months after transplantation, the homograft still had intrahepatic evidence of large duct obstruction. *B,* The original reconstruction was with cholecysto–Roux-en-Y jejunostomy. This was converted to a choledochojejunostomy. The patient is well 5 years later. *C,* The original reconstruction was with cholecysto–Roux-en-Y jejunostomy. This was converted to a choledochojejunostomy. The patient is well 5⅔ years later. CD = common bile duct; CyD = cystic duct; GB = gallbladder; J = Roux-en-Y limb of jejunum. (From Starzl, T.E. et al.: Surg. Gynecol. Obstet., 142:487–505, 1976.)

details of operative technique and complications can be found in the appropriate references.[1, 3, 4]

IMMUNOSUPPRESSION

The immunosuppressive therapy in liver transplantation has borrowed heavily from the experience gained with human renal transplants. Two general treatment programs were developed with the simpler kidney model and later applied to the liver recipients.

The first protocol, which was used from 1962 to 1966 for all organ recipients at the University of Colorado, consisted of "double-drug" treatment with azathioprine and the synthetic adrenal cortical steroid prednisone.[3] Experience with the combined use of these agents, appreciation of their marked synergism, and demonstration that rejection could be readily reversed by increasing the steroid doses were among the advances that made clinical transplantation practical. But in spite of fair results with renal transplantation, the double-drug therapy either did not prevent rejection of hepatic homografts or else proved too toxic to permit host survival. Six patients treated with liver transplantation from 1963 to 1965 died in a month or less. The double-drug regimen is still used by the Cambridge team.[1]

In 1966, heterologous antilymphocyte serum (ALG) was introduced clinically at our center as a third immunosuppressive agent in addition to the drugs mentioned previously.[3] Almost all of our human liver recipients who achieved long-term survival were treated with the combination of azathioprine, prednisone,

and intramuscular ALG (Fig. 7). In the event of a rejection episode, it is the steroid component that is most amenable to quick adjustment of dosage according to need. When hepatotoxicity of azathioprine is suspected, the alkylating agent cyclophosphamide, which has immunosuppressive qualities equivalent to those of azathioprine, may be substituted.[4]

Thoracic Duct Fistula

Recently there has been revitalized interest in thoracic duct fistula as an immunosuppressive adjunct.[4] With this procedure, lymphocytes are mechanically removed from the cervical thoracic duct lymph with reinfusion of the cell-free lymph. In cadaveric kidney recipients, pretreatment by this method for at least 3 weeks and preferably longer has had such a profoundly immunosuppressive effect that irreversible early rejection after transplantation has been almost eliminated. The patients require postoperative therapy with azathioprine (or cyclophosphamide) and prednisone. Whether this advance can be applied to liver transplantation, however, remains to be seen.

Complications of Immunosuppression

RISKS WITH ALL ORGANS. The most obvious penalty of a depressed immune system is heightened susceptibility to infection. It has also become obvious that chronically immunosuppressed patients have an increased vulnerability to de novo malignancies.[3] This complication is presumably due to failure of the depressed immunologic surveillance mechanism to identify the tumor tissues as alien and to eliminate them or restrict their growth.
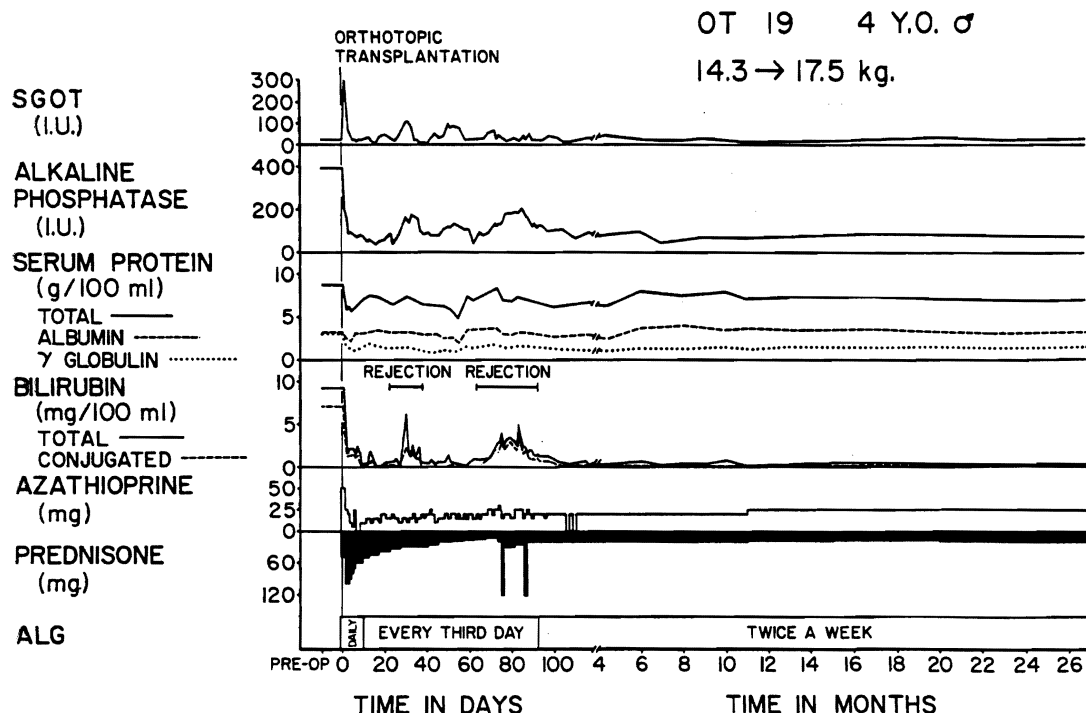

Figure 7. A 5-year-old child (OT 19) with intrahepatic biliary atresia who was treated with orthotopic liver transplantation. A very transient rejection occurred after 1 month. This underwent almost immediate and complete remission. A late rejection, which began on postoperative day 72, was easily controlled. Note the change in time after 4 months. The patient had stable liver function for 39 months before dying a few weeks after a bout of Hemophilus influenza. Our current practice is to limit ALG to a few weeks instead of the long course depicted.

EXTRA RISKS FOR LIVER RECIPIENTS. There are some special risks for the candidate for liver transplantation. One is the fact that hepatic injury in all kinds of organ recipients has commonly been produced by the agents, individually or in combination, of the therapeutic regimen.[3,4] In some instances, viral hepatitis, apparently made chronic by the partial immunologic invalidism of the host, has been a plausible explanation. In others, hepatotoxicity of the drugs was probably responsible. With liver malfunction, dose control of some of the agents may become difficult, since the liver participates in their pathways of action or degradation. These hepatic factors are obviously important in any situation requiring immunosuppression, but they have heightened significance for a traumatized liver transplanted to a new and hostile environment.

It was mentioned earlier that infection was a major risk to any immunosuppressed patient. In the liver recipient, postoperative sepsis of the graft itself has proved to be a special problem, without 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 be brought into contact with the transplanted liver via the intestinal veins draining into the portal vein or, far more importantly, by retrograde spread up the duct system after passage through the biliary anastomosis. In either event, the presence of nonviable hepatic tissues provides a perfect medium for bacterial growth. Eventually, abscesses or partial gangrene of the transplant can result, with characteristic nonvisualizing areas on the liver scans, gram-negative bacteremia, and all the findings of generalized sepsis.

AVOIDANCE OF HOMOGRAFT SEPSIS. Antibiotics are given for the first several postoperative days, after which therapy is stopped. Our prophylactic protocol includes agents effective against gram-negative bacteria. The most important step in reducing hemograft sepsis has been to use biliary reconstructive techniques that prevent systematic contamination by gastrointestinal contents (see Fig. 5B, C, and D).

INDICATIONS FOR LIVER REPLACEMENT

The first human orthotopic liver transplantation was performed in March 1963. Between then and December 1977, a total of 141 consecutive patients were treated with this operation with potential follow-up now for all survivors of 1 1/2 years. The indications are shown in Table 1.

Infants and Children

The indications for operation were wide ranging. Patients below 18 years of age accounted for more than half of our first 141 recipients (74 in all). Within this pediatric group there were 48 examples of biliary atresia. The other indications for liver replacement in our pediatric series accurately reflect our present attitude toward appropriate case selection, with the exception of primary hepatic malignancy. All three children whose reason for operation was hepatoma developed recurrences within a few months. However, our longest postoperative survivor (9 2/3 years) has been cured of an incidental hepatoma in her excised biliary atretic liver. A small hepatoblastoma was found in the liver of another child with alpha$_1$-antitrypsin deficiency who is tumor-free 1 2/3 years later. Thus, the extent of the malignancy would seem to be a prime factor in survival.

It has become clear that manifestations of liver-based inborn errors of metabolism can be cured with liver replacement. We have had experience with Wilson's disease, alpha$_1$-antitrypsin deficiency, tyrosinemia, and Type IV glycogen disease (alpha-glycosidase deficiency). The metabolic abnormalities in all these patients were corrected. Other indications in children have included chronic aggressive hepatitis and neonatal hepatitis.

TABLE 1.   Indications for Orthotopic Liver Transplantation at the University of Colorado

Diagnosis	Number of Cases	Lived > 1 Year	Alive at Present (1 2/3–9 2/3 Years)
Biliary atresia	48	16	8
Chronic aggressive hepatitis	36*	12	7
Primary liver malignancy	19	5	2
Alcoholic cirrhosis	15	4	4
Alpha$_1$-antitrypsin deficiency	5	3	2
Primary biliary cirrhosis	5	1	
Sclerosing cholangitis	4	0	
Secondary biliary cirrhosis	2	1	1
Wilson's disease	2	2	1
Massive hepatic necrosis (B virus)	1	0	
Congenital biliary cirrhosis†	1	1	1
Budd-Chiari syndrome	1	1	1
Congenital tyrosinemia	1	0	
Type IV glycogen storage disease	1	0	
Total	141	46	27

*Two had neonatal hepatitis and were treated at ages 7 1/2 and 30 years.
† With congenital deafness.

Adults

Sixteen liver transplantations were carried out to treat nonresectable hepatomas, duct cell carcinomas, angiosarcoma, and cholangiocarcinoma. Seven of these recipients lived beyond 3 months, and six of them later developed metastases. Similarly, the recurrence rate in the Cambridge–King's College series in England has been 70 percent.[1] As more such cases have been documented, we have had decreasing enthusiasm for, and indeed have usually avoided, transplantation for malignancy. Still, there is no denying that some patients with malignancy have benefited from liver replacement. Three of our adult patients lived for more than 2 years in spite of recurrences, and two are still alive after 2 2/3 and almost 5 years.

Less questionable reasons for liver transplantation in adults are included in Table 1. In the future, the leading indications undoubtedly will be chronic aggressive hepatitis and Laennec's cirrhosis. The presence of HB_sAg viremia is not a contraindication, since effective postoperative treatment can be given with hyperimmune serum.[1, 4] Cases of cirrhosis pose a supreme technical challenge. If results are to be improved, candidates will need to be selected at an earlier time. Too often in the past the recipients have been moribund by the time of operation.

There is little point in exhaustively discussing different liver diseases in connection with transplantation, since anyone with end-stage liver disease theoretically might be a candidate. Relative contraindications include advanced age (beyond 50 years) and infections. Judgment must be exercised not to proceed too early in the natural history of the patient's disease and not to make the equally or more serious error of waiting too long.

RESULTS

During the 13 years from May 1963 to July 1976, 111 consecutive patients underwent attempted liver replacement — 50 adult and 61 pediatric recipients. Of the 111 patients, only 31 (28 percent) lived for as long as 1 year (Table 2). Ten of the 1-year survivals were among the 50 adult patients, and 21 were among the 61 pediatric patients.

After 1 year, 17 of the 31 patients who were alive at the 1-year mark died after total survival periods of 1 to 6 years. The most common reasons for late death were chronic rejection, uncorrected biliary obstruction, systemic infection, and recurrent malignancy, in that order.[4]

Fourteen of the patients included in the 1963–1976 series are still alive with follow-ups that now range from 3 2/3 to 9 2/3 years. These patients have had a very high order of rehabilitation. The adults and adolescents have all returned to school or work, and the infants have entered and done well in school.

Another 30 patients (Table 2) were treated from July 1976 to December 1977, using the technical, diagnostic, and management improvements mentioned earlier. There were 17 adults and 13 infants or children. The 1-year survival in this group was 15 of 30 (50 per cent), including 7 of the 17 adults and 8 of the 13 pediatric recipients. Two late deaths occurred, one at 16 1/2 months because of portal vein thrombosis, and the other at 23 months because of systemic chickenpox. The other 13 patients were still alive after 1 2/3 to 3 1/3 years.

Future Prospects

It had been hoped that the results would eventually become acceptable, with better technical performance, more discriminating case selection, and sharpening of criteria for the differential diagnosis of postoperative hepatic malfunction. Such optimistic expectations have been only partly realized. Although the 1-year survivorship gradually rose to 50 per cent, it has not been possible to improve these figures. During the last year and a half, 23 more patients were treated. The probability is that only six of these will live for as long as 1 year. The combination of such a complex technical undertaking and the handicap of unsafe immunosuppression has remained too formidable for consistent success.

The prospect of safer and more effective immunosuppression is currently in sight. Possibilities include better drug treatment, especially with the fungus extract cyclosporin A, which is receiving its first clinical trials in renal recipients. Total lymphoid irradiation is a promising but less well developed immunosuppressive adjunct. Finally, there is evidence in human kidney recipients, as mentioned earlier, that pretreatment with thoracic duct drainage (TDD) can more effectively control rejection, resulting in less morbidity and mortality.

The applicability of any of these methods in liver

TABLE 2. Survival in the Early and Late Phases of the Colorado Experience
(Follow-up to September 1979)

	Total	Lived > 1 Year	Alive Now
Series I (March 1963–July 1976)	111*	31 (28%)	14 (after 3 2/3 to 9 2/3 years)‡‡
Series II (August 1976–December 1977)	30†	15 (50%)	13 (after 1 2/3 to 3 1/2 years)§

*With patients ≤ 18 years of age, the 1-year survival was 21/61 (34%). Among adults, survival was 10/50 (20%).
†With patients ≤ 18 years of age, the 1-year survival was 8/13 (62%). Among adults, 1-year survival was 7/17 (41%).
‡The 17 late deaths were after 1 to 6 years.
§One late death was at 23 months and the other after 16 1/2 months.

transplant recipients remains to be established. The ideal will be a form of treatment so effective and so safe that hepatic malfunction postoperatively can automatically be ascribed to factors other than rejection. Until this can be achieved, liver transplantation will remain a heroic form of therapy with limited applicability.

AUXILIARY LIVER TRANSPLANTATION

The alternative to hepatic replacement is to leave the native liver in place and to transplant an extra liver which is in some ectopic site, such as the splenic bed, the right or left paravertebral gutter (see Fig. 2), or the pelvis. The main theoretical advantage of auxiliary transplantation is that the recipient is not at the outset placed totally at the mercy of homograft function. A second possible advantage would be avoidance of the technical hazards of recipient hepatectomy.

By May 1969, nine clinical attempts had been made, four at the University of Colorado and one each at five other institutions.[3] The longest survival was 35 days. Of the many problems encountered, not the least was difficulty in finding room for an extra organ in an already overcrowded abdomen. In addition, it had been learned from animal studies that the optimal condition for the transplanted liver was portal venous inflow of splanchnic venous blood which contains specific hepatotrophic substances (especially endogenous insulin).[5]

Fortner and associates of New York have maintained an interest in auxiliary transplantation, and in September 1978 they summarized their results as well as those obtained elsewhere.[2] By that time, they had information on 43 cases, including 7 of their own. There was one unqualified success, a patient with biliary atresia who was alive 5 1/2 years postoperatively. The other recipients died early from a variety of complications.

Our view is that auxiliary transplantation should be reserved for patients with acute hepatic disease in whom the objective is temporary life support while 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.

Selected References

Calne, R. Y., and Williams, R.: Liver transplantation. Curr. Probl. Surg., 16:3, 1979.
  The important clinical series of 74 cases from the Cambridge-King's College London group is described as well as laboratory research in these institutions. Although almost all of the recipients were adults, the opinions expressed have applicability to pediatric patients. Opinions about patient selection, biliary tract reconstruction, and immunosuppression are somewhat different from those expressed in this chapter.

Fortner, J. C., Yeh, S. D. J., Kim, D. K., Shui, M. H., and Kinne, D. W.: The case for technique of heterotopic liver grafting. Transplant. Proc., 11:269, 1979.
  This collection of 43 clinical auxiliary liver transplantations from many different centers was presented to the International Transplantation Society in Rome in September 1978. The case for auxiliary transplantation is made optimistically, perhaps excessively so, in view of the poor results.

Starzl, T. E. (with the assistance of C. W. Putnam): Experience in Hepatic Transplantation. Philadelphia, W. B. Saunders Company, 1969, pp. 1–553.
  This text contains the total world literature (299 references) on experimental and clinical liver transplantation up to the spring of 1969. An account is given of all 42 attempted human liver homotransplantations including 29 (25 orthotopic, 4 auxiliary) at the University of Colorado. Surgical and anesthetic techniques and metabolic and immunoglobulin changes following liver transplantation are described in detail. The laboratory development and clinical practice of immunosuppression for all transplanted organs are reviewed. Two chapters by Professor K. A. Porter of St. Mary's Hospital and Medical School, London, constitute a complete monograph of the pathology of animal and human auxiliary and orthotopic liver homografts as well as two chimpanzee-to-human heterografts.

Starzl, T. E., Koep, L. J., Halgrimson, C. G., Hood, J., Schroter, G. P. J., Porter, K. A., and Weil, R., III: Fifteen years of clinical liver transplantation. Gastroenterology, 77:375, 1979.
  The first 141 orthotopic liver homotransplantations at the University of Colorado are described. These include the 74 pediatric cases described in this chapter plus the 67 adult cases. There is detailed documentation of causes of early and, especially, late deaths. The recent literature of clinical liver transplantation is brought up to date. This is the most recent review of liver transplantation with a bibliography that is current to January 1979.

Starzl, T. E., and Terblanche, J.: Hepatotrophic substances. Prog. Liver Dis., 6:135, 1979.
  This new field of hepatic physiology is summarized, describing the specific effects of venous blood from nonhepatic splanchnic organs in regulating liver structure, function, and capacity for regeneration. This background is essential for understanding the physiology and vascularization requirements of auxiliary liver grafts.