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any of these four factors are not met, the kidney should not be used. This decision can be difficult at times, but the principle that no kidney is better than a bad kidney cannot be overemphasized. The disadvantage of continuous hypothermic perfusion involves primarily the expense of the equipment and need for a trained perfusion technician.

Comparison of Methods

In general, graft survival at 1 year is about equal in kidneys preserved by simple cold storage or continuous perfusion when the donor organ is harvested under "ideal" conditions. Damaged kidneys or kidneys stored for longer than 40 hours appear to function better if stored by continuous perfusion.

Long-Term Preservation

Long-term preservation (7 to 14 days) awaits a breakthrough in either the development of new perfusion fluids or drug therapy or the freezing of whole kidneys with the use of cryoprotectants. The advantage of long-term preservation, however, will not be fully realized until more predictable methods of crossmatching donor and recipient are available or until methods to alter the immunologic aspects of the cadaver organ or recipient are developed.

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VIII

LIVER HOMOTRANSPLANTATION

Thomas E. Starzl, M.D., Ph.D., Shunzaburo Iwatsuki, M.D., and Byers W. Shaw, Jr., M.D.

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 14½ 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

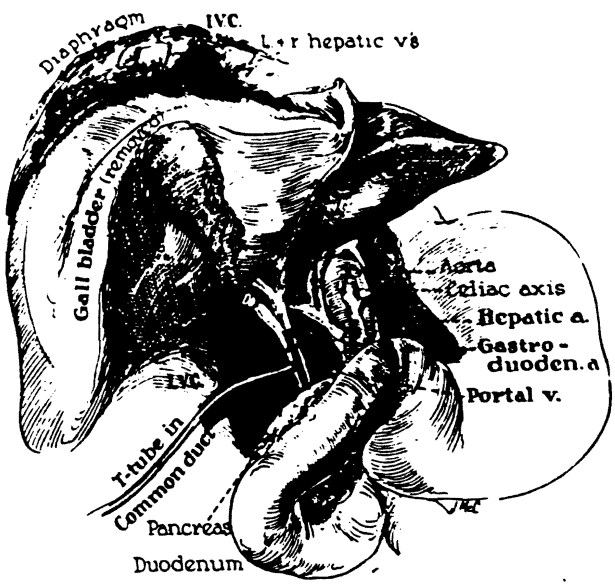

Figure 1. Completed orthotopic liver transplantation (liver replacement).

either with no signs of rejection or with rejection episodes that waxed and waned remittently. 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 advantage of the liver has been even more clearly noted in pigs, some of which can survive chronically with no immunosuppressive therapy at all, in spite of the fact that pigs regularly reject skin and kidney grafts. The 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 heptatic rejection may be difficult or impossible in spite of very heavy immunosuppressive therapy.

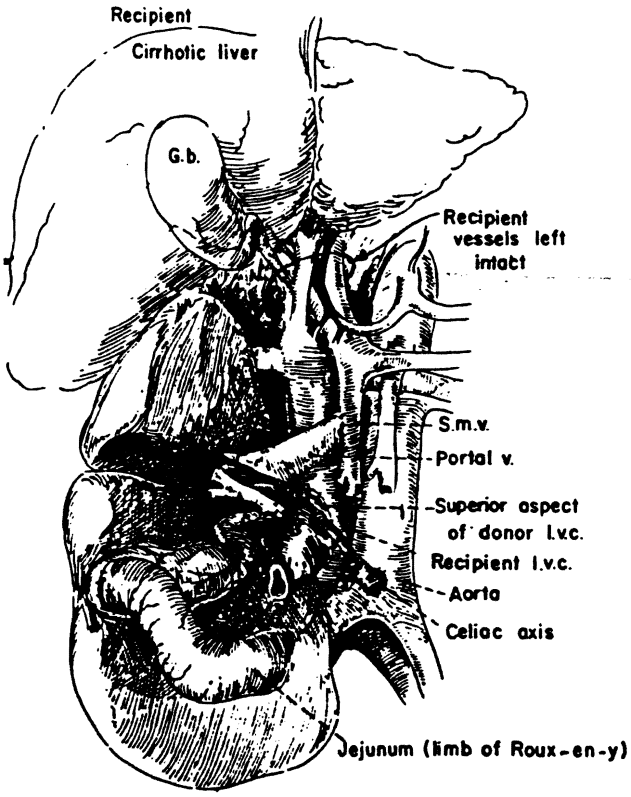

Figure 2. Auxiliary liver transplantation with a technique that provides an adequate blood supply for the homograft. Note that the transplant is given a double blood supply and that the venous component is from the nonhepatic splanchnic bed. Biliary drainage can be with a Roux-en-Y cholecystojejunostomy.

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, 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 deliberately, but one of our patients is known to have stopped all therapy 4 years ago with no subsequent problems.

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.

The concept of specific, differential tolerance through "clone stripping" can partly explain the characteristic

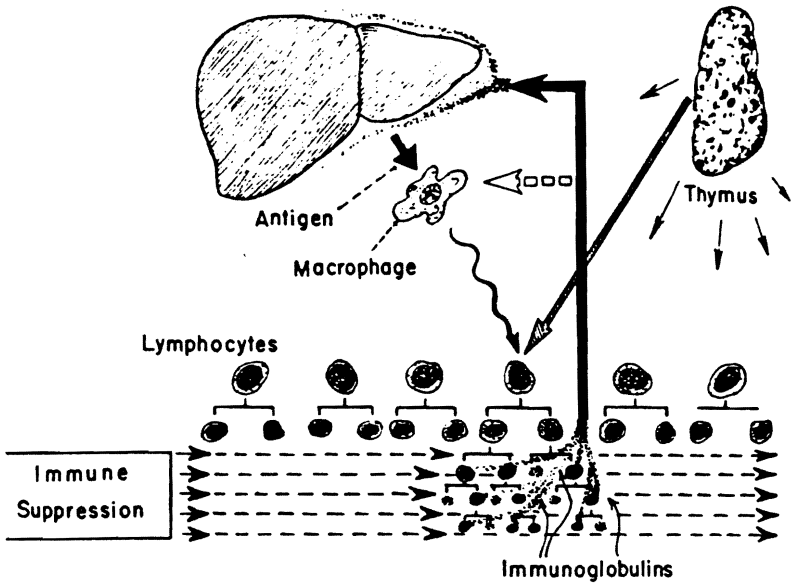

Figure 3. Hypothetical mechanisms by which nonspecific immunosuppression may lead to selective abrogation of the host immune response. Special susceptibility to these agents of a fraction of the lymphoid population could lead to exhaustion of a clone, and hence, tolerance. Since maintenance of such cell 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.

cycle of rejection and reversal occurring after whole-organ transplantation both in treated animals and in man as well as 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 specificity 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 one other 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 HLA typing has not been a precise method of selecting biologically suitable cadaveric 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.

Because of urgent needs, numerous liver transplantations have been performed despite the presence in the recipients of cytotoxic antibodies that were anti–donor-specific. In addition, we have proceeded in more than one dozen 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, as well as Calne, 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 have been made in transplantation has been social in nature, i.e., 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. During the last few years, the need for the procurement of multiple organs from the same donor has sharply increased. The most common combinations have been kidneys-liver, kidneys-liver-heart, and kidneys-heart in that order. Techniques have been developed that permit such removel without jeopardy to any of the individual grafts. The guiding principle is avoidance of warm ischemia in all organs. This is achieved by carefully timed and controlled *in situ* infusion of cold solutions into anatomic regions, the limits of which are defined by preliminary dissection.

The Cambridge–King's College team has used a plasma solution for cold infusion of the homografts, and we have employed an electrolyte (Collins') solution with a composition similar to that found in cells. In dogs, the two approaches yield comparable results and permit safe preservation of organs for up to 12 hours. The same applies to 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 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 procurement and 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

THE BYPASS QUESTION. With removal of the host liver it is necessary to temporarily cross-clamp 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. In contrast, humans with liver disease often have tolerated this venous obstruction surprisingly well. The tolerance to portal and inferior vena caval cross-clamping 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 the size and ramifications of these veins in consequence of the underlying liver disease.

The fact that most patients can recover from portal and inferior vena caval cross-clamping may have created a false impression about the safety of this practice. Venous hypertension of the obstructed venous beds contributes significantly to the bleeding of the anhepatic phase. Usually, there is gross swelling of the intestine during the period of occlusion. Subsequently, many patients suffer from third-space fluid sequestration and postoperative renal failure.

The extent to which these complex physiologic events can contribute to the high perioperative mortality has become increasingly evident. For this reason, we now perform venous bypasses in all adults. Cannulas are placed into the inferior vena cava through an iliac or femoral vein and into the portal system through the open end of the transected portal vein. During the anhepatic phase, the blood is pumped to a large vein in the neck or arm with equipment that does not require total body heparinization (Fig. 4). The safety of liver transplantation in adults has been greatly improved with this technique. Venous bypasses usually are not required for infants and small children.

HEMORRHAGE. Other problems during and after operation may be caused by derangements in the coagulation mechanism, which may result in either hemorrhage or thrombosis. 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 if bypasses are not used. 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.

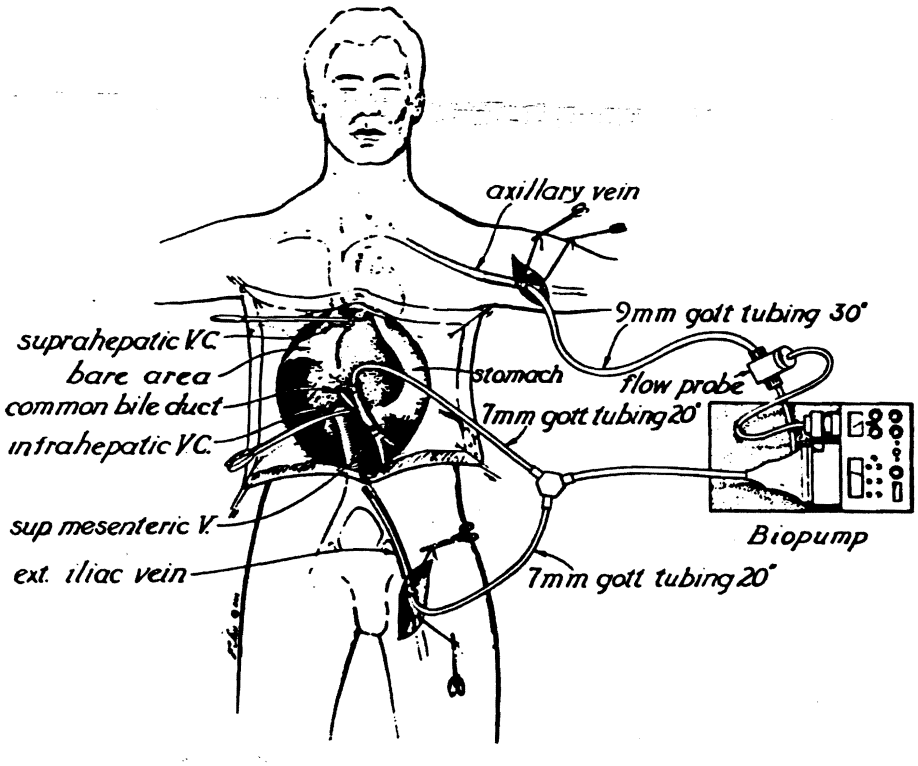

Figure 4. Venovenous bypass developed for use during the anhepatic phase of liver transplantation during which the new liver is connected to recipient vessels. By using coagulation-resistant tubing and an atraumatic pump, it has been possible to bypass large volumes of blood without using any heparin. The venovenous bypass has had a revolutionary effect on the ease of liver transplantation in adults. (From Griffith, B. P., et al.: Surg. Gynecol. Obstet., *160*:270–272, 1985.)

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. 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.

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. 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.

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. 5). 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. 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. 6A). Although the operation was simple, obstruction or bile fistula formation occurred in 30 per cent of the patients, almost always leading to death. Furthermore, homografts seemingly were subjected to repeated bacterial contam-

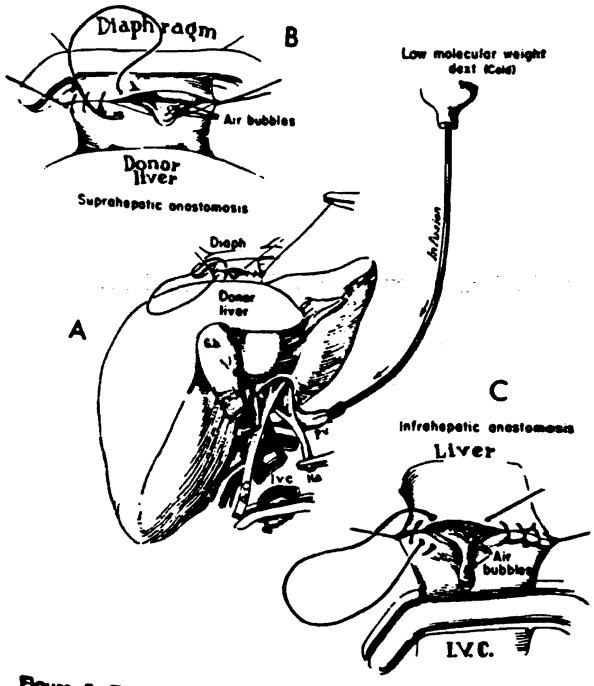

Figure 5. Technique to prevent air embolism from orthotopic liver homografts. *A*, Continuous perfusion of solution through the portal vein as vena caval anastomoses are constructed. *B* and *C*, Escape of air bubbles as the anastomoses are completed. (From Starzl, T. E., et al.: Ann. Surg., *187*:236, 1978.)

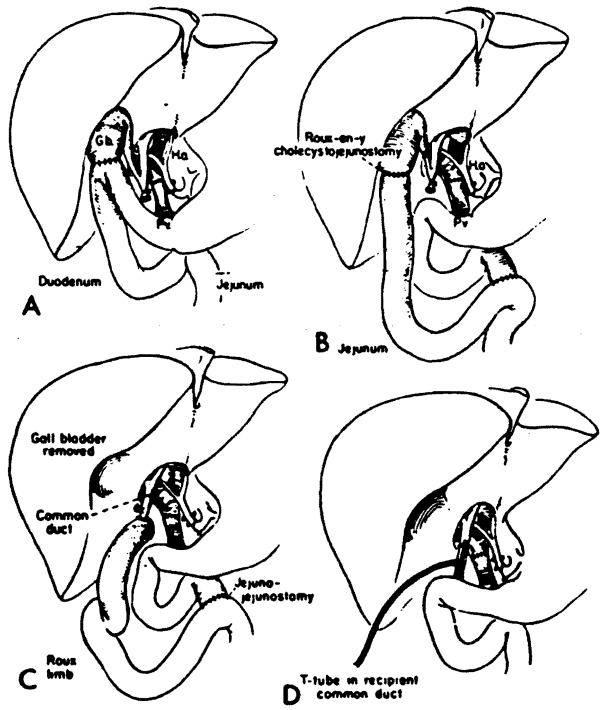

Figure 6. Techniques of biliary duct reconstruction used for most liver transplant recipients. *A*, Cholecystoduodenostomy. *B*, Cholecystojejunostomy. *C*, Choledochojejunostomy after removal of gallbladder. *D*, Choledochocholedochostomy. Note that T-tube is placed if possible in the recipient common duct. (From Starzl, T. E., et al.: Surg. Gynecol. Obstet., *142*:487, 1976.)

ination, 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. 6*D*) that 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 an alternative we perform choledochojejunostomy (Fig. 6*C*) to a Roux limb of jejunum. Cholecystojejunostomy (Fig. 6*B*) is not satisfactory, since obstruction of the cystic duct has often occurred (Fig. 7). 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 8 patients died from this complication.

Calne and Williams have advocated a different surgical approach. 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 studied or irrigated frequently. 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_sAg, 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 correctly administer drugs that, first, are not hepatotoxic, and second, do not depend primarily on the liver for their degradation. In our early cases, reliance was placed mainly on combinations of volatile agents in nonexplosive concentrations. Such management permitted use of the electrocautery, gave flexibility in lightening or deepening anesthesia, and allowed anesthesia to be abruptly stopped if required by changing physiologic circumstances. In recent years, less effort has been made to use volatile anesthetics. Further details of operative technique and complications can be found in texts cited in the bibliography.

IMMUNOSUPPRESSION

DOUBLE-DRUG THERAPY. 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. 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 of all organs a possibility. 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 also was extensively used by the Cambridge team.

TRIPLE-DRUG THERAPY. In 1966, heterologous antilymphocyte globulin (ALG) was introduced clinically at our center as a third immunosuppressive agent in addition to the drugs mentioned previously. Almost all of our human liver recipients who achieved long-term survival during the next 14 years were treated with the combination of azathioprine, prednisone, and intramuscular ALG (Fig. 8). In the event of a rejection episode, it was the steroid component that was most amenable to quick adjustment of dosage according to need. When hepatotoxicity of azathioprine was suspected, the alkylating agent cyclophosphamide, which has immunosuppressive qualities equivalent to those of azathioprine could be substituted.

THE CYCLOSPORINE ERA. The watershed year for improved organ transplantation was 1978. In that year, there were at least three possible ways in which it was envisioned that immunosuppression could be improved. One was by mechanical removal of lymphocytes through a thoracic duct fistula. A second possibility also involved a direct attack on the lymphoid system, by means of irradiation through the same ports used for the treatment of Hodgkin's disease. The third possibility of improving immunosuppression was with an interesting drug then called cyclosporin A (now known as cyclosporine). Many great expectations for transplantation in the future rest with use of cyclosporine.

Cyclosporine is an extract of a fungus that was discovered and characterized to an unusually complete degree by Dr. Jean Borel and other scientists of the Sandoz Corporation, Basel, Switzerland. After the impressive immunosuppressive qualities of this agent had been demonstrated in a number of autoimmune models, including skin homotransplantation in rodent experiments, the first clinical trials for solid organ transplantation were undertaken in mid-1978 by Professor Roy Calne and his associates at Cambridge, England. It was recommended from this trial that cyclosporine be used as the sole immunosuppressive agent.

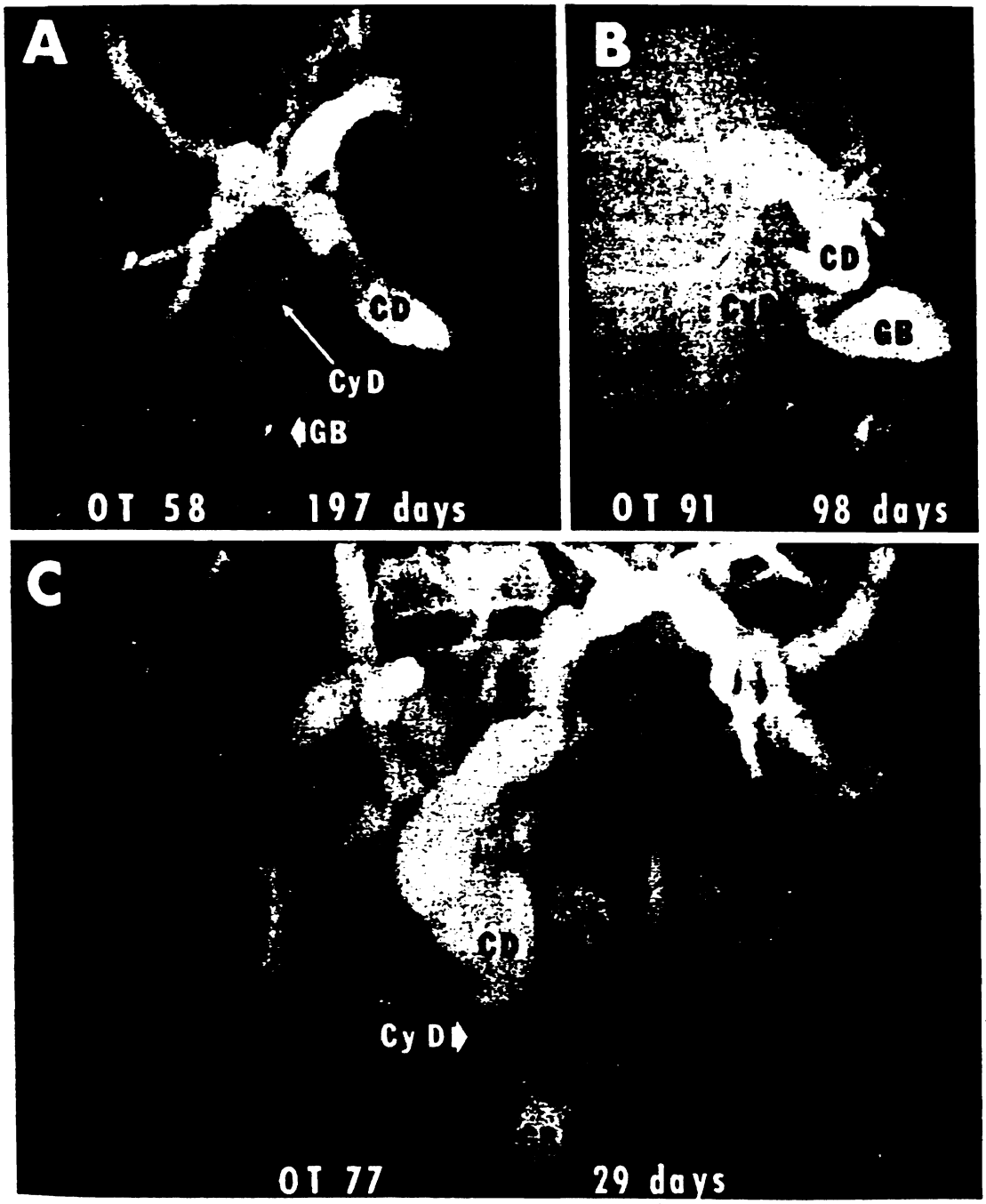

Figure 7. Examples revealed by transhepatic cholangiography of homograft cystic duct obstruction after biliary reconstruction with cholecystoenterostomy. *A*, Original procedure was cholecystoduodenostomy. After this transhepatic cholangiogram, conversion was made to choledochoduodenostomy. At operation, 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; Cy D = cystic duct; GB = gallbladder; J = Roux-en-Y limb of jejunum. (From Starzl, T. E., et al.: Surg. Gynecol. Obstet., 142:487, 1976.)

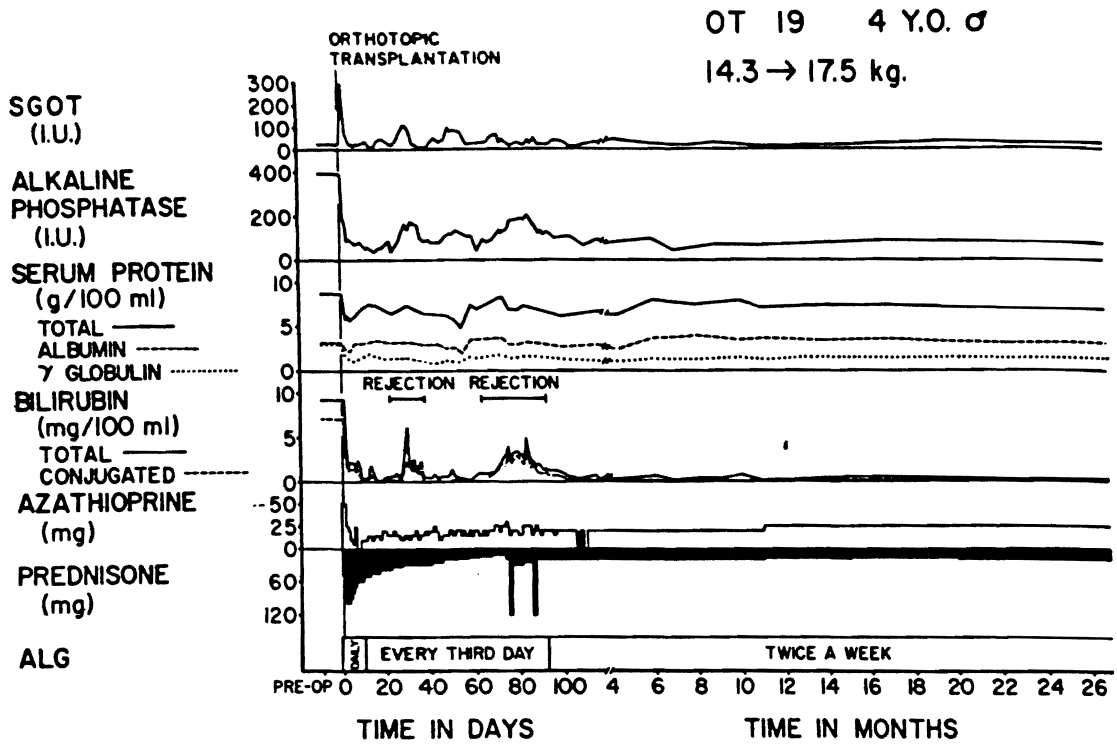

Figure 8. A 5-year-old child (OT 19) with intrahepatic biliary atresia who was treated with orthotopic liver transplantation. A very transient rejection occurred after 1 month. This underwent almost immediate and complete remission. A late rejection, which began on postoperative day 72, was easily controlled. 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 *Haemophilus* influenza. Our current practice is to limit ALG to a few weeks instead of the long course depicted.

In the first American trials more than a year later, it was realized at once that cyclosporine could not prevent rejection systematically when used alone and that the optimal exploitation of the drug would require ancillary treatment with steroids. Although the treatment schedules were not fully standardized at that time, the 1-year primary cadaveric kidney graft survival in the pilot trials at the University of Colorado was nearly 80 per cent. In the following year, a randomized trial comparing cyclosporine-steroid therapy with therapy by azathioprine and prednisone was carried out. The 1-year graft survival in the experimental group was 90 per cent versus the expected 50 per cent in the "controls." In the meanwhile, extensive trials had been undertaken with cyclosporine-steroid therapy in liver transplantation. As will be noted, the prognosis after liver transplantation has been remarkably improved following use of these drugs.

Much has been learned about how to use cyclosporine for liver transplantation. The drug, which is lipophilic and hydrophobic, is absorbed unpredictably after oral ingestion in patients with changing liver function. Because of this, all of our liver recipients now receive cyclosporine by both the intravenous and the oral route for the first several weeks postoperatively (Fig. 9). The effectiveness of drug delivery can be monitored by measuring the whole blood (or plasma) concentrations of cyclosporine. If these measurements are obtained just before the next oral or intravenous doses, they define the "trough" levels. During the first several postoperative weeks, the patient is weaned from the intravenous therapy and is eventually stabilized on an oral dose, which is usually given twice a day (Fig. 9). There is little justification for management of patients without this kind of pharmacologic monitoring.

The second component of therapy is with prednisone. A 5-day burst of steroid therapy is given during the first postoperative week. At the end of this time, adults usually are on a maintenance dose of 20 mg. per day. Children and infants have a proportionately lower maintenance dose (Fig. 9). When rejection occurs, it is treated mainly by steroid dose adjustments.

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. 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 restict their growth.

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. In some instances, viral hepatitis, apparently made chronic by the partial immunologic invalidism of the host, has been a plausible explanation. Lethal hepatitis from adenovirus, cytomegalovirus, and herpes simplex and herpes zoster virus has been recorded. In other patients, hepatotoxicity of the drugs was probably responsible. With liver malfunction, dose

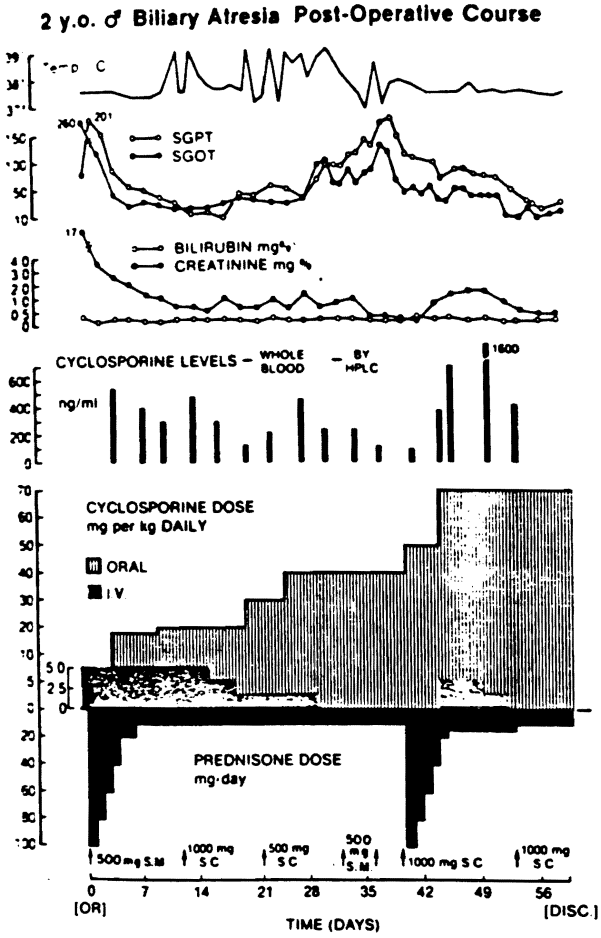

Figure 9. The administration of cyclosporine by the intravenous as well as by oral routes postoperatively. The objective was to maintain the blood cyclosporine as measured by high performance liquid chromatography (HPLC) at about 300 mg. per ml. The intravenous doses were weaned and the oral doses were increased under the guidance of the monitoring.

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 intraoperatively and for the first several postoperative days, after which time therapy is stopped. Our prophylactic protocol includes agents effective against gram-negative bacteria. The most important surgical technical step in reducing hemograft sepsis has been to use biliary reconstructive techniques that prevent systematic contamination by gastrointestinal contents (see Fig. 6*C* and *D*).

Until 1980, infection was the primary or an important contributory cause of the great majority of deaths. Furthermore, the development of almost any kind of intra-abdominal or intra-thoracic complication could lead quickly to untreatable sepsis. The situation was dramatically improved when therapy with cyclosporine and low doses of prednisone was introduced in early 1980. The relative ease with which infections could now be controlled while preventing irreversible rejection accounted for the improved results.

INDICATIONS FOR LIVER REPLACEMENT

The first human orthotopic liver transplantation was performed in March 1963. Between then and March 1984, a total of 367 consecutive patients were treated by this operation, with potential follow-up now for all survivors of at least 3 months.

INFANTS AND CHILDREN. The indications for operation were wide ranging. Patients below 18 years of age accounted for 169 (46 per cent) of our first 367 recipients. Within this pediatric group there were 94 patients with biliary atresia (Table 1). The other indications for liver replacement in our pediatric series accurately reflect our present attitude toward appropriate case selection (Table 1), with the exception of

TABLE 1. Indications for Liver Transplantation in Pediatric Patients (≤ 18 Years)

Main Indication	Pre-Cyclosporine Era (March 1, 1963–February 29, 1980) (No. Patients)	Cyclosporine Era (March 1, 1980–March 31, 1984) (No. Patients)
Biliary atresia	51	43
Inborn metabolic errors	13	21
Nonalcoholic cirrhosis	13	7
Primary liver malignancy	3	0
Neonatal hepatitis	2	2
Congenital hepatic fibrosis	2	1
Secondary biliary cirrhosis*	2	1
Byler's disease	0	5
Budd-Chiari syndrome	0	1
Inflammatory pseudotumor	0	1
Subacute hepatitis	0	1
	86	83

*Trauma or choledochal cyst.

primary hepatic malignancy. All three children whose primary reason for operation was hepatoma developed recurrences within a few months. However, our longest postoperative survivor (14½ 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 6⅓ years later. Four other children, three with tyrosinemia and one with the sea-blue histiocyte syndrome, have had hepatomas in their cirrhotic livers but have not had recurrences after as long as 3½ years. Thus, the extent and nature of the malignancy would seem to be prime factors in survival.

The second largest recipient group has been made up of patients with several inborn errors of metabolism (Table 2), including alpha$_1$-antitrypsin deficiency, Wilson's disease, tyrosinemia, glycogen storage diseases, the sea-blue histiocyte syndrome, and homozygous Type II familial hypercholesterolemia (FH) (Table 2). The 6-year-old child with FH also had her heart replaced at the same operation because of coronary artery and valvular disease.

With the possible exception of the sea-blue histiocyte syndrome, the inborn metabolic abnormalities listed in Table 2 were cured or palliated by successful liver transplantation. The child with the sea-blue histiocyte syndrome (which is a lipid storage disorder of unknown etiology) had a progressive and very serious neurologic syndrome that was arrested but not reversed after successful liver transplantation. A liver biopsy from this patient 1 year postoperatively showed moderate deposition of lipid droplets. Although she is now 2 1/2 years postoperative, we do not believe that her basic problem has been corrected.

In contrast, patients with alpha$_1$-antitrypsin deficiency assume the Pi (protease inhibitor) type of their donors, and the low serum values of the deficient alpha globulin are promptly and permanently restored to normal. The abnormal amino acid patterns of tyrosinemia are rectified within hours. The same holds true for the aberrations caused by glycogen storage diseases (GSD), as exemplified by a patient with Type I GSD who became able to fast for 1 or 2 days without the hypoglycemia that previously occurred within hours.

It is noteworthy that some of these diseases are known to be caused by specific enzyme deficiencies, whereas the pathogenesis of other disorders such as Wilson's disease is not understood. This state of knowledge or lack thereof has not influenced the effectiveness of the "biochemical engineering" in Wilson's disease, and it is now obvious that disease recurrence after liver transplantation need not be feared.

The 6-year-old child with familial hypercholesterolemia whose heart and liver were replaced had a striking fall of serum cholesterol concentration from about 1000 mg. per 100 ml. to a new level averaging 300 mg. per 100 ml. It is probable that the correction is incomplete, since the normal serum cholesterol level in children of this age should be below 200 mg. per 100 ml.

The third leading indication for liver replacement in children has been chronic active hepatitis (nonalcoholic cirrhosis) (see Table 1). Twenty of our 169 pediatric recipients had this diagnosis. With this diagnosis, decisions about candidacy for transplantation have become relatively easy, once it was realized that no patient accepted as a candidate for whom a liver could not be promptly found lived for more than a few months. These patients have been difficult to treat. Some have had a portacaval shunt or other previous operations in the hepatic hilum. Their metabolic abnormalities, when first seen, often have been profound, and the removal of their shrunken livers sometimes has presented extraordinary technical difficulties. Such patients have accounted for the legendary "marathon" operations for liver transplantation with the loss of dozens of units of blood.

In adults carrying the B virus, disease recurrence has been a problem, with recrudescence of their original disease in the grafts. Such carriers have also been responsible for causing hepatitis among the hospital staff. Recurrent chronic active hepatitis has not yet been encountered in children.

Other indications for pediatric liver transplantations in our past experience are listed in Table 1. There have been five examples of familial cholestasis (Byler's disease).

ADULTS. The indications for liver transplantation in adults are shown in Table 3. Both in the precyclosporine era and more recently, nonalcoholic cirrhosis has been the most frequent reason for operation. Primary biliary cirrhosis, which was not well represented until 1980, has more recently come to account for almost 20 per cent of cases (Table 3), and a similar increase has been seen in sclerosing cholangitis.

Both before and after the introduction of cyclosporine, efforts were made to utilize transplantation for patients with primary hepatic malignancies that could not be resected by conventional techniques. Until 1980, the incidence of recurrence in the new liver and/or other sites was almost 90 per cent. Since March 1980, the recurrence rate in patients treated with cyclosporine and steroids has decreased to about 50 per cent. However, the latter follow-ups are short, and it is still not certain if liver transplantation will play a major

TABLE 2. Inborn Metabolic Errors Treated with Liver Transplantation in Pediatric Patients (≤ 18 Years)

Main Indication	Pre-Cyclosporine Era (March 1, 1963–February 29, 1980) (No. Patients)	Cyclosporine Era (March 1, 1980–March 31, 1984) (No. Patients)
Alpha 1-antitrypsin deficiency	9	13
Wilson's disease	2	3
Tyrosinemia	1	2
Glycogen storage disease	1	1
Sea-blue histiocyte syndrome	0	1
Homozygous familial hypercholesterolemia	0	1
	13	21

TABLE 3. Indications for Liver Transplantation in Adult Patients (> 18 Years)

Main Indication	Pre-Cyclosporine Era (March 1, 1963–February 29, 1980) (No. Patients)	Cyclosporine Era (March 1, 1980–March 31, 1984) (No. Patients)
Nonalcoholic cirrhosis	33	33
Primary liver malignancy	15	18
Alcoholic cirrhosis	15	3
Sclerosing cholangitis	7	17
Primary biliary cirrhosis	6	21
Inborn metabolic errors	4	7
Secondary biliary cirrhosis	2	6
Budd-Chiari syndrome	1	4
Acute hepatic necrosis	1	3
Hemochromatosis	0	1
Cryptococcal cholangitis	0	1
	84	114

role in treating primary tumors of the bile ducts and liver.

The decrease in the number of alcoholics treated in recent years has not been by any specific intention. It is probable that a subsegment of the alcoholic population, particularly those who have foregone alcohol consumption, could be benefited with liver transplantation.

The heterogeneity of indications for liver transplantation is evident from the long list of diseases with which we have had actual experience (Table 3). Disease recurrence in the homograft will continue to be a matter of great interest. So far, recurrence has been seen of malignancies (see earlier discussion), B virus hepatitis, the Budd-Chiari syndrome, and primary biliary cirrhosis. However, in all of these disorders, with the possible exceptions of hepatic malignancies and B virus hepatitis, the threat of recurrence has not been great enough to vitiate the value of transplantation.

RESULTS

During the 21 years from May 1963 to May 1984, 367 consecutive patients underwent liver replacement—198 adults and 169 infants, children, or adolescents. The results have been stratified according to whether the patients were adults or in the pediatric age group (18 years or younger). Throughout the entire experience, the survival of the pediatric recipients has been greater than adult recipients.

INFANTS, CHILDREN, AND ADOLESCENTS. Until early 1980, the 1-year survival in 86 pediatric recipients was almost 40 per cent (Fig. 10). Subsequent deaths occurred relatively gradually, so that one in

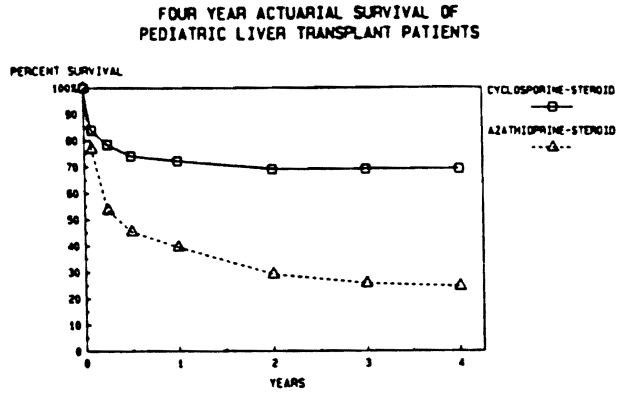

Figure 10. Life survival curves of pediatric recipients using conventional immunosuppression *(lower curve)* until early 1980 and a cyclosporine with steroids *(upper curve)* after this time. The survival in the pre-cyclosporine (azathioprine) era years is actual, whereas that in the cyclosporine era is actuarial.

four of the original patient population was still surviving at the end of 4 years. Eighteen (21 per cent) of the original 86 patients are still alive, with follow-ups from 4½ to 14½ years.

After the introduction of cyclosporine, the survival was remarkably improved, with a 1-year graft survival that rose to more than 70 per cent and with a virtually flat subsequent survival curve (Fig. 10). The improved results in the cyclosporine era could be expressed in other than mere survival terms. The ability to treat these recipients with smaller doses of prednisone than ever before has allowed the infants and children to grow at a normal rate. When they are seen in the clinic or on the streets, they cannot be distinguished from normal children by the steroid facies and stunted growth that were such common penalties of immunosuppression until recent times.

ADULTS. In the pre-cyclosporine era, only about 25 per cent of the adult patients survived for as long as 1 year (Fig. 11). After this time, the decay in survival did not differ from that in children. Fourteen (17 per

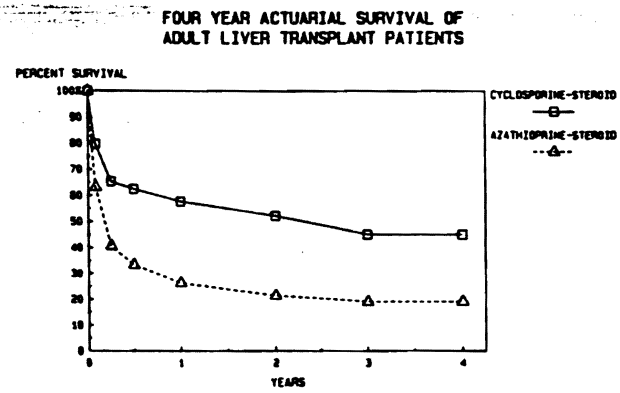

Figure 11. Life survival curves of adult recipients before and after the introduction of cyclosporine-steroid therapy. Note the remarkably improved outlook in last 4 years. The curve in the pre-cyclosporine (azathioprine) era is actual, whereas that in the cyclosporine era is actuarial.

cent) of the original 84 adult recipients are still alive after 5 to 10 years.

As with children, the introduction of cyclosporine in early 1980 had a major influence on survival, with the 1-year survival more than doubling to nearly 60 per cent. Even at 3 years, the actuarial survival is projected at approximately 50 per cent (Fig. 11).

In both the pediatric and the adult age groups, a distressing perioperative mortality continued to plague our efforts until the spring of 1983. Since early 1983, we have been attempting to reduce perioperative mortality by (1) the use of venovenous bypasses in adults, (2) the use of double-route cyclosporine therapy (see earlier discussion), and (3) aggressive retransplantation in the event of poor or deteriorating liver homograft function whether due to rejection or other factors. From our recent experience in the last year, it may be suggested that the true survival expectation of the orthotopic liver transplant recipient today is even better than that expressed in past cumulative survival curves.

AUXILIARY LIVER TRANSPLANTATION

The alternative to hepatic replacement is to leave the native liver in place and to transplant an extra liver that 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. 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 that contains specific hepatotrophic substances (especially endogenous insulin).

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. 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 5½ years postoperatively. The other recipients died early from a variety of complications. Since then, another patient treated in Paris has survived for more than 2 years.

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.

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