VIII

LIVER TRANSPLANTATION

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The liver has a far more complicated metabolism than other transplanted organs and malfunction leads to more complex physiologic derangements. Patients with liver disease are further handicapped by the lack of satisfactory means of artificial support comparable to renal dialysis. The transplanted liver must function efficiently from the time of anastomosis, or the patient may be lost. Despite these and other difficulties, the therapeutic power and appeal of liver transplantation has had a pervasive impact on hepatology and liver surgery. Today, it is difficult to envision a hepatology center without the capability for transplantation. Almost all victims of nonneoplastic chronic liver disease can at least be considered for liver transplantation, and even some of those with malignant hepatic tumors may be benefited. Acute liver disease was rarely suggested as a reason to consider liver transplantation until the mid 1980s, but now the rescue by this means of patients with fulminant hepatitis is common. Human survival of more than 20 years after liver transplantation has been achieved.

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 transplantation) (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 is concerned primarily with this replacement operation. However, long survival has also been accomplished with auxiliary hepatic transplantation, and this option is briefly considered in a special section.

IMMUNOLOGIC CONSIDERATIONS

Is the liver a privileged graft? When liver replacement was first successfully performed in dogs, immunosuppression was discontinued after 4 months. A surprising number of animals continued to thrive either with no signs of rejection or with remittent rejection episodes.[9] One such dog lived in the authors' laboratory for more than 11 years after transplantation. The phenomenon of "graft acceptance" has been noted in dogs with renal transplants, although less frequently. The apparently immunologic advantage of the liver has been more clearly noted in pigs, some of which can survive chronically with no immunosuppressive therapy, despite the fact that the pigs regularly reject skin and kidney grafts.

In later years, numerous studies in inbred rats with known

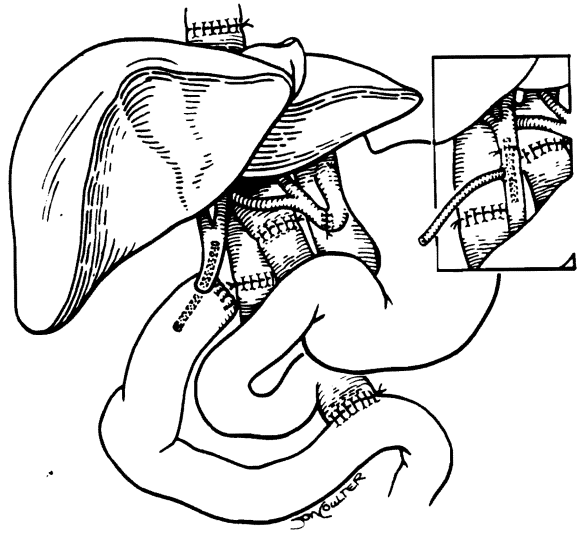


Figure 1. Orthotopic liver transplantation (liver replacement). Biliary tract reconstruction is usually done with choledochojejunostomy (to a Roux limb) or (inset) with a choledochocholedochostomy, which is stented with a T-tube. (From Starzl, T. E., Demetris, A. J., and Van Thiel, D. H.: Medical progress: Liver transplantation. N. Engl. J. Med., *321*:1014, 1989.)

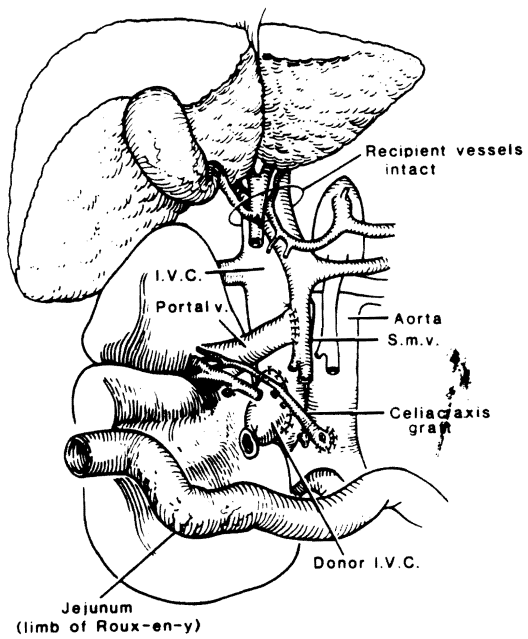


Figure 2. Auxiliary liver transplantation with a technique that provided an adequate blood supply for the homograft. Note that the transplant is given a double blood supply and that the venous component is from the nonhepatic splanchnic bed. Biliary drainage can be with a Roux-en-Y cholecystojejunostomy.

histocompatibility barriers have confirmed that the liver is more resistant to rejection than any other major organ. Permanent acceptance can be routinely induced in rats across major histocompatibility barriers with only 3 or 4 injections of immunosuppressive drugs during the early postoperative period.[8] Nearly a year later, the recipient animals retain an intact immunologic apparatus including the ability to vigorously reject skin from the original donor species. This kind of graft acceptance of hearts, kidneys, and other organs is much more difficult to achieve.

Another important advantage of the liver is resistance to antibody-mediated (humoral) rejection. Whereas kidneys and hearts usually are destroyed by hyperacute rejection in patients whose serum contains cytotoxic antibodies of the IgG class which are directed against HLA and other antigens in the donor, livers are spared this fate in most cases. The pathogenesis of hyperacute rejection includes obstruction of the microvasculature of nonhepatic grafts with clotting products and formed blood elements. This process usually does not occur in liver grafts, and what can be expected clinically is an unusually vigorous cellular rejection that can be treated with aggressive conventional immunosuppression. The practical implication is that a negative cytotoxic crossmatch that is a necessary condition for transplantation of other organs is not required for successful liver transplantation. Moreover, it has been established that the liver can provide a protective screen for otherwise vulnerable kidneys in highly sensitized recipients who need both a liver and a kidney. In such patients who receive a liver first, the titer of antidonor antibodies is drastically reduced during the first few hours after hepatic revascularization, making it possible then to insert a kidney from the liver donor without peril.[3]

The reasons the liver has these advantages are not understood. 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 despite very heavy immunosuppressive therapy.[10] When routine biopsies are obtained in patients after orthotopic liver transplantation, histopathologic evidence of rejection can be found in more than two thirds of patients. Effective management of this complication is the key to successful transplantation.

REJECTION REVERSAL

Rather than being unique, it is probable that liver homografts differ from other organs only by the degree of the host immunologic response they evoke. This has been demonstrated with genetically standardized inbred rat strains, and exceptionally clearly in mouse models in which knowledge of the major histocompatibility complex is even more complete. 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 pre-existing therapy, which suggests that such recoveries had an element of spontaneity. Long survival has been achieved in many, and possibly even most, patients without complete control of rejection. The grafts of such patients develop characteristic lesions of the intrahepatic portal triads in which the small bile ducts appear to be selectively and progressively damaged. Small numbers of lymphocytes are found in the vicinity of, or lifting up and destroying, ductal epithelial cells. This leads to the "disappearing bile duct syndrome." Studies of the antigenicity of the ducts and other constituents of liver grafts have demonstrated changing expression of Class 2 HLA antigens during rejection and have demonstrated that the areas of greatest injury are in vessels and ducts where dendritic cells of the macrophage system are heavily concentrated. These dendritic cells are important for efficient antigen presentation. The practical consequence is that patients with slowly rejecting liver grafts can have intrahepatic biliary obstruction (with jaundice), arteriopathy, and even graft cirrhosis while retaining good synthetic and other functions of the hepatocytes.[9,10] Such patients eventually become prime candidates for late retransplantation.

GRAFT ACCEPTANCE

The second observation of overriding practical and theoretic 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 demonstrated that disappearance 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 at least a dozen of the authors' liver recipients have for religious, noncompliance, or other reasons discontinued all therapy 5 to 10 years ago or longer with no subsequent problems.

The degree to which graft acceptance develops is a prime determinant of the long-term prognosis. More than one immunologic pathway may be involved.[8,9] 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 remainder of the lymphocyte population (Fig. 3). Inasmuch as the maintenance of such activated cell lines appears to be thymus-dependent even in adult life, it is reasonable to be curious about the effect of thymectomy as an adjuvant immunosuppressive measure. The results of thymectomy in a series of the authors' human renal transplants compiled more than 25 years ago were inconclusive.

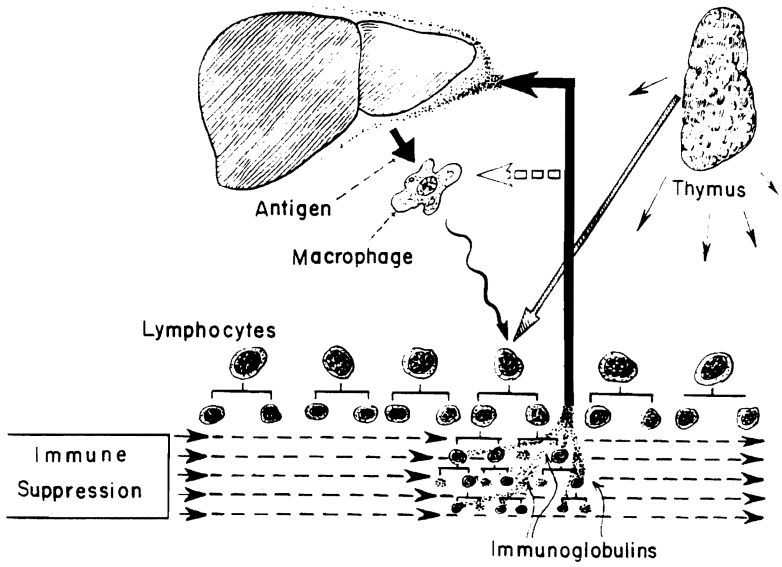


Figure 3. Hypothetical mechanisms by which nonspecific immunosuppression may lead to selective abrogation of the host immune response. Special susceptibility to these agents of a fraction of the lymphoid population could lead to exhaustion of a clone and, therefore, tolerance. Because maintenance of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

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

These findings do not disprove tolerance through clonal deletion so much as they suggest that other mechanisms can be contributory. One mechanism, termed *passive enhancement*, has been envisioned as a process in which immunoglobins synthesized by the activated lymphoid tissues circulate to the target tissue and coat or protect it in some way that is not yet understood (see Fig. 3). The even more ambiguous term *active enhancement* describes a hypothesis that antibodies cause a central donor specific immunosuppression of the recipient immune apparatus.

During the last decade, techniques have been developed which allow the detailed identification of cells, cytokines, and other components of the immune response. When these methods were used in the study of rats that bore permanently accepted liver grafts almost a year after discontinuing all immunosuppression, the findings were surprising.[8] There were no alterations of lymphocyte subset distribution, no changes in suppressor cells, and no qualitative changes in anti-donor alloreactivity as measured *in vitro* with mixed lymphocyte culture techniques and *in vivo* by skin grafting from the donor species. There also was evidence of low level graft-versus-host activity, which presumably came from "carrier lymphocytes" still viable in the liver grafts. It was as if a symbiotic relationship had been established between the host and the graft, each without hazard to the other. This was not classic tolerance.

The hypothesis shown in Figure 3 is multifactorial. The observations cited above leave open the possibility of changes in the graft itself or functions that it performs that decrease its vulnerability to rejection. In humans, the macrophage (Kupffer) system is replaced entirely by differentiating host monocytes within 100 days after transplantation, an alteration that does not occur in the vascular endothelial cells or hepatocytes.[9] In addition, the liver graft permanently secretes significant amounts of soluble donor HLA antigens, enough to confer new HLA types to the recipient.[1] The role of these events in promoting graft acceptance is speculative.

TISSUE TYPING

ABO blood types of donor and recipient ideally should be the same; failing this, they should be compatible (example: O to A). 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 as an instrument of donor selection, 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, most of the matches for liver transplantation worldwide have been poor ones. Puzzling reports have been published from two large centers (Pittsburgh and Cambridge) that survival after liver transplantation is actually inversely related to the quality of HLA matching.[10] This would be such a violation of an important biologic principle that much verifying data are required before indulging in speculation about what may prove to be a sampling error.

PROCUREMENT AND PRESERVATION OF ORGANS

In contrast to typing, the procurement of a fresh, functioning, nonischemic liver is of paramount advantage. Unquestionably, one of the most important advances that has 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 nearly 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 brain death.

During the last few years, the need for the procurement of multiple organs from the same donor has sharply increased. Exclusive of the pancreas, the most common combinations have been kidneys and liver; kidneys, liver, and heart; and kidneys and heart, in that order. Techniques have been developed that permit such removal 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.[12]

Until late 1987, the safe outer limit for human liver preservation was set at 6 or 8 hours. The Cambridge-King's College team in England and many European teams had used a plasma solution for cold infusion of the homografts. The alternative was a

preservation fluid (Collin's solution) with a composition similar to that found in cells. In dogs, the two approaches yielded comparable results. These techniques permitted the shipment of livers from city to city. It was learned that excessive ischemia or bile left within the ducts could cause autolysis and facilitated delayed mucosal sloughing and cast formation.

The situation was dramatically improved with the introduction by Belzer, Jamieson, and Kalayoglu of the University of Wisconsin (UW) solution.[4,6] Although this solution has more than a dozen constituents, the essential ingredients are thought to be two sugars, lactobionate and raffinose, which are impermeants that prevent water imbibition by the cells. In addition to protecting the hepatocytes, there is much evidence that the microvasculature also is benefited. After perfusion with UW solution, cadaveric human livers can be stored safely for at least 18 hours. Beyond this time, there is a slowly increasing incidence of primary nonfunction, which reaches unacceptable levels after 24 hours.[16]

The gains in the effectiveness of organ procurement and distribution made possible by the UW solution have been large. All parts of North America have been placed within the range of all others. Even intercontinental sharing is now practical although infrequently practiced. Even with short periods of preservation, the quality of grafts is better when they are preserved with the UW solution versus the Collin's solutions, and the incidence of hepatic artery thrombosis is reduced. The UW solution is thought to be a generic advance applicable to all solid organs.

The next step in liver preservation probably is continuous perfusion techniques, using either blood or asanguineous fluids. This approach was demonstrated to be feasible more than 20 years ago, but the equipment was too cumbersome to be practical.

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 was 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 authors were able to develop liver transplantation to an acceptable service level without decompressing the obstructed venous systems, and some surgeons continue to believe that this expedient usually is unnecessary.

However, the fact that most patients can recover from portal and inferior vena caval cross-clamping 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. The authors now perform venous bypasses in all adults and in most children weighing more than 15 kg. 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).

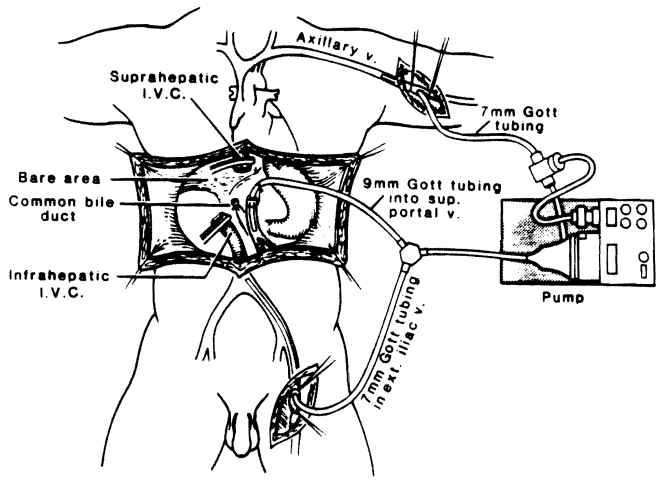


Figure 4. Venovenous bypass developed for use during the anhepatic phase of liver transplantation during which the new liver is connected to recipient vessels. By using coagulation-resistant tubing and an atraumatic pump, it has been possible to bypass large volumes of blood without using any heparin.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

The safety of liver transplantation in adults has been greatly improved with this technique.

HEMORRHAGE

Other problems during and after operation may be caused by derangements in the coagulation mechanism, which may lead to 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 in some cases can assume formidable proportions during the procedure. Many of the normal coagulation factors that might help control hemorrhage are dependent on the liver and are therefore defective. In addition, fibrinolysis can cause or complicate the coagulopathy in many cases. 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 is appropriate coagulation function. If hemorrhage cannot be controlled, fresh frozen plasma, platelets, and antithrombolytic agents such as ϵ-aminocaproic acid (EACA) may be required. With earlier patients, whose homografts were often of less than optimal quality, an attempt was made to treat bleeding problems by administering massive amounts of thrombogenic agents. However, hypercoagulability was caused in some instances with consequent thrombosis of the graft vessels. Ironically, the better the condition of the recipient and of the grafts, the greater the risk of unwanted coagulation if clot promoting therapy is used. Almost every series of liver transplants has had examples of thrombosis. Effective management of coagulation has been a special contribution of the anesthesiologists.[7]

AIR EMBOLI AND NEUROLOGIC DAMAGE

Eventually lethal neurologic invalidism was observed in 9 of the first 98 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, including brain stem syndromes such as akinetic

mutism. They died within a few days to 2 months. It ultimately was realized that air emboli from the homografts were responsible for some, although not all, of these cerebral or brain stem catastrophes.[13] 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 performed, air bubbles could escape from the graft vessels before a blood supply was restored (Fig. 5). Since the institution of this simple preventive measure, the incidence of neurologic complications has been reduced.

However, despite all efforts, neurologic complications can destroy an apparently perfect liver transplantation because of pre-existing abnormalities in the brain that can be the basis for perioperative or postoperative tragedies. Pathologic changes can almost always be found in the central nervous system of nontransplant patients who die of chronic liver disease. These include Alzheimer (proliferative) changes in the glial tissue, depletion of the myelin in the pons (central pontine myelinolysis) or elsewhere in the brain stem or higher brain (extrapontine myelinolysis), cortical atrophy, and edema. Alzheimer changes and central pontine myelinolysis can be produced reliably in rats and subhuman primates by portacaval shunt even though the animals appear well clinically. More recently, a role of perioperative hypernatremia in aggravating such lesions has been suggested.

VASCULAR ANOMALIES

In planning 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 the authors' patients. Multiple arteries have been the most frequent anomalies. If these are in the donor, the guiding principle is to convert these by back table anastomoses to a single vessel for anastomosis to a single recipient vessel (Fig. 6). If there are multiple recipient vessels, it may be possible to dissect back to a common trunk, or even to the celiac axis, for an anastomotic site. However, the best solution may be to place a donor iliac graft, which should always be brought back with the liver, from the infrarenal recipient aorta into the hilum (Fig. 7).

Thrombosis of the portal vein was formerly thought to be a contraindication to orthotopic liver transplantation. All that is necessary in such cases is to find an open segment in the superior mesenteric vein and to interpose a segment of donor iliac vein into the hilum. The vein graft is passed anterior to the pancreas and beneath the pylorus (Fig. 8). Retrieving a liver without the iliac artery and vein grafts may be responsible for the recipient's death, since the need for these vascular grafts is sometimes completely unexpected.

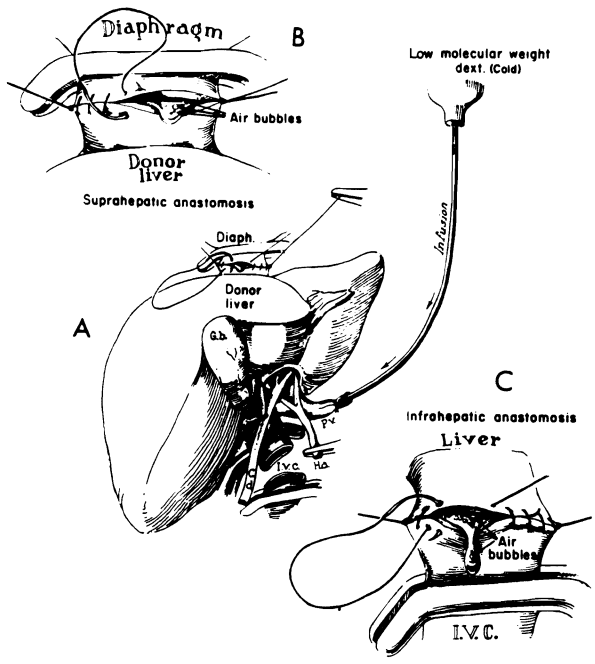


Figure 5. Technique to prevent air embolism from orthotopic liver homografts. *A*, Continuous perfusion of solution through the portal vein as vena caval anastomoses are constructed. *B* and *C*, Escape of air bubbles as the anastomoses are completed. (From Starzl, T. E., et al.: Acute neurological complications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

BILIARY TRACT PROBLEMS

Obstruction or bile fistula formation leads to repeated bacterial contamination, with resulting cholangitis and consequent systemic infection. An acceptable method of biliary reconstruction is choledochocholedochostomy, using a T-tube stent (see Fig. 1, inset) that is left in place for about 2 months. After the T-tube is removed, periodic retrograde cholangiography via the duodenum can be performed in such recipients.

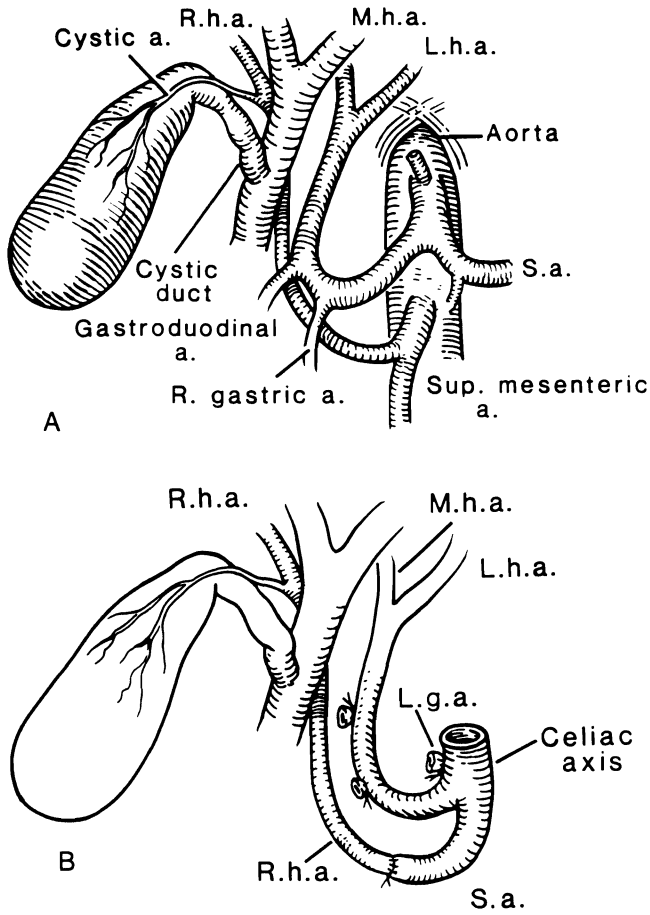


Figure 6. *A*, A common anomaly in which a right hepatic artery originates from the superior mesenteric artery. This right artery always is posterior to the portal vein. *B*, With the anomaly shown in *A*, the splenic artery can be anastomosed to the anomalous right hepatic artery, thereby converting the origin of the blood supply to a single vessel based on the celiac axis.

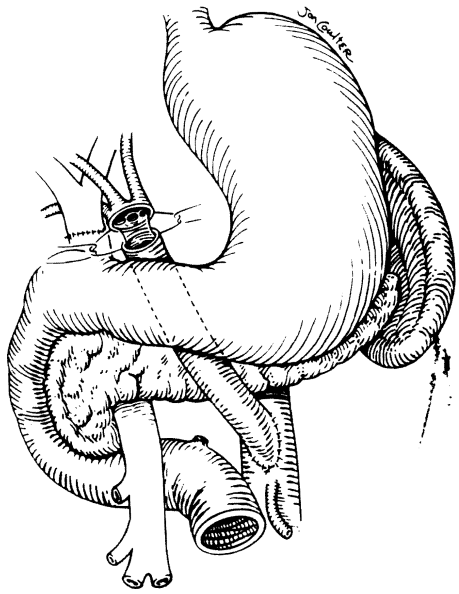


Figure 7. An antepancreatic route for a vascular graft placed onto the infrarenal abdominal aorta. The graft is brought either to the right or left of the middle colic vessels, anterior to the pancreas, and beneath the pylorus. Note the homograft anomaly in which a right, middle and left hepatic artery arise separately from the donor aorta. All three vessels were included in a Carrel patch, which was anastomosed as a cap onto the end of the iliac artery graft. (From Tzakis, A. G., Todo, S., and Starzl, T. E.: The arterial route for arterial graft in liver transplantation. Transpl. Int., 2:121, 1989.)

Choledochocholedochostomy often is not feasible, as for example in children with biliary atresia. Choledochojejunostomy (Fig. 1) to a Roux limb of jejunum is a highly satisfactory option and should be chosen if there is the slightest question about the quality of duct-to-duct repair.

With the simple techniques demonstrated in Figure 1, the descriptive term *Achilles heel of liver transplantation,* which formerly was applied to biliary tract reconstruction, no longer pertains. Nevertheless, the possibility of duct obstruction must be entertained in the postoperative management of liver transplantation whatever 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, was frequently responsible. Even in the absence of a biliary tract problem, rejection may not be responsible. Hepatitis associated with hepatitis B surface antigen (HBsAg), cytomegalovirus (CMV), C virus, and other viruses has been observed as well as drug toxicity.[10] 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.

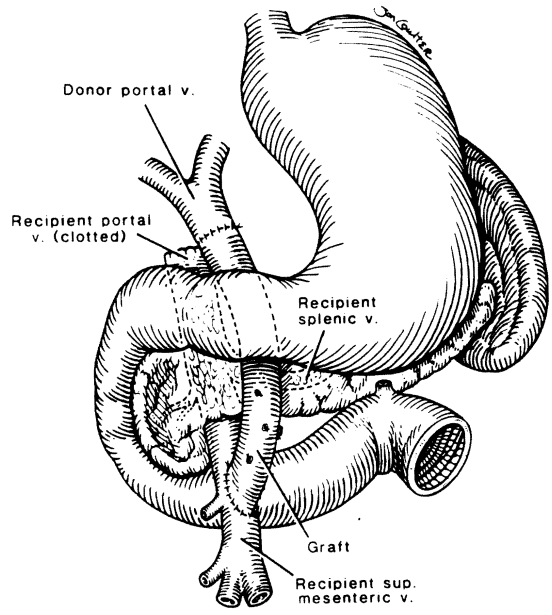


Figure 8. The use of antepancreatic iliac vein graft from the superior mesenteric vein circumvents portal vein thrombosis as a contraindication to transplantation, providing a good superior mesenteric vein is still open. (From Tzakis, A. G., Todo, S., Stieber, A., and Starzl, T. E.: Venous jump grafts in patients with portal vein thrombosis. Transplantation, *48*:530, 1989.)

ANESTHESIA

During operation there are metabolic abnormalities other than those concerned with coagulation that 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 inherently impaired, absent, or untried in its new setting. Therefore, the task of the anesthesiologist is to correctly administer pharmacologic agents that, first, are not hepatotoxic and, second, do not depend primarily on the liver for their degradation. In the authors' early cases, reliance was placed primarily on combinations of volatile agents in nonexplosive concentrations. Such management permitted use of electrocautery, gave flexibility in lightening or deepening anesthesia, and allowed anesthesia to be abruptly discontinued if required by changing physiologic circumstances. Recently, less effort has been made to use volatile anesthetics.

IMMUNOSUPPRESSION

The immunosuppressive regimens used and the year of their first clinical applications are summarized in Table 1. The movement through the years was toward increasing specificity of the immunologic target, culminating in the introduction of cyclosporine. The use of cyclosporine with steroids, and later the use of these two drugs with azathioprine and antilymphoid globulins, had an immediate impact on the transplantation of all organs, but especially of the liver.[5] The 1-year patient survival, which had been approximately 35 per cent before 1980, doubled (Fig. 9) or, in the case of low-risk patients, nearly tripled.

During the 1980s transplantation developed as a highly defined multidisciplinary special branch of medicine. In addition to the impetus provided by cyclosporine, the improvements in organ storage and the establishment of organ distribution systems that linked all parts of the United States and Canada were crucial pragmatic improvements.

Collateral developments in an understanding of the mechanisms of rejection and better understanding of how these are effected by immunosuppression have facilitated what may be even more important advances during the next decade. Cyclosporine inhibits the activation of T lymphocytes and depresses the production and expression of multiple cytokines of which interleukin-2 and interferon-γ have been most extensively studied.[5] The cyclosporine binding site is a low-molecular-weight cytosolic protein (cyclophilin) that is probably only one of a family of binding sites that participate in a broad range of physiologic effects.

It was realized at the outset that nephrotoxicity was the principal and dose-limiting side effect of cyclosporine; even when serum creatinine remains normal, hypertension and decreases in glomerular filtration occur. The remarkable spectrum of cyclosporine's actions can be demonstrated by other side effects, including gingival hyperplasia and hirsutism. Subtle changes in carbohydrate metabolism occur. Insulin secretion by the pancreatic islets is depressed with increased peripheral insulin re-

TABLE 1. Immunosuppressive Drug Regimens Used Clinically for Whole-Organ Transplantation

Agents	Year Described and Reported	Place	Deficiencies
Azathioprine	1962	Boston	Ineffective, dangerous
Azathioprine, steroids	1963	Denver	Suboptimal
ALG as adjunct to 2	1966	Denver	High incidence of infection
Cyclophosphamide substitute for azathioprine	1970	Denver	No advantage except for patients with azathioprine toxicity
Cyclosporine	1978–1979	Cambridge	Suboptimal
Cyclosporine, steroids with or without other adjuncts*	1980	Denver	Nephrotoxicity limits dose: rejection not always controlled
Monoclonal OKT3	1981	Boston	High incidence of infection
FK 506, steroids	1989	Pittsburgh	Being evaluated

*Lymphoid depletion with thoracic duct drainage, antilymphocyte globulin (ALG), OKT3, and/or azathioprine.

sistance. Other metabolic changes caused by cyclosporine include hypercholesterolemia and hyperuricacidemia. In addition, neurotoxicity is a pervasive finding in almost all patients. Although serious neurotoxicity occurs in about 20 per cent of patients, more subtle manifestations are trembling, sensitivity to light, paresthesias, mood changes, and insomnia.

These manifold effects of cyclosporine were not completely recognized until after more than 10 years of clinical use. It was assumed that the side effects of cyclosporine were largely idiosyncratic and not related to the desired effects on the immune system. The possibility that this may be an incorrect assumption has been raised by clinical observations with another agent called FK 506, which has a molecular structure completely different from that of cyclosporine.[11] Its binding site is distinct from cyclophilin, without cross-immunoreactivity to specific monoclonal antibodies, although both drugs have a *cis-trans* peptidyl-prolyl isomerase backbone.

Weight for weight, FK 506 is 100 times or more potent than cyclosporine. Insofar as it has been determined, its effect on the lymphocyte population and cytokines is similar to, if not identical to, that of cyclosporine. The side effects are similar to those of cyclosporine, although there are important differences. FK 506 is less nephrotoxic, does not cause hypertension, causes a decline instead of an increase in cholesterol, and does not produce gingival hyperplasia. Instead of causing hirsutism, FK 506 may even cause hair loss. Thus, these two drugs affect the same clinically significant end points, but not to the same extent and sometimes not even in the same direction.

The molecular basis for these effects is not known. An unlikely possibility is that there is immune modulation of the diverse functions that are affected. Far more likely is an effect on secondary messenger systems, including but not limited to peptidyl-prolyl isomerase, which could modulate the amount or expression of hormones and other biologically active compounds. A better understanding of such details could provide a pathway for searching for other immunosuppressive drugs.

In the meanwhile, extensive clinical trials with FK 506 have been initiated in the United States and Europe. At the University of Pittsburgh, more than 350 patients have been administered this drug for primary therapy or for the rescue of failing liver grafts under cyclosporine regimens.

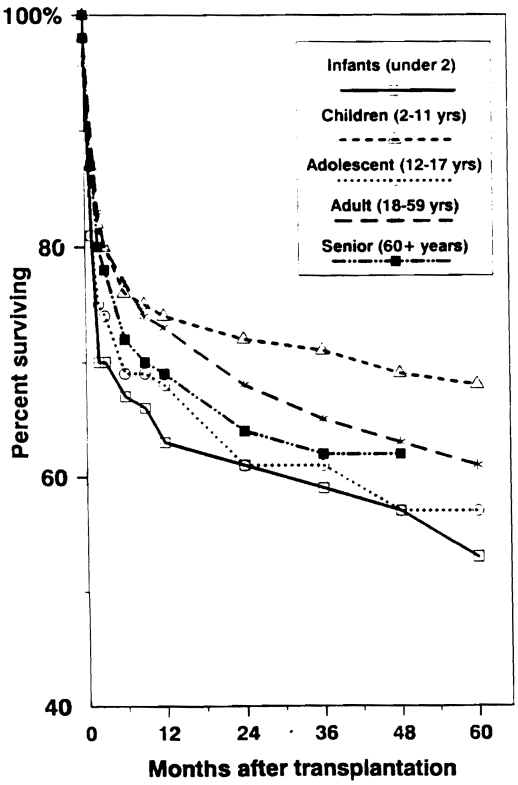


Figure 9. Actuarial (life-table method) patient survival rates for different age groups after liver transplantation under cyclosporine and low-dose prednisone. Based on 1565 patients receiving liver transplants at the University of Pittsburgh between 1981 and 1989.

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 mechanisms to identify the tumor tissues as alien and to eliminate them or restrict 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 types 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 due to adenovirus, cytomegalovirus, and herpes simplex and herpes zoster viruses has been recorded.[10] In other patients, 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.

In the liver recipient, postoperative bacterial sepsis of the graft itself has proved to be a special problem, undoubtedly in

part 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 type, can be brought into contact with the transplanted liver via the intestinal veins draining into the portal vein or, far more important, 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 occur, with characteristic unvisualized areas of liver scans, gram-negative bacteremia, and all the findings of generalized sepsis.

AVOIDANCE OF HOMOGRAFT SEPSIS. Antibiotics are administered intraoperatively for the first several postoperative days. The authors' prophylactic protocol includes agents effective against gram-negative bacteria. The most important surgical technical step in reducing homograft sepsis has been to use biliary reconstructive techniques that prevent systematic contamination by gastrointestinal contents (see Fig. 1). All such efforts are futile if rejection with consequent tissue necrosis is allowed to occur. The paradox is that the immunosuppressive agents that weaken natural immune defenses against infection must be considered the foremost weapon in maintaining the tissue barrier against infection.

Until 1980, infection was the primary, or an important, contributory cause of most deaths. Moreover, the development of almost any type of intra-abdominal or intrathoracic 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 was responsible for the improved results. In addition, the antiviral agents acyclovir and gancyclovir became available to treat or prevent infections by viruses of the herpes family, including, above all, CMV.

INDICATIONS FOR LIVER REPLACEMENT

Liver transplantation is being performed for a wide variety of indications. Under cyclosporine/steroid-based immunosuppression, over 1500 patients have received liver transplants since the program transferred from the University of Colorado to the University of Pittsburgh in 1981. High survival rates have been achieved, even in higher-risk patients such as infants and adults over the age of 60 (see Fig. 9).

INFANTS AND CHILDREN. The most common cause of conjugated hyperbilirubinemia persisting beyond the first 2 weeks of life is congenital biliary atresia, and more than half of the liver transplantations performed in infants are done for this indication. Portal decompression by portoenterostomy (Kasai operation) is possible in 20 to 30 per cent of patients but must be performed within 60 to 90 days after birth to be successful. Even with a successful Kasai operation, biliary cirrhosis is nearly certain to develop later in life. Recurrent cholangitis is the most common late complication after a Kasai operation. Although successful portoenterostomy can gain valuable time and permit growth of the patient, the possibility of making transplantation the first operation for biliary atresia has been discussed more openly in recent years now that techniques have been developed for using partial liver fragments from larger donors. If Kasai operations are used, it is important to avoid reoperation after an initial portoenterostomy, because these are usually fruitless, except for repair of minor technical faults or for relief of obstructions due to biliary stones. Multiple operations can seriously jeopardize a subsequent transplant procedure. Neonatal (giant cell) hepatitis is another important but much less common cause of persistent jaundice in infants. It is also an excellent indication for liver transplantation.

Liver transplantation in children has also been performed in patients with a wide variety of inherited inborn errors of metabolism such as alpha$_1$-antitrypsin deficiency, tyrosinemia, glycogen storage disease, Type II familial hypercholesterolemia (FH), protein-C deficiency, and some forms of hemophilia. The growing list of inborn errors which can be palliated with liver transplantation is given elsewhere.[10] The first survivor of a simultaneous heart-liver transplant was a 6-year-old child with FH who had a normal-appearing liver but had devastating coronary artery disease caused by a metabolic abnormality based in the liver. Replacement of a normal-appearing liver from this nonjaundiced child was necessary to prevent recurrence of disease in the transplanted heart.

Patients with inborn errors should undergo liver transplantation before developing irreversible sequelae such as neurologic injury (Wilson's disease, urea cycle enzyme deficiency), advanced pulmonary disease (alpha$_1$-antitrypsin deficiency), or hepatocellular cancer (tyrosinemia). In many of these disorders, the genetic defect is well understood, and cure by liver transplantation can be anticipated. For example, 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 pattern characteristic of tyrosinemia is almost completely rectified within hours. The same holds true for the aberrations caused by Type I glycogen storage disease (glucose-6-phosphatase deficiency), as exemplified by the ability of these patients to fast for 1 or 2 days after transplantation without the hypoglycemia that previously occurs within hours. Some of these inborn errors are known to be caused by a specific enzyme deficiency, whereas the pathogenesis of others, such as Wilson's disease, is not understood. Nevertheless, liver transplantation appears to be equally effective in the treatment of Wilson's disease, and recurrence has not been demonstrated for as long as 18 years after liver transplantation.

Other indications for liver transplantation in children have included postnecrotic cirrhosis, familial cholestasis, fulminant hepatic failure (viral or drug induced), secondary biliary cirrhosis, Budd-Chiari syndrome, and primary hepatobiliary cancers. As in adults, there is a high recurrence rate after liver transplantation for most hepatocellular or bile duct cancers. However, long-term survival has been achieved after liver transplantation for hepatoblastoma.

ADULTS. The most common indication for liver transplantation in adults is postnecrotic cirrhosis. Most of these patients have cryptogenic cirrhosis or non-A, non-B chronic aggressive hepatitis (hepatitis C). The true incidence of hepatitis C in this population is not yet known, but will become better defined in the next few years with the introduction of a specific test for detecting serum antibody to this agent. Also, it should be possible to determine the risk of reinfection with hepatitis C after liver transplantation.

In some regions of the third world, infection with the hepatitis B virus (HBV) is endemic and is the most common cause of advanced liver disease. It is also associated with an increased incidence of hepatoma. Recurrence of infection in HBsAg$^+$ patients after liver transplantation is high. More than 80 per cent of such patients remain carriers after transplantation, but the frequency and severity of reinfection is unpredictable and can be well tolerated by a significant proportion of patients. Although efforts to reduce the incidence and severity of reinfection with interferon and active and passive immunization have been disappointing, the value of transplantation has not been vitiated.

Alcoholic cirrhosis, the most common cause of chronic liver failure in Western society, has been a controversial indication for liver transplantation because of the social stigmata associated with the disease, fear of recidivism, and the poor medical condition of many of these patients. However, recent experience with a series of over 100 patients receiving liver transplants

for this disease at the University of Pittsburgh has demonstrated excellent survival rates with follow-up to 4 years. Behavior modification through participation in a rehabilitation program for chemical dependency is an important part of the postoperative care of these patients.

Cholestatic liver diseases, including primary biliary cirrhosis and primary sclerosing cholangitis, are excellent indications for liver replacement. Previous surgical forays into the hepatic hilum in patients with sclerosing cholangitis can complicate eventual liver transplantation; and as a consequence, these operations are no longer employed.

Both before and after the introduction of cyclosporine, efforts were made to utilize liver transplantation for patients with primary hepatic malignancies that could not be managed by subtotal hepatic resection. Although some patients have had prolonged periods of effective palliation, recurrence of tumor within 3 to 18 months of transplantation is common and has limited the effectiveness of this approach. More radical operations, including the upper abdominal exenterations, in addition to transplantation and aggressive adjuvant chemotherapy are currently under investigation.

Fulminant hepatic failure may require emergency liver transplantation. It is unusual for patients with hepatitis A to require liver transplantation. Many patients with acute acetaminophen intoxication can recover despite alarming abnormalities of hepatocellular enzymes and prothrombin time. Approximately 40 per cent of patients with fulminant HBV infection recover with skilled medical care. However, it may be necessary to explore some of these patients with a new liver available and to determine by intraoperative biopsy of the native liver whether or not liver replacement is advisable. Fulminant non-A, non-B hepatitis has a poor prognosis, and liver transplantation is an important consideration early in the management of patients with this disease.

Regardless of etiology, the prognosis after liver transplantation for fulminant hepatic failure is influenced by renal failure, metabolic acidosis, and central nervous system deterioration. Early consultation with a liver transplant program is an important part of the modern management of the patient with fulminant hepatic failure.

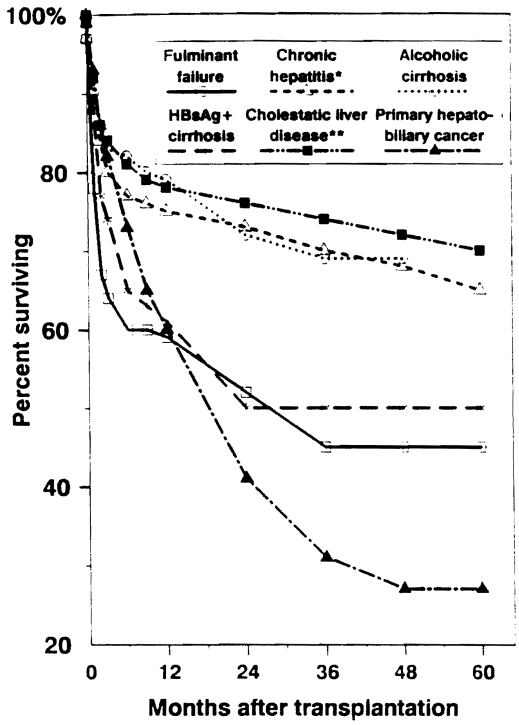
As in children, there are many other conditions for which liver transplantation has been successfully performed in adults, including, but not limited to, congenital hepatic fibrosis, inborn errors of metabolism, Budd-Chiari syndrome, secondary biliary cirrhosis, massive hepatic trauma, cystic fibrosis, and polycystic liver disease.

RESULTS AND COMPLICATIONS

Improvements in operative technique and the routine use of the venovenous bypass in adults and large children have reduced intraoperative mortality to less than 1 per cent and perioperative (30-day) mortality to under 10 per cent for most groups of patients.

The life-table survival rates for major diagnostic groups after liver transplantation under cyclosporine and prednisone in 1565 patients at the University of Pittsburgh between 1981 and 1989 are summarized in Figure 10. Most of the mortality occurs within the first 6 months after transplantation. After transplantation for cholestatic liver disease, chronic active hepatitis (except $HBsAg^+$), and alcoholic cirrhosis, 1-year patient survival is near 80 per cent and remains above 70 per cent or better at 5 years. Similar survival rates are seen after liver transplantation for most other causes of nonmalignant chronic liver disease.

Despite the significant risk of recurrent infection, survival at 5 years after liver transplantation for $HBsAg^+$ cirrhosis is 50 per cent. Significant salvage has also been achieved for fulminant hepatic failure, and this may improve further with more aggressive referral of patients to transplant centers before irreversible



*excluding alcoholic or HBsAg+ cirrhosis
**includes primary biliary cirrhosis and primary sclerosing cholangitis.

Figure 10. Actuarial (life-table method) survival rates after liver transplantation for major diagnostic classes. HBsAg + cirrhosis = end stage cirrhosis in patients positive for the hepatitis B surface antigen. Based on 1565 patients receiving liver transplants at the University of Pittsburgh between 1981 and 1989.

medical complications occur. The poor long-term survival after transplantation for primary tumors reflects the high rate of recurrent disease for most tumors.

Approximately 20 per cent of patients require one or more retransplantations for primary graft nonfunction, rejection, technical complications (most often hepatic artery thrombosis), infections (viral hepatitis), or recurrent disease. Approximately 8 per cent of grafts fail to function within the first few days after transplantation. Some of these failures may be mediated by immunologic events that have yet to be completely delineated, and others are failures of preservation. Survival after retransplantation for chronic rejection is over 70 per cent. The outcome after retransplantation for technical failure or recurrent disease is dependent upon etiology.

Hepatic arterial thrombosis may cause acute hepatic gangrene; biliary tract necrosis with hepatic abscess formation; or relatively asymptomatic bacteremia, which may respond well to intravenous antibiotic therapy. Dearterialization must be suspected in any patient with fever and gram-negative sepsis or a biliary leak after liver transplantation. Because of the variable clinical presentation, not all patients require early retransplantation, and a few have not required it at all. However, the majority of patients who do not develop hepatic necrosis or abscess eventually develop intrahepatic biliary strictures that necessitate replacement of the graft.

Portal vein and vena caval thrombosis after liver transplantation are both uncommon but usually require replacement of the graft. Some patients with late portal vein thrombosis have been managed by performing distal splenorenal shunts. Biliary tract complications have been previously discussed. Ampullary dysfunction with generalized dilatation of the biliary system is the most frequent complication after duct-to-duct reconstruction over a T-tube stent. It is best treated by revision to a Roux-en-Y

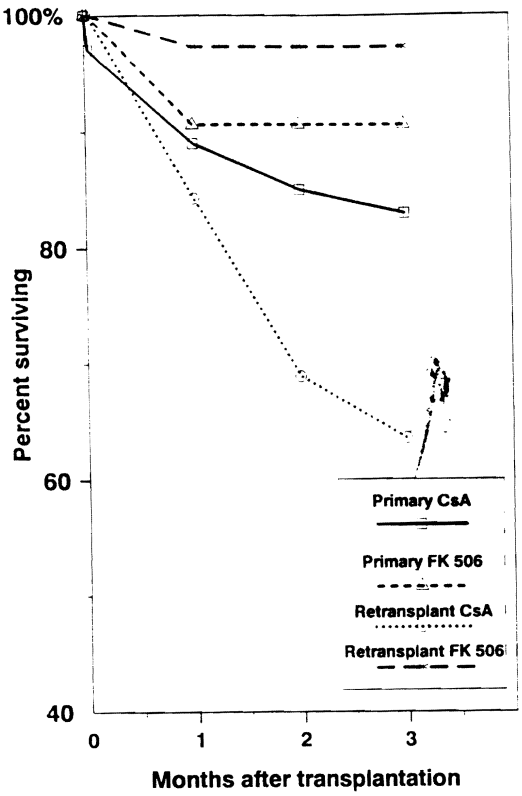


Figure 11. A comparison of early patient survival after primary liver transplantation and retransplantation under immunosuppression with cyclosporine or FK 506. The FK 506 results were in 76 patients treated during Phase 1 clinical trials of FK 506, conducted at the University of Pittsburgh during 1989, compared with the historical experience with cyclosporine from 1981 to 1989.

choledochojejunostomy, although some centers have managed this complication by endoscopic papillotomy.

The most common cause of death after liver transplantation is infection complicating immunosuppressive therapy. Sulfazoxasole-trimethoprim (Bactrim) prophylaxis has dramatically reduced the incidence of *Pneumocystis carinii* pneumonia in transplant recipients. Treatment with gancyclovir has also significantly reduced the morbidity and mortality of posttransplantation CMV infections.

With the use of FK 506, the early death rate after liver transplantation may have been influenced favorably. In Figure 11 is shown the 3-month survival after primary transplantation under FK 506/steroid treatment versus the historical record with the use of cyclosporine regimens. These hopeful but preliminary observations require extension, as well as confirmation by other workers.

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, or the pelvis. The main theoretic 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.

The provision of splanchnic venous inflow is critical for optimal graft function because this blood contains "hepatotrophic factors" of which insulin is the most important.[14] The condition of providing a splanchnic venous inflow to the auxiliary graft has been met in almost all clinical trials, which by 1978 numbered more than 50.[2]

Auxiliary liver transplantation with real prolongation of life was first achieved at the New York Memorial Hospital on December 13, 1972.[2] The recipient, who had biliary atresia, is still alive more than 16 years later (personal communication, J. G. Fortner, April 1989). In 1980, a 29-month survival of an adult was reported from Paris. The patient, who had hepatitis B, died of a hepatocellular carcinoma in his host liver 8 years after transplantation (personal communication, H. Bismuth, January 1989).

With the increased success of orthotopic liver transplantation, interest in auxiliary transplantation waned. However, there has been a recent report of the transplantation of whole livers or liver fragments to the right paravertebral gutter of six adult recipients, by essentially the same operation as that tried earlier.[15] At the time of reporting, with follow-up of 5 to 23 months, all six recipients were alive. Cautious further trials undoubtedly can be expected.

SELECTED REFERENCES

Calne, R. Y. (Ed.): Liver Transplantation: The Cambridge-King's College Hospital Experience, 2nd ed. Orlando, Grune & Stratton, 1987, pp. 1–571.
This text is an updated account of what now is a 20-year experience with liver transplantation at Cambridge University and King's College Hospital, London. It summarizes briefly what has been accomplished in other centers as well, and annotates the wide-ranging basic and clinically oriented animal and bench research that has been a collateral theme throughout the entire time. The book provides information on the specific topic of liver transplantation that no new group can afford to ignore. More important, it provides insight into the intellectual processes of Calne, who ranks as one of the supreme surgeon-scientists of this or any era. Cyclosporine was introduced into clinical medicine by Calne, and the consequences of this major contribution can be traced through the pages of his book.

Kahan, B. D.: Cyclosporine. N. Engl. J. Med., 321:1725, 1989.
This scholarly account summarizes the world experience with cyclosporine over the first 10 years of its use. Although it is not specifically concerned with liver transplantation, all of the information is relevant. There has been no better description of the fundamental mechanisms of cyclosporine, its therapeutic powers, and its side effects.

Maddrey, W. C. (Ed.): Transplantation of the liver. New York, Elsevier, 1988, pp. 1–352.
The collection of chapters including contributions from experienced guest authors was largely an exercise of preparation for the addition of liver transplantation to the treatment armamentarium at the hepatology center at Thomas Jefferson University, Philadelphia. The perspective of the text was therefore different from the other recommended texts. The value of Maddrey's approach has been illustrated by the subsequent success of his program and its many contributions to the growth and policies of the field.

Starzl, T. E., and Demetris, A. J. (Eds.): Liver Transplantation. Chicago, Mosby–Year Book Inc., 1990, pp. 1–194.
A three-part modern day account of liver transplantation published in Current Problems in Surgery *was converted to this textbook. The vast literature of the topic was summarized through the end of 1989, including the advances made possible with the UW preservation solution, and the first trials with the new immunosuppressive agent FK 506. An extensive update is included about developments in liver transplantation pathology.*

Starzl, T. E., Porter, K. A., and Francavilla, A.: The Eck fistula in animals and humans. Curr. Probl. Surg., 20(11):687, 1983.
This monograph describes knowledge of the so-called hepatotrophic substances found in portal venous blood and describes the specific effects of venous blood from nonhepatic splanchnic organs in regulating liver structure and function. Hepatotropic physiology was developed as a consequence of research in auxiliary liver transplantation, and the resulting background is essential to an understanding of the physiology and vascularization requirements if auxiliary liver grafts are to be used.

Williams, J. W. (Ed.): Hepatic Transplantation. Philadelphia, W. B. Saunders Company, 1990, pp. 1–245.
In the late 1970s, Williams established at the University of Tennessee the second successful liver transplant program in the United States. He moved in 1984 to his present location at the Rush Presbyterian–St. Luke's Medical Center in Chicago. This book reflects Williams' passion for this kind of treatment, not only now when it is respectable, but at an earlier time when it was not. Williams' contributions to the field have been many, and perhaps less well recognized than their uniformly high quality and common sense merit.

REFERENCES

1. Davies, H. F. F. S., Pollard, S. G., and Calne, R. Y.: Soluble HLA antigens in the circulation of liver graft recipients. Transplantation, *47*:524, 1989.
2. Fortner, J. G., Yeh, S. D. J., Kim, D. K., Shiu, M. H., and Kinne, D. W.: The case for and technique of heterotopic liver grafting. Transplant. Proc., *11*:269, 1979.
3. Fung, J., Griffin, M., Duquesnoy, R., Tzakis, A., and Starzl, T.: Successful sequential liver-kidney transplantation in patients with preformed lymphocytoxic antibodies. Clin. Transplant. *1*:187, 1987.
4. Jamieson, N. V., Sundberg, R., Lindell, S., Laravuso, R., Kalayoglu, M., Southyhard, J. H., and Belzer, F. O.: Successful 24 to 30 hour preservation of the canine liver: A preliminary report. Transplant. Proc., *20*(Suppl. 1): 945, 1988.
5. Kahan, B. D.: Cyclosporine. N. Engl. J. Med., *321*:1725, 1989.
6. Kalayoglu, M., Sollinger, W. H., Stratta, R. J., D'Alessandro, A. M., Hoffman, R. M., Pirsch, J. D., and Belzer, F. O.: Extended preservation of the liver for clinical transplantation. Lancet, *1*:617, 1988.
7. Kang, Y. G., Martin, D. J., Marquez, J., Lewis, J. H., Bontempo, F. A., Shaw, B. W., Jr., Starzl, T. E., and Winter, P. M.: Intraoperative changes in blood coagulation and thrombelastographic monitoring liver transplantation. Anesth. Analg., *64*:888, 1985.
8. Murase, N., Kim, D. G., Todo, S., Cramer, D. V., Fung, J. J., and Starzl, T. E.: FK 506 suppression of heart and liver allograft rejection II: The induction of graft acceptance in rats. Transplantation (in press).
9. Starzl, T. E. (with the assistance of C. W. Putnam): Experience in Hepatic Transplantation. Philadelphia, W. B. Saunders Company, 1969.
10. Starzl, T. E., Demetris, A. J., and Van Thiel, D. H.: Medical progress: Liver transplantation. N. Engl. J. Med., *321*:1014; 1092, 1989.
11. Starzl, T. E., Fung, J. J., and Todo, S.: Contempo 90: transplantation. J.A.M.A., *263*:2686–2687, 1990.
12. Starzl, T. E., Hakala, T. R., Shaw, B. W., Jr., Hardesty, R. L., Rosenthal, T. J., Griffith, B. P., Iwatsuki, S., and Bahnson, H. T.: A flexible procedure for multiple cadaveric organ procurement. Surg. Gynecol. Obstet., *158*:223, 1984.
13. Starzl, T. E., Schneck, S. A., Mazzoni, G., Aldrete, J. A., Porter, K. A., Schroter, G. P. J., Koep, L. J., and Putnam, C. W.: Acute neurological complications after liver transplantation with particular reference to intraoperative cerebral air embolus. Ann. Surg., *187*:236, 1978.
14. Starzl, T. E., Watanabe, K., Porter, K. A., and Putnam, C. W.: Effects of insulin, glucagon, and insulin/glucagon infusions on liver morphology and cell division after complete portacaval shunt in dogs. Lancet, *1*:821, 1976.
15. Terpstra, O. T., Schalm, S. W., Weimar, W., Willemse, P. J. A., Baumgartner, D., Groenland, T. H. N., Ten Kate, P. W. J., Porte, R. J., De Rave, S., Reurers, C. B., Stibbe, J., and Terpstra, J. L.: Auxiliary partial liver transplantation for end-stage chronic liver diseases. N. Engl. J. Med., *319*:1507, 1988.
16. Todo, S., Podesta, L., Ueda, Y., Imventarza, O., Casavilla, A., Oks, A., Okuda, K., Nalesnik, M., Vendataramanan, R., and Starzl, T. E.: A comparison of UW with other solutions for liver preservation in dogs. Clin. Transplant., *3*:253, 1989.

IX

PANCREAS TRANSPLANTATION

Hans W. Sollinger, M.D., Ph.D., and Mark Stegall, M.D.

HISTORICAL ASPECTS

According to Erich Lexer, the first surgical step in treating Type I diabetes mellitus by transplantation of the pancreas was in 1891, 30 years before the discovery of insulin. An English surgeon, Williams, transplanted extracts of sheep pancreas into the abdominal wall of a comatose diabetic patient and his early trial demonstrates that the concept of replacing nonfunctioning islets by means of transplantation of vital endocrine tissue is a very old one. The first clinical pancreas transplant was performed by Kelly and Lillehei on December 17, 1966.[8] The type of transplant was a segmental graft transplanted to the iliac fossa with the pancreatic duct ligated. In 1973, Gliedman and associates[6] suggested for the first time the use of the urinary tract for exocrine pancreatic drainage. Merkel and colleagues[9] reported end-to-side anastomosis of the pancreatic duct to the ureter, with the belief that this would obviate the need for native nephrectomy when transplantation is performed in a nonuremic patient. In the mid 1970s the Stockholm group, headed by Groth, embarked on a larger series of enterically drained grafts.[7] A new method of handling exocrine secretions was suggested by Dubernard and associates.[5] They thought exocrine secretions could be obliterated by injecting the pancreatic duct with a polymer. In 1982, Cook and Sollinger, from the University of Wisconsin, suggested channeling of the exocrine secretions to the urinary bladder. In their initial clinical experience, the pancreatic duct of a segmental graft was sutured to the bladder mucosa. They later turned to whole pancreatic grafts, using the duodenal button technique, and, more recently, to the duodenal segment method as described by Nghiem and associates.[11] Other techniques of managing exocrine pancreatic secretions are enterically drained pancreaticoduodenal grafts, paratopic grafting with exocrine drainage into the stomach[4], and a variety of modifications of the bladder technique such as skeletonizing the pancreatic duct prior to implantation into the bladder, by the Göteborg group,[14] or implanting the entire cut edge of the pancreas end-to-side into the bladder.

INDICATIONS

The indications for transplantation of the pancreas remain controversial. It can be performed in three settings: alone in the preuremic patient; after successful kidney grafting; and simultaneously with a kidney transplant. Clearly, pancreas transplantation should be performed before the patient develops end-stage secondary complications such as advanced retinopathy leading to blindness, disabling neuropathy, end-stage nephropathy, or extensive macrovascular and microvascular disease. In the authors' view, pancreas transplantation in the preuremic patient is justified only in a setting in which careful long-term monitoring of its potential effect on secondary complications can be performed. These studies must include extensive investigation and monitoring of the progression of retinopathy and nephropathy. Transplantation of the pancreas after successful transplantation of the kidney has the advantage that the patient is already on immunosuppressive therapy. Unfortunately, the results of preuremia and sequential grafting are significantly worse than the results in combined transplantation of kidney and pancreas. For this reason, the majority of pancreas transplants in the past years have been combined transplants. In this setting, only one surgical procedure is required, and the patient receives an immunosuppressive regimen similar to that of a patient undergoing a kidney transplant alone. Absolute contraindications for pancreas transplantation are similar to the contraindications for kidney transplantation. They include the presence of malignancy and active infection. Patients with advanced cardiovascular disease, major amputations, blindness, and inability to understand the investigational nature of the procedure are excluded in the authors' program. Of major importance is the evaluation of the patient's cardiac status, because many diabetic patients, as a result of neuropathy, do not present with the classic symptoms of angina, even in the presence of advanced coronary artery disease. Therefore, preoperative evaluation requires thallium stress testing in all patients over the age of 30. If the thallium stress test is suggestive of