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PEDIATRIC SURGERY

44

LIVER TRANSPLANTATION*

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Two centers have accumulated the vast majority of the world experience in liver transplantation, our own and the English team headed by Calne and Williams, which works at Cambridge University and Kings College in London.[1] The British group has treated very few children because they rarely have had pediatric donors. In addition, they have been fearful of the growth limitation and cosmetic deformity inherent in long-term steroid therapy. Consequently, most of the comments and practically all of the data in this chapter are from the University of Colorado series. The potential bias in this parochial situation may have been partly compensated by our ability to obtain accurate follow-ups and analyses of every patient to January 1979.

Two kinds of whole liver transplantation have been used clinically, orthotopic liver transplantation (liver replacement) and auxiliary liver transplantation. Both will be described, but most of this chapter will deal with the replacement procedure, since it has yielded the best — although still unsatisfactory — results. The problems of an experience with auxiliary transplantation will be covered in this introduction.

Auxiliary Liver Transplantation

Auxiliary liver transplantation is the placement of an extra liver in some ectopic site such as the right paravertebral gutter, pelvis, or splenic fossa. This operation was described in dogs by C.S. Welch in 1955 and shortly thereafter was attempted in humans.[3] Fortner and colleagues[2] recently compiled a

total of 43 clinical trials contributed from many centers, including 4 from the University of Colorado and 7 from their own institution. There had been only one unqualified success, that being the 5½-year postoperative survival of a child with biliary atresia in whom the auxiliary liver was still functioning well. All of the other patients died within a few weeks or months postoperatively. No difference between pediatric and adult recipients was seen in these cases.

Both the appeal and the disadvantages of auxiliary liver transplantation derive from retention of the diseased native liver.[3] By not removing the diseased organ, some technical problems are avoided. In addition, the recipient is not placed totally and immediately at the mercy of function of the homograft. This may not be a significant theoretic benefit in patients with truly end-stage liver disease, but in children with biliary atresia, many synthetic and other metabolic functions are still quite adequate at the time of transplantation. Unfortunately, one infant with Crigler-Najjar syndrome whose liver was functioning normally except for the inability to conjugate bilirubin died when the blood supply to the cadaveric auxiliary liver clotted several days after auxiliary transplantation. Such technical problems result from the awkward revascularization procedures necessitated by placement of an extra organ in an abdomen that is frequently already overcrowded. The most natural place for a new organ is the liver fossa vacated by host hepatectomy.

The extent to which function remains in the native liver influences the fate of an auxiliary organ. When two functioning livers coexist, they compete for so-called hepatotrophic substances that are normally brought to the liver via the portal vein from splanchnic organs. The most important of these factors is endogenous insulin. The removal of hepatotrophic substances by the organ with first access to portal blood jeopar-
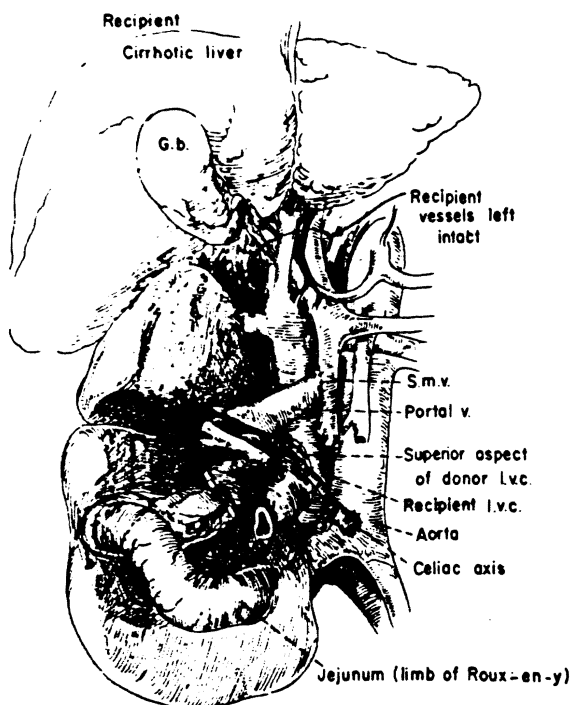
Figure 44-1 Auxiliary liver transplantation in a patient with cirrhosis. Note that the transplant in the right paravertebral gutter was given a double blood supply and that the venous component was from the non-hepatic splanchnic bed. Homograft portal inflow was assured by the portal hypertension caused by cirrhosis. (From Starzl, T. E.: *Experience in Hepatic Transplantation.* Philadelphia, W. B. Saunders Company, 1969.)

dizes the structure, function, and capacity for regeneration of the other liver. Although this aspect of hepatic physiology is complex, the practical conclusion is that optimally vascularized auxiliary homografts must be given a portal inflow from splanchnic sources. The operation in Fortner's long-surviving patient met this criterion, being in principle like that shown in Figure 44-1.

In the future, the most important use of auxiliary liver transplantation may be to tide patients over a bout of fulminant hepatic failure, allowing time for the acutely damaged native liver to regenerate. The concept has been validated in controlled animal experiments and even in partially successful clinical trials at our institution, but long-term survival of such patients has not yet been accomplished.

Orthotopic Liver Transplantation

Cannon first reported unsuccessful orthotopic liver transplantation in animals. The technical feasibility of the procedure was established by work at the Peter Bent Brigham Hospital and at the University of Colorado.[3] The recipient liver is removed and the donor liver inserted in its place. In principle, the operation is simple, requiring reconnection of the vena cava above and below the liver and anastomosis of the hepatic artery and portal vein (Fig. 44-2). Biliary tract reconstruction is a critical detail, as will be mentioned later. The orthotopic operation has been the most widely used and successful kind of liver transplantation.

It is interesting that two of our long-term survivors after liver replacement (9 years and 1 year) had unsuspected incidental tumors in their livers, which were removed because of biliary atresia and alpha$_1$-antitrypsin deficiency. The first was a hepatoma and the second a hepatoblastoma. Neither has recurred. Three other children (two with biliary atresia and one with tyrosinemia) who had similar incidental hepatomas died early postoperatively. Such a high incidence of incidental neoplasia in our series of 74 pediatric cases of liver replacement (see succeeding sections and Table 44-1) is an extra notation in favor of recipient hepatectomy and orthotopic liver transplantation as opposed to the auxiliary grafting procedure.
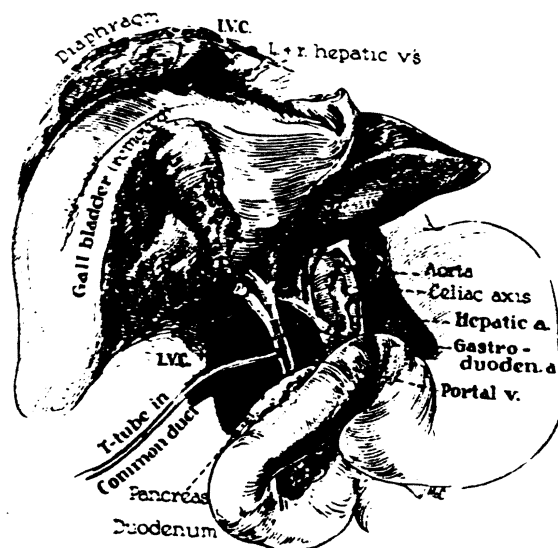

Figure 44-2 Completed orthotopic liver transplantation, with duct-to-duct biliary reconstruction. (From Starzl, T. E.: *Experience in Hepatic Transplantation.* Philadelphia, W. B. Saunders Company, 1969.)

TABLE 44-1 INDICATIONS FOR ORTHOTOPIC LIVER TRANSPLANTATION AND OUTCOME IN 74 PEDIATRIC CASES (1963-1977)

Diagnosis	Number of Examples	Survival at 1 Year*	Alive Now	Duration of Survivor Follow-up (Months)
Biliary atresia	48	16	8	12, 21, 52, 65, 72, 84, 91, 109
Chronic aggressive hepatitis	12	4	3	16, 51, 60
Alpha₁-antitrypsin deficiency	4	3	2	12, 26
Hepatoma	3	2†	0	
Wilson's disease	2	2	1	95
Neonatal hepatitis	2	1	1	26
Congenital biliary cirrhosis	1	1	1	81
Tyrosinemia	1	0	0	
Type IV glycogen storage disease	1	0	0	
Total	74	29	16	

*Deaths after 1 year were at 12, 13, 13½, 14, 16½, 17, 20, 23, 26, 28, 30, 41 and 72 months. Follow-up on all cases to January 1979.

†Both late deaths due to recurrent hepatoma.

BASIC SCIENCE

The unique and pervasive element of liver transplantation, however, is immunologic. The liver, like other tissues and organs, evokes a recipient reaction to its alien presence. Classically, the response that is termed rejection was said to be a pure expression of cell-mediated immunity, the kind that is responsible for delayed hypersensitivity (like the tuberculin skin test) reactions. Later it became clear that rejection represented a wide-ranging immunologic assault in which subpopulations of lymphocytes (T and B cells among others) played out their roles and in which humoral antibodies frequently participated. The explosion of new knowledge in immunology has not delineated the exact mechanisms of rejection. It has only made it clear that rejection is an immunologic event of great complexity.

Within a short time after it became technically feasible to perform hepatic transplantation, the manifestations of untreated rejection in dogs were delineated.[3] The homografts functioned normally for a few days. The recipients then became jaundiced, and serum transaminase levels increased markedly. Histopathologically, the livers were overrun with mononuclear cells, and various degrees of necrosis presaged death 7 to 10 days postoperatively. By electron microscopy, lymphoid cells could be seen to squeeze through cell junctions of the endothelial lining of the microvasculature and to work their way toward hepatocytes. There were declines in hepatic blood flow during this time. Such changes were variably observed in other species. In particular, the pig was shown to have an especially weak and late rejection response that often was not fatal.[1, 3]

Poor understanding of the details of rejection did not deter research to prevent or control the process. In 1963 and 1964 the cytotoxic drug azathioprine was shown in dogs to permit long survival after liver replacement.[3] One dog from that original Colorado series lived for almost 12 years. Later, similar results were accomplished in our laboratories with antilymphocyte serum (ALS) or its globulin derivative (ALG). Eventually, such work helped in evolving multiple agent programs to prevent and control rejection. Generally, these were tested clinically in the simpler clinical circumstances of renal transplantation and applied secondarily to liver patients.

CLINICAL ASPECTS OF LIVER REPLACEMENT

Indications for Operation

When orthotopic liver transplantation was first contemplated clinically, it was thought that one highly justifiable use would be for the treatment of primary hepatic malignancies that could not be resected with conventional techniques but that had not yet spread beyond the liver. The logic was flawed. There was the overwhelming recurrence rate of 85 per cent in our combined adult and pediatric series[5] and a 70 per cent rate in the English experience from Cambridge Univer-

sity and Kings College, London.[1] Three of our early pediatric recipients were treated for hepatoma (Table 44–1). One died of massive metastases after 143 days, and the two others succumbed to tumor recurrence shortly after the first postoperative year. Although an occasional cure of malignancy has been obtained,[1, 5] today we discourage parents who solicit such treatment for their children.

At the University of Colorado, 74 pediatric patients (18 years or younger) had liver transplantation performed between March 1963 and December 1977 (Table 44–1). Thus, a minimum potential 1 year follow-up is available in every case. All patients had chronic liver disease.

Biliary atresia was the most common diagnosis, accounting for almost twice as many cases as all other diseases combined. Chronic aggressive hepatitis was the next most common indication. Eight patients had inborn errors of metabolism, including alpha-$_1$-antitrypsin deficiency, Wilson's disease, tyrosinemia, and type IV glycogen disease. It has been established that the enzyme specificity and protein synthetic phenotypes of liver homografts remain permanently those of the donor.[3, 5] Thus any liver-based inborn error of metabolism is potentially curable with liver transplantation.

The appropriate time to recommend liver transplantation requires judgment. The predictable and tragic course of victims of biliary atresia usually makes it easy to proceed relatively early, but here also long survival may be possible, particularly if a partially successful porticoenterostomy has been performed. Moreover, it is a technical advantage if the potential recipient can be allowed to grow and live to be a year or older in other than a moribund state.

Practically all of the other nonneoplastic liver diseases for which liver transplantation could be the last resort have less predictable natural histories. Consequently, these patients tend to be operated on late. A reasonable general rule is to proceed with the advent of social invalidism. This means the inability to continue education or to work because of encephalopathy or other reasons. The need for chronic hospitalization for a variety of complications is a sure sign that the end is approaching. Unfortunately, further decline from this point onward tends to occur so rapidly that many prospective recipients have been lost when a donor could not be found promptly.

Tissue typing has played virtually no role in directing patient selection, partly because the need of recipients becomes so great that they usually cannot wait for a well-matched organ. Even the presence of preformed antidonor cytotoxic antibodies in the recipient serum does not contraindicate operation. Such hostile preformed antibodies, which immediately destroy kidney grafts, have not had adverse effects on liver transplants.[1, 5] We strive for red blood cell group compatibility except in situations of extreme urgency, although the antidonor red blood cell isoaggultinins have usually not had adverse effects on the transplanted liver.[5]

Surgical Considerations

In recent years all cadaveric livers have been obtained from "brain dead" donors whose circulation is supported until organ removal. After dissection, the grafts are abruptly cooled by infusion with a cold electrolyte solution containing low molecular weight dextran. If preservation is necessary for many hours, a final flush with special solutions increases the safety factor and has permitted the transport of livers that were excised in distant cities.[1, 5]

During the two vena caval anastomoses in the recipient, a slow infusion of intraportal chilled solution is resumed to float out air bubbles trapped in the graft. Failure to observe this precaution has resulted in lethal air embolization at the time of restoration of hepatic blood flow.[5] The usual order of vascular anastomoses is suprahepatic vena cava, infrahepatic vena cava, portal vein, and hepatic artery. If these can be done quickly, all are completed before the hepatic blood supply is restored. The liver is revascularized with portal blood only if more than 60 to 90 minutes are invested in the first three anastomoses or if the recipient has an unstable circulatory state from combined caval and portal obstruction. Under these circumstances, the hepatic artery is reconstructed when the situation has stabilized. If the portal anastomosis is a good one, there usually is prompt transhepatic decompression of portal hypertension, allowing adequate hemostasis despite continuing coagulation abnormalities.

Accurate timing between the donor and recipient teams is essential to avoid unnecessary ischemia of the graft on one hand or excessively prolonged obstruction of the recipient caval and portal systems on the

other. A completed orthotopic liver transplantation is shown in Figure 44–2. The details of the procedure have been fully described elsewhere.[1, 3, 5] Some special comments about the operation in pediatric recipients follow.

Removal of the diseased liver usually is much easier in children than in adults, even after multiple previous operations, including Kasai porticoenterostomies. The extensiveness of venous collaterals caused by portal hypertension is less in infants and children than in adults with cirrhosis, making it often possible to perform the operation with 500- or 1000-ml blood transfusions in spite of serious coagulation defects. The mobility of the costal margins usually allows the procedure to be performed through a transverse abdominal incision without a thoracic extension. The younger the patient, the more pronounced are these advantages.

Unfortunately, there have been disadvantages to smallness. In evaluating the causes of death in our first 141 cases of adults and children, the major impact of technical accidents was obvious,[5] including vascular thromboses, which were particularly common in patients with biliary atresia. Consequently, we have recently used microsurgical techniques, particularly for the hepatic artery and portal vein. The essential ingredients are loop magnification glasses, fine sutures (6–0 to 8–0), and fine needle holders and pickups.

In our early experience, there was an appalling 35 per cent incidence of obstruction of or bile fistula from the reconstructed biliary tract. The obstructions frequently were ascribed to rejection and not diagnosed until autopsy. The most common technique then used was cholecystoduodenostomy after ligation of the common duct (Fig. 44–3A). Even with seemingly satisfactory biliary drainage, the patients had an extraordinarily high incidence of bacteremia, which was probably caused by repeated contamination through the anastomosis.

We abandoned cholecystoduodenostomy

Figure 44–3 Techniques of biliary duct reconstruction used for most of the transplantation recipients in the Colorado series. A, Cholecystoduodenostomy. This operation is no longer performed. B, Cholecystojejunostomy. C, Choledochojejunostomy after removal of gallbladder. D, Choledochocholedochostomy. Note that the T-tube is placed, if possible, in recipient common duct. (From Surg. Gynecol. Obstet., 142:487–505, 1976.)
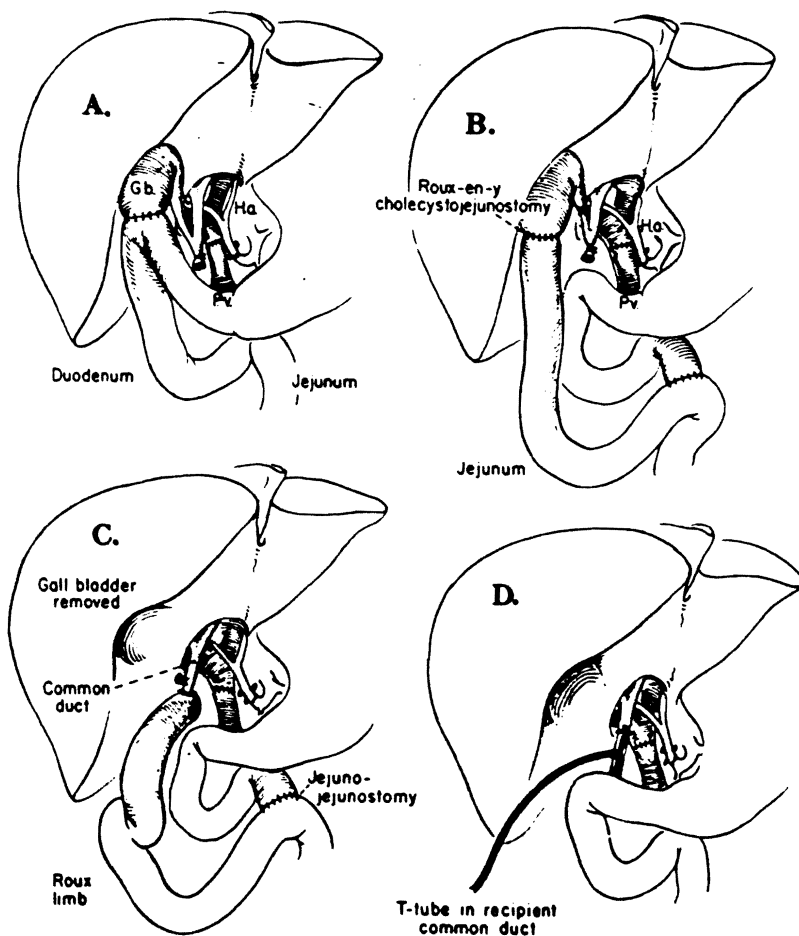
in 1974 and now do duct-to-duct anastomoses over a T tube (Fig. 44–3D) except in patients with biliary atresia. Reasonable options for treatment of that disease are cholecystojejunostomy (Fig. 44–3B) and choledochojejunostomy (Fig. 44–3C), using an 18-inch Roux limb. With cholecystojejunostomy, about a third of recipients develop obstruction of the cystic duct, but cholecystectomy and conversion to choledochoenterostomy (Fig. 44–3B, C) has proved to be easy. It may be safer to anastomose secondarily such a dilated common duct to bowel than to attempt this with the tiny common duct of a normal infant liver. Primary choledochocholedochostomies and choledochojejunostomies are drained through the wound, but this is not necessary with cholecystojejunostomies. Formation of a Roux limb is hazardous in heavily immunosuppressed recipients. Seven patients in our combined adult-pediatric series of 141 have died from later perforations at the enteroenterostomy.[5]

An important component of the reforms instituted several years ago was constant postoperative suspicion of the biliary reconstruction. Postoperative jaundice, fever, or abdominal pain has become a signal for cholangiography (usually T tube or transhepatic), re-exploration, or often both.

Anomalies have been common in children with biliary atresia. The most serious, which we have seen four times, was a combination of a preduodenal portal vein, an hepatic artery originating from the superior mesenteric artery, absent inferior vena cava, and malrotation of the gut.[3] We considered such cases to be untreatable until success was obtained in a child who is now 4 years and 4 months postoperative. Other less ominous donor and recipient anomalies and their technical implications are described elsewhere.[3]

In many patients, splenectomy is advisable because of hypersplenism or massive splenomegaly. Failure to remove the spleen may lead to an inability to give the important drug azathioprine in the postoperative period because of persistent leukopenia.

It is essential that hemostasis be meticulous before closing. Since full correction of clotting abnormalities may require hours or even days, the main recourse is mechanical hemostasis to which intravenous infusions of platelets and fresh frozen plasma may be added. Persistent hemorrhage is often from the back of one of the vascular anastomoses. Venous infarction of the right

adrenal gland may be responsible, since the right adrenal vein must be sacrificed during the recipient hepatectomy.[3] Adrenalectomy is the only way to control this kind of bleeding, which manifests as a diffuse ooze behind the right lobe of the liver.

POSTOPERATIVE MANAGEMENT

There are two fundamental guidelines. The first is to prevent or control rejection by combination drug therapy, which is begun on the day of operation and continued indefinitely thereafter. The second is to be sure that postoperative hepatic dysfunction is actually due to rejection. Numerous technical surgical pitfalls were mentioned earlier, of which biliary tract problems were the most important and treatable. Besides ruling out biliary complications with cholangiography, frequent liver biopsies can strengthen the diagnosis of rejection, or they can point out other possibilities such as ischemic or drug injury and hepatitis. In short, the patient should be approached unprejudicially as a diagnostic problem.

If other factors are ruled out, the patient's survival (short of retransplantation) depends upon control of rejection. Azathioprine (which can be replaced with cyclophosphamide) and prednisone are used.[1, 3, 4, 5] As much azathioprine is given as is possible without causing bone marrow depression and leukopenia. The prednisone dose may be varied to treat crises. We recommend, in addition, a 2- to 3-week course of intravenous ALG. Although these double or triple agent regimens usually can prevent or reverse rejection, the price of prolonged high-dose steroid therapy is all too frequently an inexorable decline of the patient's health capped in the end by a fatal infection.

To provide better immunologic control with less steroid treatment, we have in the last year used thoracic duct drainage as a lymphocyte-depleting immunosuppressive adjunct, usually starting on the day of transplantation and continuing for 1 to 3 months.[5] It is too early to judge the value of this procedure or to preclude the possibility that its greatest effectiveness will be for pretreatment in advance of transplantation. The next major improvement in survival will likely depend on improvement in the double and triple drug programs that have been so dangerous in the past.

RESULTS

The outcome in 74 pediatric patients treated 1 to almost 16 years ago is summarized in Table 44–1. Twenty-nine (40 per cent) of the 74 recipients lived for at least 1 year after operation, and 16 (22 per cent) still survive, all but 4 with follow-ups of more than 2 years. Ten of the 16 long survivors have follow-ups of at least 4 years with a maximum of 9 years. The 13 late deaths occurred from 1 to 6 years postoperatively at the exact times annotated in a footnote in Table 44–1. It has been documented that many of the patients who died after 1 year could have been identified as doomed at the 12-month convalescence mark[5] and might have been saved by earlier consideration of retransplantation.

Although the results have slowly improved over the years, the overall percentage of 1-year survival rate from 1963 to the summer of 1976 was only 35 per cent. By this time the technical and management improvements described earlier had been completed. From then until December 1977, the 1-year survival rate in pediatric recipients was 62 per cent.

The results in patients with biliary atresia were inferior to those with other diagnoses (Table 44–2), a 33 per cent versus a 50 per cent 1-year survival rate. The difficulties in patients with atresia were ascribable in part to technical difficulties of anastomosing small structures, problems that can be largely circumvented with microvascular techniques. Avoidance of patients with complex additional anomalies should also improve the record.

The quality of life achieved by long-term survivors is a particularly important issue in pediatric patients. A detailed study of this question in all our patients has been made.[5] It was mentioned earlier that the patients who died late were often identifiable by 12 months as unsatisfactory, having either poor liver function or dangerously high steroid requirements. This was reflected in hospitalization times that exceeded 50 per cent both

TABLE 44–2 ONE-YEAR AND LATER SURVIVAL WITH BILIARY ATRESIA VERSUS OTHER DISEASES

	Number	1-Year Survival	Survival Now (1-9 Years)
Biliary atresia	48	16 (33%)	8 (17%)
Other diseases	26	13 (50%)	8 (31%)

in the first year and afterward until the deaths of the patients. Almost all of the infants in this failed group created severe domiciliary problems for their parents. Of the preadolescents and teen-agers, only a few returned to school or work for significant periods of time. The best rehabilitation was in two patients who had an excellent clinical result at 1 year after treatment. A 4-year-old child was well for 3 years but sustained crippling liver and renal damage after a *Hemophilus* infection and died several weeks later. His homograft had chronic rejection. Another patient died from biliary tract complications and chronic rejection 6 years after transplantation for Wilson's disease.

In contrast to those who died after 1 year, the 16 patients who are still alive had an identifiably good prognosis at 12 months. At the 1-year mark, none were jaundiced and the average prednisone doses were reasonable. Although they spent about a third of their time in the hospital during the first year posttransplantation, they ultimately became independent of the institution, and after the first 12 months they have been hospitalized an average of less than 3 per cent of the time. The adolescents and children have been in public or special schools. Many of the children who were infants at the time of transplantation eventually became students. These children with good clinical results have tended to remain small as a result of long-term steroid therapy, but they have achieved steady growth.

Selected References

Perusal of the five references below will provide a nearly complete picture of the history and present state of liver transplantation. Scholars interested in original publications will be able to track these easily, especially in reference 3. Reference 5 is the most recently written, with a bibliography that is current to January 1979.

1. Calne, R. Y., and Williams, R.: Liver transplantation. In Ravitch, M. M. (ed.): Current Problems in Surgery. Chicago, Year Book Medical Publishers. 1979, pp. 3–44.
   The important clinical series of 74 cases from the Cambridge–Kings College London group are described, as well as laboratory research in these institutions. Although almost all of the recipients were adults, the opinions expressed have applicability to pediatric cases. Opinions about patient selection, biliary tract reconstruction, and immunosuppression are somewhat different from those expressed in this chapter.
2. Fortner, J. G., Yeh, S. D. J., Kim, D. K., Shui, M. H., and Kinne, D. W.: The case for technique of

heterotopic liver grafting. Transplant. Proc., 11: 269–275, 1979.

This collection of 43 clinical auxiliary liver transplantation cases from many different centers was presented to the International Transplantation Society in Rome, September, 1978. The case for auxiliary transplantation is presented optimistically, perhaps excessively so in view of the poor results.

3. Starzl, T. E. (with the assistance of Putnam, C. W.): Experience in Hepatic Transplantation. Philadelphia, W. B. Saunders Company, 1969, pp. 1–553.

This text contains the total world literature (299 references) on experimental and clinical liver transplantation to the spring of 1969, an account of all 42 human liver homotransplantations attempted to that time, including 29 (25 orthotopic, 4 auxiliary) at the University of Colorado, and detailed descriptions of surgical and anesthetic techniques; metabolic and immunoglobulin changes after liver transplantation are also described. The laboratory development and clinical practice of immunosuppression for all transplanted organs are reviewed. Two chapters by Professor K. A. Porter of St. Mary's Hospital and Medical School, London,

constitute a complete monograph on the pathology of animal and human auxiliary and orthotopic liver homografts as well as two chimpanzee to human heterografts.

4. Starzl, T. E., and Terblanche, J.: Hepatotrophic substances. In Popper, H., and Schaffner, F. (eds.): Progress in Liver diseases, Vol. 6. New York. Grune & Stratton, 1979, pp. 135–152.

A new field of portal physiology is summarized, describing the specific effects of venous blood from nonhepatic splanchnic organs in regulating liver structure and function and the capacity for regeneration. The material is relevant to planning optimal revascularization of any kind of liver homograft, but particularly one to be used as an auxiliary organ.

5. Starzl, T. E., Koep, L. J., Halgrimson, C. G., Hood, J., Schroter, G. P. J., Porter, K. A., and Weil, R., III: Fifteen years of clinical liver transplantation. Gastroenterology, 77:375–388, 1979.

The first 141 orthotopic liver homotransplantations at the University of Colorado are described. These include the 74 pediatric cases of this chapter plus 67 adult cases. There is detailed documentation of causes of early and especially late deaths. The recent literature of clinical liver transplantation is brought up to date.