40 Thomas E. Starzl / Shunzaburo Iwatsuki / Byers W. Shaw, Jr.
Liver Transplantation

There are two kinds of liver transplantations. In one (Fig 40–1), an extra organ is placed in an ectopic site (usually the right paravertebral gutter) and arterialized from a regional vessel, such as the distal aorta. The grafts need the so-called hepatotrophic factors in splanchic venous blood, and thus an effort is made to provide portal venous inflow from the splanchic system (see Fig 40–1). Venous outflow is arranged by anastomosing the graft vena cava to the recipient vena cava. Only two of 100 patients treated with this procedure throughout the world have had long survival. One of these recipients was a child.

The most encouraging results have been with the second approach, orthotopic transplantation (liver replacement), whereby the diseased organ is removed and replaced with a graft placed in the evacuated hepatic fossa. The blood vessels are reanastomosed in normal a way as possible, and provisions are made for biliary drainage (Fig 40–2). This chapter will be concerned with the orthotopic operation.

The Laboratory Origins

As with other organs, the central problem after liver transplantation has been the prevention of rejection. In untreated dog rejection begins in 3 or 4 days. On histopathologic examination mononuclear cells infiltrate the entire graft, but especially in the portal and central areas of the liver lobules. Massive necrosis eventually occurs. Prevention of this process of rejection has...
The Pace of Clinical Trials

Nevertheless, the first seven attempts at clinical transplantation in three different institutions were failures. It was not until 1967 that the first prolonged survival of a human recipient for more than a year was obtained. That first child subsequently died of metastases from the hepatoma for which she had been treated. In January 1970, a child with biliary atresia and an incidental hepatoma was given a new liver. She is now more than 14 years post-transplantation, the longest survival yet achieved. Over the years, an increasing number of chronic survivors have been reported by us, by Calne and Rolles et al., of England, from Holland, and from France, Canada, and China. In the United States, liver transplantation programs are active at our university (Pittsburgh) and at the universities of Tennessee, Minnesota, Harvard, and California. Many more are planned.

Until 1980, the first year cyclosporine was available, at the University of Colorado we performed between ten and 20 liver transplants per year. In 1981, at the University of Pittsburgh where our program was transferred, 30 liver transplants were performed. In 1982, the number was increased to 80 per year, and in 1983 the annual number was 104 (Fig 40-3). In the first 3 months of 1984, 35 transplants were performed at a pace that, if continued, will yield a yearly total of nearly 150.

During the 4 years since cyclosporine was introduced, 266 transplantations have been performed, compared with the 192 in the preceding 17 years. Our grand total of orthotopic liver transplantations by the end of March 1984 had reached 438 in 377 recipients. Retransplantation, a relatively easy undertaking, particularly if the first graft fails early, has been done 81 times.

Of the 377 patients treated with liver transplantation through March 1984, 169 (45%) were in the pediatric age category (less than 18 years). The following remarks will emphasize this pediatric portion of our total experience.

Indications for Liver Transplantation

Biliary Atresia.—Patients with biliary atresia or hypoplasia amounted for 94 of the 169 total pediatric liver recipients (Table 40-1). Although hepatic portoenterostomy is the first operation to be performed for children with biliary atresia, many such procedures are unsuccessful, leaving hepatic transplantation as the only option. The use of liver transplantation in infants and children sometimes has been questioned because of the unsatisfactory survival and high morbidity. Even after "successful" transplantation, the quality of life has too often been degraded by the side effects of high-dose corticosteroid therapy. That situation has changed since the use of cyclosporine-corticosteroid therapy.

The decision about candidacy in patients with biliary atresia and failed portoenterostomy is easy. In the past, these little victims have become pariahs of nature with a massive social, medical, and economic input, but with little meaningful ultimate benefit for themselves or their families. The synthetic function of the liver frequently is relatively good until shortly before death. Although these children always have had a previous operation, the technical difficulties at transplantation are only moderate. The most serious technical problems have been caused by anomalies of the portal vein or hepatic artery. There is no threat of disease recurrence.

Inborn Errors of Metabolism.—The second largest recipient group has been made up of children with several inborn errors of metabolism (see Table 40-1), including alpha-1-antitrypsin deficiency disease, Wilson's disease, tyrosinemia, glycogen metabolism.

The table above provides a summary of the indications for liver transplantation in pediatric patients under 18 years.

TABLE 40-1.—Indications for Liver Transplantation in Pediatric Patients ≤ 18 Years

<table>
<thead>
<tr>
<th>MAIN INDICATION</th>
<th>PRE-CYCLOSPORINE ERA</th>
<th>CYCLOSPORINE ERA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>March 1, 1965–February 29, 1980</td>
<td>March 1, 1980–March 31, 1984</td>
</tr>
<tr>
<td></td>
<td>No. Patients</td>
<td>No. Patients</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>51</td>
<td>43</td>
</tr>
<tr>
<td>Inborn metabolic errors</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Nonalcoholic cirrhosis</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Primary liver malignancies</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Congenital hepatic fibrosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Secondary biliary cirrhosis*</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Byler's disease</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Inflammatory pseudotumor</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Subacute hepatitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>53</td>
</tr>
</tbody>
</table>

*Trauma or choledochal cyst.
Indications for Liver Transplantation

storage diseases (GSD), the sea-blue histiocytic syndrome, and homozygous type 2 hypercholesterolemia (FH) (Table 40–2). A 6-year-old child with familial hypercholesterolemia also had her heart replaced at the same operation because of coronary artery and valvular disease, after two coronary bypass procedures and a valve replacement.

With the possible exception of the sea-blue histiocytic syndrome, the inborn metabolic abnormalities listed in Table 40–2 were cured or palliated by successful liver transplantation. The child with sea-blue histiocytic syndrome (which is a lipid storage disorder of unknown cause) had a progressive and very serious neurologic syndrome that was arrested but not reversed after successful liver transplantation. A liver biopsy of this patient 1 year postoperatively showed moderate disposition of lipid droplets. Although she is now more than 2 years postoperative, we do not believe that her basic problem has been corrected.

In contrast, patients with alpha-1-antitrypsin deficiency assume the protease inhibitor (Pi) type of their donors, and the low serum values of the alpha globulin are promptly and permanently restored to normal. The abnormal amino acid patterns of tyrosinemia are rectified within hours. The same holds true for the aberrations caused by glycogen storage diseases, as ex-

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**Fig 40-2—Completed orthotopic liver transplantation.** A, biliary tract reconstruction with choledochocholedochostomy. B, biliary tract reconstruction with choledochojejunostomy, using a Roux limb. (Used by permission.)

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**Fig 40-3—Orthotopic liver transplantsations at the University of Colorado (1963–1980) and the University of Pittsburgh (1981–1983): Number of liver grafts implanted per calendar year. Note the increasing numbers of second and third transplantations.**
emphsized by a patient with type 1 GSD who became able to fast for 1 or 2 days without the hypoglycemia that previously occurred within hours (Fig 40-4).

Some of these metabolic diseases are known to be caused by specific enzyme deficiencies. The pathogenesis of other disorders, such as Wilson's disease, has not been understood. This state of knowledge has not influenced the effectiveness of the "biochemical engineering" by organ transplantation in Wilson's disease, and it is now obvious that disease recurrence after liver transplantation need not be feared. Figure 40-5 depicts the course of a child with Wilson's disease who had liver transplantation more than 13 years ago. After operation, the serum ceruloplasmin rose from zero to normal levels. There was a massive decoppering process by copper excretion in the urine and probably feces, during which time Kayser-Fleischer rings disappeared, as shown by slit-lamp examination, and severe neurologic abnormalities were reversed.

The 6-year-old child with familial hypercholesterolemia whose heart and liver were replaced had a striking fall of serum cholesterol concentration from 1,000 mg% to new levels averaging 300 mg%. It is probable that the correction is incomplete, because the normal serum cholesterol in children of this age is about 150 mg%.

**CHRONIC ACTIVE HEPATITIS.**—The third leading indication for liver replacement in children has been chronic active hepatitis (nonalcoholic cirrhosis) (see Table 40-1). Twenty of our 169 childhood recipients had this diagnosis. Decisions about candidacy became relatively easy, once it was realized that no patient accepted as a candidate (for whom a liver could not be promptly

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**TABLE 40-2.—INBORN METABOLIC ERRORS TREATED WITH LIVER TRANSPLANTATION IN PEDIATRIC PATIENTS ≤ 18 YEARS**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Pre-Cyclosporine Era</th>
<th>Cyclosporine Era</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Patients</strong></td>
<td><strong>No. Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency disease</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sea-blue histiocytoid syndrome</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Homozygous familial hypercholesterolemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>21</td>
</tr>
</tbody>
</table>

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*Fig 40-4.—Response of blood glucose to fasting in a patient with type 1 glycogen storage disease before and after liver transplantation. (Used by permission.)*
found) lived for more than a few months. These patients present many problems in management. Some have had a portacaval shunt or other operation in the hepatic hilum. Their metabolic abnormalities when first seen often have been profound, and the removal of their small shrunken liver sometimes has presented extraordinary technical difficulties. Such patients have accounted for the legendary marathon operations of liver transplantation with the loss of dozens of units of blood.

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

**LE S S C O M M O N I N D I C A T I O N S.**—Other indications for liver transplantations in children are listed in Table 40-1. Many efforts have been made to treat unresectable primary hepatic malignancies. Most of this experience has been with adults, but a few children have been included (see Table 40-1). It was first thought that decision of candidacy was an easy matter, but tumor recurrence in our early experience was as high as 85%. We now believe that with better case selections, disease recurrence can be much less, although this has not been verified in children. Most patients with hepatic malignancies do not have overt liver failure. More than 90% have had previous operations, but the technical difficulties have not been great.

**Surgical Technique**

**The Donor Operation**

Having emphasized that the difficulty of transplantation is dictated largely by the original disease and previous operations, we turn now to some surgical details, beginning with the donor operation. The principles of liver removal, methods of hepatic preservation, and the relation of total hepatectomy to extirpation of other organs in the same donor were discussed in Chapter 38. Livers that are preserved with the potassium-rich Collins' solution before placing them in ice slush can be safely preserved for at least 6-8 hours, long enough to allow transport of the organs to the transplant center from any part of the United States. We have accepted livers in Pittsburgh from the East, West, and South coasts and from Canada. Livers have been successfully preserved for 11 or 12 hours on at least ten occasions. Similar logistic links exist in Europe, supplying livers to the English, Dutch, and German centers.

In infants and children whose livers are being obtained for grafting, it is often advisable to keep the celiac axis in continuity with the upper abdominal and thoracic aorta. The donor thoracic aorta can be turned down 180 degrees for anastomosis to the recipient's lower abdominal aorta (Fig 40-6). The use of the aortic anastomotic technique is particularly valuable when the liver graft receives part of its blood supply from the superior mesenteric artery, in which case the blood from both the celiac axis and the superior mesenteric arteries can be channeled into the liver with the single aortic anastomosis.

**Fig 40-5.**—Treatment with orthotopic liver transplantation in a 16-year-old boy with Wilson's disease. The operation was on March 23, 1971, and the patient is still alive. Note the massive urinary copper excretion postoperatively and the increase of serum ceruloplasmin to normal levels. The recipient's neurologic findings reversed slowly over a 2-year period, during which regression of Kayser-Fleischer rings was documented by ophthalmoscopic examination. Immunosuppression was with cyclophosphamide (or azathioprine, used interchangeably), prednisone, and antilymphocyte globulin. (SGPT = serum glutamic pyruvic transaminase).

**The Vascular Anastomoses**

The anastomoses (particularly of the artery and portal vein) and biliary reconstruction are more difficult and require more technical skill in children than in adults.

Transplantation begins with the vena cava anastomoses above
Chapter 40: Liver Transplantation

and below the liver. If the air entrapped in the graft is not washed out (Fig 40-7), bubbles that are released into the circulation can pass by right-to-left shunts, characteristically well developed in liver disease, to the systemic circulation and then pass to the brain. The cold saline or lactated Ringer’s solution, which is used for a final flush (Fig 40-7), washes out the potassium-rich preservation fluid from the liver before the circulation is opened.

If all goes quickly, the portal venous and arterial anastomoses are performed before blood is allowed to circulate through the liver. Otherwise, the portal circulation should be reopened first, allowing partial perfusion of the liver while the arterial anastomosis is being performed. Every effort is made to restore a partial or complete blood supply within 60 minutes of removing the graft from the refrigeration chamber.

We employ a continuous suture of monofilament polypropylene (Prolene) for all vascular anastomoses. To avoid purse-stringing, excessive traction on the continuous sutures is avoided. Each half of the circumference is completed with each end of an original corner suture. The knots for the portal vein and hepatic artery anastomoses are placed away from the vessel wall in order to leave extra Prolene that slowly works its way back into the suture line (Fig 40-8). This “growth factor” technique is an important means of eliminating strictures in the small-caliber anastomoses that must be constructed during liver transplantation in children.

Biliary Tract Reconstruction

The ideal form of biliary duct reconstruction is a choledochocholedochostomy with a T-tube stent (see Fig 40-2, A), but in patients with biliary atresia, that option does not exist. Cholecystoenterostomy, which depends upon bile drainage through the cystic duct, is not used because of the high incidence of subsequent obstruction of the cystic duct. End-to-side anastomosis of graft common duct to a Roux-en-Y loop of jejunum with an internal stent (choledochojejunostomy) has been the reconstruction of choice in cases of biliary atresia and for other disorders in which the recipient common duct is inadequate (see Fig 40-2, B). Choledochojejunostomy has proven to be one of the most satisfactory of all the methods of biliary reconstruction. Even the small common ducts of liver obtained from infant donors can be satisfactorily anastomosed to the intestine.

In patients with biliary atresia, the Roux limb previously constructed for hepatic portoenterostomy can be reused at the time of liver transplantation, providing the limb has not been irreparably damaged in the hilar dissection during recipient hepatectomy. The risk of Roux limb injury has been particularly great when an external jejunostomy was used with the Kasai procedure, in hope of decreasing cholangitis. Even if the ostomy has been closed by the time of transplantation, this portion of the Roux limb frequently has had to be resected, often with great difficulty.

Calne has recommended a procedure for biliary tract reconstruction that was originally described by Waddell and Grover. The donor common duct is anastomosed to the gallbladder, and the tip of the gallbladder is anastomosed to the intestine or to the recipient common duct. We rarely use this operation and limit its use to cases in which extra length is needed to bridge a gap between the donor ducts and recipient intestine.

Immunosuppression and Survival

As was summarized in Chapter 38, the immunosuppression used to prevent rejection of hepatic grafts was developed with
the far simpler clinical model of renal transplantation. The main regimens developed in renal transplantation are summarized in Table 38-1. The "modern era" of transplantation began with the so-called double-drug treatment with azathioprine plus prednisone. When antilymphocyte globulin (ALG) was used to potentiate the effectiveness of azathioprine and prednisone, the regimen became known as triple-drug therapy.

Most of the 170 orthotopic liver recipients who were treated before March 1980 were given the triple-drug immunosuppressive cocktail (see Fig 40–5) of azathioprine (or cyclophosphamide), prednisone, and ALG. Almost two out of every three recipients during this 17-year period died before the end of the first postoperative year (Fig 40–9). Between March 1980 and early November 1983, another 170 patients were treated, this time with cyclosporine and corticosteroids as described in Chapter 38. The overall results, pooling both adult and pediatric recipients, were greatly improved (see Fig 40–9) in that two out of every three recipients now survived for at least 12 months or, by actuarial analysis, are expected to survive.

Conventional Immunosuppression

Both in our early experience with conventional immunosuppression and subsequently, the results were better in the children than in adults. Of the 170 patients treated with conventional immunosuppression between 1963 and 1980, 86 were children. Survival of the children was about 10% better throughout the observation period (Fig 40–10).

Fifty-three of the 86 childhood patients died within a year after transplantation under conventional immunosuppression. The causes of death were usually multiple, but a single most important factor was usually identifiable (Table 40–3). Bacterial, fungal, and viral infections were the main causes of death. There

<table>
<thead>
<tr>
<th>TABLE 40-3.—MAIN CAUSES OF DEATH WITHIN A YEAR AFTER LIVER TRANSPLANTATION AMONG 86 CHILDREN IN PRE-CYCLOSPORINE ERA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE-CYCLOSPORINE ERA (86 CHILDREN)</td>
</tr>
<tr>
<td>Intra- and perioperative death</td>
</tr>
<tr>
<td>Technical surgical complication</td>
</tr>
<tr>
<td>Unsatisfactory liver graft</td>
</tr>
<tr>
<td>Graft rejection</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Recurrent malignancy</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*One died from pulmonary emboli at 52 days and another from respiratory insufficiency resulting from an oversized graft.
were 9 deaths from abdominal sepsis, 5 from viral infection (adenovirus, chickenpox, and herpes), 4 from systemic bacterial and fungal sepsis, and 2 from pulmonary infections. Technical surgical complications played a significant role, contributing to 15 deaths (see Table 40-3). Eight of the 15 technical failures were of biliary duct reconstruction, and the other seven were of the vascular anastomoses (4 hepatic artery, 3 portal vein, and 1 suprahepatic vena cava).

The kind of data shown in Table 40-3 undoubtedly understates the role of rejection in the high rate of failure under conventional immunosuppression. Although irreversible rejection was only third as a cause of death, the enormous incidence of infectious complications reflected the necessity for excessive immunosuppression in order to maintain satisfactory function of the grafts. There was no margin of safety between a satisfactory therapeutic level of immunosuppression and toxicity.

The 1-year actual survival of the 86 pediatric recipients in the pre-cyclosporine era is shown in Figure 40-11. The survival of children with biliary atresia was substantially lower than that with other diseases, and it was markedly inferior to that of children treated for inborn metabolic errors. The poor survival with biliary atresia was partly due to the fact that previous major procedures, such as hepatic portoenterostomy, made the transplant operations more difficult. In addition, anatomical anomalies such as hypoplastic, sclerotic, and sometimes thrombosed portal veins were more common in children with advanced biliary atresia.

Cyclosporine-Corticosteroid Therapy

The survival expectations have greatly increased in patients whose immunosuppression has been with cyclosporine-corticosteroid therapy. During the last 4 years, 83 pediatric recipients have been treated, and, of these, almost three fourths are still alive. The actual survival of patients followed for at least 1 year and the actuarial projections of the much larger group shown in Figure 40-12 are similar, although the chances of survival have improved during the last year as will be noted later. The children with biliary atresia have continued to fare less well than those with other hepatic diseases, and the superior results in inborn errors of metabolism noted in the pre-cyclosporine era have continued. Death from infection has almost been eliminated.

Reduction of Perioperative Mortality

Although the improvement in survival coincident with the introduction of cyclosporine-corticosteroid therapy was encouraging, the perioperative mortality continued to be unacceptable both in adults and children until relatively recently. An assessment in early 1983 of the reasons for the early mortality suggested that many of the losses could be avoided by more effective dose control of cyclosporine and by more aggressive use of retransplantation.

DOUBLE-ROUTE ADMINISTRATION OF CYCLOSPORINE.—Since early 1983, cyclosporine has been given intravenously as well as orally during the first few postoperative weeks. When pharma-
The Place of Liver Transplantation in Pediatric Hepatology

TABLE 40-4.—PEDIATRIC PATIENTS TREATED FROM MARCH 1, 1983—APRIL 1, 1984

<table>
<thead>
<tr>
<th>Patients</th>
<th>Alive</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>33*</td>
<td>3</td>
</tr>
</tbody>
</table>

*Eight after retransplantation.
†One after retransplantation.

tation in children. Beginning March 1, 1983, and ending in late March 1984, 36 patients have been treated with orthotopic liver transplantation. Thirty-three (91.6%) of these recipients are alive (Table 40-4). Of the 33 survivors, eight are alive by virtue of retransplantation. Two of these survivors have had two retransplantations. If aggressive retransplantation had not been performed, the present survival of this group of patients would have been less than 70%.

The reasons for the 11 retransplantations in nine children are summarized in Table 40-5. Rejection was the leading cause of graft loss. Hepatic artery thrombosis was a close second. The hepatic artery thromboses have not necessarily represented technical errors, because in several instances the arteries have thrombosed as they originated from aortic grafts, which in turn were Anastomosed to the recipient aorta. In experimental animals, rejection is associated with low flow. Thus, the underlying factor may have been incomplete control of rejection.

Age vs. Survival of the Child Recipient

Iwatsuki et al. have studied the influence of age at the time of liver transplantation upon survival in a group of patients for whom at least 15 months follow-up was available. In the pre-cyclosporine era, 28 (53%) of 53 infants and preschool children (less than 6 years), 8 (50%) of 16 school-age children (between 6 and 12 years), and 13 (76%) of 17 adolescents lived more than 3 months (Fig 40-14). In the cyclosporine era, 16 (76%) of 21 infants and preschool children, 8 (67%) of 12 school-age children, and 6 (86%) of 7 adolescents lived more than 3 months (see Fig 40-14). Thus, the 3-month survival of infants and preschool children was similar to that of school-age children both in the pre-cyclosporine era and the cyclosporine era. Five of seven (71%) infants less than a year old lived more than 3 months. The technical difficulties in infant surgery have been overcome in liver transplantation. The age of children should not be a consideration in accepting them as candidates for liver transplantation, though liver donors for very small infants are quite scarce.

The Place of Liver Transplantation in Pediatric Hepatology

With the major improvements in patient survival that began in 1980, it was not surprising that a Consensus Development Conference held in 1983 in Bethesda, Maryland, came to the conclusion that liver transplantation was a service rather than an
The positive Consensus Development Conference has opened the possibility of much broader funding for liver transplantation and for the establishment of an interconnecting series of centers in the United States that could share both organs and recipients. Our estimate is that 30 centers will be needed in the United States. The majority will serve both adults and the pediatric population. The need for only low doses of corticosteroids in patients treated with cyclosporine has allowed child recipients of various organs to grow and develop in a way not previously possible using conventional immunosuppression.17

We have within our grasp the means by which the practice of hepatology can be changed in the same way as became possible in nephrology with the development of renal transplantation. The exploitation of these advances will require regional transplantation centers. Procedures of marginal benefit such as portal diversion for variceal hemorrhage and repetitive biliary tract reconstructions in diseases such as biliary atresia will become less common as it is appreciated that the final option of liver transplantation can be severely jeopardized by earlier interventions.

The use of liver transplantation for "metabolic engineering" will be a special feature of liver transplantation in pediatric hospitals. The principle of permanently correcting hepatic-based inborn errors of metabolism with liver transplantation has been validated.

REFERENCES