Indications and Timing of Liver Transplantation in Metabolic Disorders

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There are several metabolic disorders which are known to evolve toward end-stage liver failure and which nowadays are generally accepted as indications for orthotopic liver transplantation (1–15). Complete cure of the basic pathology can be expected only in those metabolic disorders that are primarily restricted to the liver. Reports on liver transplantation for metabolic disorders, although still sparse, are promising (3,5,7–10,13–16).

The metabolic diseases form only a small but still important group among the patients in whom liver transplantation is indicated (Table 1). In an update to 31.12.1988, the European Liver Transplantation Registry (11) reported a frequency of 5% of metabolic diseases in 2962 patients transplanted in 55 centers throughout Europe (Table 2). Within the group of metabolic disorders, the pediatric patients evidently comprised the majority (14.6% versus 3%). In this chapter we review our experience with 23 patients who received a liver graft for various inborn errors of metabolism in order to evaluate the indications, the timing, and the results that can be obtained in this group.

PATIENTS

From 1984 to 1988, 210 patients underwent liver transplantation at the University of Louvain Medical School in Brussels. There were 117 children and 93 adults (Table 1). Metabolic disorders represented 15.4% of the indications for liver transplantation in children and 5.3% in adults (Table 2). The different indications for liver transplantation in metabolic disorders are listed in Table 3. There were three patients with α1-antitrypsin deficiency. Wilson disease was encountered in seven patients,

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### TABLE 1. Indications for orthotopic liver transplantation (1984–1988,

<table>
<thead>
<tr>
<th>Condition</th>
<th>Children (n = 117)</th>
<th>Adults (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic liver failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Ductular paucity</td>
<td>4</td>
<td></td>
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<tr>
<td>Sclerosing cholangitis</td>
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<td>2</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Secondary biliary cirrhosis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Posthepatic biliary cirrhosis</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>3</td>
<td>19</td>
</tr>
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<td>Alcoholic cirrhosis</td>
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<td>5</td>
</tr>
<tr>
<td>Autoimmune cirrhosis</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Liver tumors</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital liver fibrosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vitamin A intoxication</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hemosiderosis</td>
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</tr>
</tbody>
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### TABLE 2. Liver transplantation in inborn errors of metabolism*

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Inborn errors</th>
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</thead>
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<tr>
<td>ELTR</td>
<td>2,962</td>
<td>147 (5%)</td>
</tr>
<tr>
<td>Adults</td>
<td>2,462</td>
<td>74 (3%)</td>
</tr>
<tr>
<td>Children</td>
<td>500</td>
<td>73 (14.6%)</td>
</tr>
<tr>
<td>UCL</td>
<td>210</td>
<td>23 (10.9%)</td>
</tr>
<tr>
<td>Adults</td>
<td>93</td>
<td>5 (5.3%)</td>
</tr>
<tr>
<td>Children</td>
<td>117</td>
<td>18 (15.4%)</td>
</tr>
</tbody>
</table>

* ELTR, European Liver Transplant Registry (55 centers); UCL, University of Louvain Medical School, Brussels.

### TABLE 3. UCL experience in inborn errors of metabolism

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adults</th>
<th>Children</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-1-Antitrypsin deficiency</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome type I</td>
<td>—</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Glycogen storage disease types I and IV</td>
<td>—</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>—</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Byler disease</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>18</td>
<td>23</td>
</tr>
</tbody>
</table>
while two children had a Crigler-Najjar syndrome type I. There was one patient with glycogen storage disease type I and one with type IV glycogen storage disease. Tyrosinemia was encountered in two children and Byler disease in seven patients.

The age of onset of symptoms and the age of transplantation are listed in Table 4. In two of the three patients with α1-antitrypsin deficiency, onset of symptoms was within the first year of life. On the other hand, in patients with Wilson's disease the onset of symptoms was mainly in the second decade. As expected in patients with Crigler-Najjar syndrome type I, onset of symptoms was within the first months of life, while the two patients with a glycogen storage disease displayed first symptoms at 5 months. Symptoms associated with tyrosinemia were first encountered at 3 and 8 months, respectively. Finally, Byler disease usually started within the first year of life. The actuarial survival rate, as displayed in Fig. 1, is 76% at 5 years.

CASE HISTORIES

α1-Antitrypsin Deficiency

Between 1984 and 1988, three patients with α1-antitrypsin deficiency underwent orthotopic liver transplantation (OLT). The first patient (OLT 2) presented with onset
of symptoms at 5 months. The parents and later also a younger brother appeared to be heterozygote PiMZ. The patient was phenotyped as PiZZ. At the age of 10 years, there was a sudden liver deterioration and liver transplantation was performed. There was a reintervention for biliary obstruction, after which liver function normalized. There was a postoperative phenotype switch to PiMM and α-1-antitrypsin levels normalized. He is now 4.8 years post-OLT and doing well.

The second patient (OLT 53) displayed a neonatal hepatitis during the first 2 months of life. α-1-Antitrypsin deficiency was diagnosed as his twin brother died at age of 3 years. He was transplanted at the age of 5 years. There was a prolonged elevation of liver enzymes postoperatively because of a stenosis of the hepatic artery. At 6 months post-OLT, he presented with an Epstein-Barr virus infection with transient liver dysfunction. At 2 years and 4 months post-OLT, he is doing well.

In these two young patients there have been no pulmonary manifestations of the disease. This is different in the third patient (OLT 70), who presented primarily with emphysema with diffusion disturbances. At the age of 26, she suffered from an acute deterioration of liver function, indicating urgent liver transplantation. The postoperative course was troubled by several rejection episodes finally resulting in chronic rejection. She was retransplanted after 4 months, but suffered from thrombosis of the hepatic artery 5 weeks later. Ultimately she developed multiple organ failure complicated by hepatic abscess. She died while waiting for retransplantation.

Wilson's Disease

The first patient (OLT 13) had a "Wilson-like" liver disease that started during the first year of life; he was later diagnosed as having copper intoxication. He was transplanted at the age of 19.5 years and is doing well 4 years after transplantation.

The second patient (OLT 20) presented with first symptoms at the age of 23 years. One year after first onset of symptoms, she suffered from severe variceal hemorrhage with rapidly progressing liver failure and encephalopathy with coma grade I. She underwent urgent liver transplantation and is doing well 3.5 years post-OLT.

The third patient (OLT 50) had onset of symptoms at the age of 13 years. After the diagnosis was made, the patient was treated initially with d-penicillamine but suffered from acute hepatic failure after discontinuance of chelating therapy with grade I coma status. This patient underwent urgent liver transplantation and is doing well 2.5 years post-OLT.

The fourth patient (OLT 73) presented with first symptoms at the age of 11 years. He did not respond to chelating therapy and suffered from fulminant liver failure with grade III coma status. He underwent emergency transplantation with an ABO-incompatible liver graft, experiencing substantial blood losses during the operation in spite of venovenous bypass. Ten days later he had to be retransplanted with a reduced size liver because of severe graft dysfunction. The postoperative course was complicated by an aspergillus pneumonia, which eventually led to his death.

The fifth patient (OLT 81) presented with liver enzyme abnormality during routine
checkup at the age of 17 years. Before further diagnosis could be performed, she underwent urgent admission for fulminant liver failure with coma grade IV. Because of onset of multiple organ failure, she underwent combined hepatorenal transplantation. The postoperative course was complicated by a superinfection with aspergillosis and cholangitis. This patient had to be retransplanted 3 days later, and although liver function improved, there was a disturbance of the patient’s cerebral condition. She eventually died of multiple organ failure.

The sixth patient (OLT 92) had onset of symptoms at the age of 10.5 years. He responded only temporary to d-penicillamine treatment and was transplanted with reduced size liver. The postoperative course was complicated by thrombophlebitis of the cerebral sinus, inducing convulsions. He also developed a coagulopathy resulting in intracerebral bleeding and death. A sister of this patient later also appeared to have Wilson’s disease.

The last patient (OLT 175) first presented with a fulminant liver failure and underwent emergency transplantation with an ABO-incompatible liver. This patient had to be retransplanted after occurrence of arterial thrombosis of the graft during reintervention for an obstructive ileus. The course thereafter was uneventful.

**Crigler-Najjar Syndrome Type I**

Two patients were transplanted for a Crigler-Najjar type I glucoronol transferase deficiency. The first child (OLT 14) thrived fairly well on phenobarbital until he had an ENT infection at 4 years of age. He thereafter developed progressive psychomotor retardation. He was transplanted at the age of 8 years with an uneventful postoperative course. At 4 years post-OLT liver function is normal but the child still displays some fine motor coordination disturbances.

The second child (OLT 77) remained clinically stable on phototherapy and cholestyramine medication. He was transplanted electively at the age of 2 years and 5 months. There were many postoperative complications because the donor liver turned out to be from a patient that had died of generalized tuberculosis. The patient is now 2 years post-OLT with normal liver function.

**Glycogen Storage Disease Types I and IV**

One patient (OLT 37) had a type I glucose-6-phosphatase deficiency presenting with recurrent episodes of hypoglycemic convulsions and therapy-resistant metabolic acidosis. He was therefore transplanted at the age of 7 years. The postoperative course was complicated by thrombosis of the hepatic artery at day 10 necessitating re-transplantation with an ABO-incompatible liver graft. Apart from two rejection episodes he is doing well 3 years post-OLT with normal liver function.

The other patient (OLT 136) had a type IV branching enzyme deficiency with progressive hepatic insufficiency. He underwent a reduced size liver transplantation at the age of 14 months. The decision for transplantation was influenced by the death
of an older brother from glycogenosis type 4 at the age of 20 months. The postoperative course was uneventful with full restoration of liver function. At 9 months post-OLT the child developed cardiomyopathy related to abnormal glycogen deposits. He died of cardiac decompensation complicated by pulmonary infection 11 months post-OLT, while awaiting cardiac transplantation.

Tyrosinemia

The first patient (OLT 143) presented primarily with progressive hepatic insufficiency and cirrhosis at the age of 8 months. Creatinine clearance was not impaired. He underwent reduced size liver transplantation at 1 year of age. He was reoperated 2 days later for a twisting of the hepatic artery. Two rejection episodes evolved toward chronic rejection; he was re-transplanted 15 months after the first transplant but died of complications due to an Epstein-Barr infection.

The second patient (OLT 232) had a brother who had died of tyrosinemia. Diagnosis was made at the age of 3 months. She developed acute liver insufficiency and had elevated α-fetoprotein levels. She was urgently transplanted at the age of 5 with a split liver graft. No tumor was found at pathological examination of the recipient liver, and the patient is now 6 months post-OLT with normal liver function. Aminolevulinate levels have also normalized.

Byler Disease

Byler disease was diagnosed in seven patients. Pruritus was a dominent symptom in all patients and started shortly after onset of jaundice. Bilirubin levels and liver enzymes, with the exception of the gamma-GT, were increased.

The first patient (OLT 43) developed an acute decompensation of his liver function at the age of 1 year and underwent urgent reduced-size liver transplantation. The child is now 2.5 years post-OLT with normal liver function.

The second patient (OLT 46) was transplanted electively for cirrhosis at the age of 4 years and 10 months. A reconstruction of the biliary digestive anastomosis was carried out 4 months post-OLT. He is now 2.5 years post-OLT with normal liver function.

The third patient (OLT 61) presented with icterus at the age of 2 years. He was transplanted at the age of 6 years and is now more than 2 years post-OLT with slightly raised liver enzymes due to a non-A, non-B hepatitis.

The fourth patient (OLT 90) was transplanted at the age of 2 years. The postoperative course was complicated by thrombosis of the hepatic artery and bile duct obstruction, necessitating reintervention. She is now 1 year and 9 months post-OLT with normal liver function.

The fifth patient (OLT 154) was transplanted at the age of 5.5 years. He is now 10 months post-OLT and doing well, with normal liver function.

The sixth and seventh patients were sister and brother (OLT 197, 217) who were
transplanted at the age of 15 years and 14 years, respectively. Both have normal liver function 6 months and 3 months post-OLT, respectively.

DISCUSSION

Liver transplantation for inborn errors of metabolism comprises only a small group of patients. According to the European Liver Transplant Registry, which has assembled all the data from 55 centers in 12 European countries, 147 patients (5%) underwent liver transplantation for inborn errors of metabolism (11). Of these 147 patients, 23 (15.6%) were transplanted at the University of Louvain Medical School in Brussels (UCL).

It was the aim of this study to evaluate the results regarding indication, timing, and outcome of liver transplantation for inborn errors of metabolism. Liver transplantation should be considered in those metabolic disorders where the disease is threatening life or the central nervous system; or in those instances where the disease is responsible for a poor quality of life. It is important, however, to take into consideration whether the metabolic disorder is restricted to the liver (i.e., whether complete cure of the disorder can be obtained by transplantation). The timing is important because it is evident that recovery is possible only if transplantation is performed before irreversible extrahepatic manifestations develop.

Complete cure of inborn errors of metabolism can be expected when the defective protein is normally excreted by the liver, when the defective enzyme is located exclusively in the liver, or when the defective membrane receptors are located mainly in the liver.

α-1-Antitrypsin deficiency is a hereditary disorder affecting the transfer of the glycan moiety of the glycoprotein, resulting in accumulation of insoluble material within the endoplasmic reticulum. This accumulation, observed in the phenotype PiZZ, is responsible for hepatocyte dysfunction, resulting in cirrhosis, portal hypertension and liver failure (4,12). After transplantation there is a phenotype switch to PiMM of the donor. Pulmonary lesions, as observed in one of our patients, can be expected to be prevented or halted by liver transplantation. An association between α-1-antitrypsin-deficiency-related cirrhosis and primary liver carcinoma has been described. Therefore, liver transplantation should be performed before onset of pulmonary lesions or gastrointestinal bleeding precipitating liver failure.

Crigler-Najjar syndrome type I is a hereditary disorder with a glucuronyl transferase enzyme deficiency leading to kernicterus in the first 18 months of life (4,17, 18), although in some instances, for example in one of our patients, progressive brain damage may be delayed. Palliative therapy consists of long hours of phototherapy, putting a heavy burden on both patient and parents. Liver transplantation is indicated when phototherapy cannot maintain serum bilirubin levels below 15 mg %, which in most cases will be during early childhood. Since the enzyme deficiency is restricted to the liver, transplantation brings complete cure.
Wilson's disease is a hereditary disorder of Cu metabolism in which there is a defective mobilization of Cu from hepatocellular lysosomes for excretion in the bile (7,12,19). The toxic accumulation of Cu results in liver and brain damage. The chronic form of Wilson's disease usually responds to chelating therapy with d-penicillamine, which promotes Cu excretion in the urine (4,7,12,20). In contrast, acute Wilson disease presents as a fulminating hepatic failure with renal impairment and massive nonimmune hemolysis with a high mortality. In our series, six patients rapidly progressed toward hepatic failure necessitating urgent or emergency transplantation. We therefore underline the conclusions of Schenker (14) and Sternlieb (21) that liver transplantation should be performed as soon as possible in patients presenting with a clinical picture of fulminant hepatitis. It should furthermore be considered in young cirrhotic patients who have failed to respond to chelating therapy with d-penicillamine or in patients effectively treated but who relapse after cessation of chelating therapy. This is a problem especially encountered in young adolescents who are sometimes difficult to motivate to continue their chelating therapy.

Hereditary tyrosinemia is a deficiency of the liver enzyme fumaryl acetoacetate fumaryl hydrolase and is characterized by progressive hepatocellular damage, tubular dysfunction, and hypophosphatemic rickets (1–4,7,12,13,22,23). In the neonatal form, presenting in the first 3 months of life, death from liver failure usually occurs by 8–12 months of age. Both our patients presented with their first symptoms within 2 months after birth, and a brother of one of them had died in the neonatal period of tyrosinemia. In the more chronic courses, hepatocellular carcinoma is responsible for about 60% of the mortality in these patients (2,7), so α-fetoprotein should be monitored in these patients. In our series we observed no hepatoma.

Because of the course of the disease and the risk of hepatoma formation, patients with tyrosinemia should be transplanted during early childhood or even in infancy when presenting symptoms in the neonatal period. With current new techniques of reduced- and split liver transplantation in children under 1 year of age becomes feasible (24,25) despite the shortage of small donors.

Byler disease is a hereditary disorder in which there is an inborn error of bile acid metabolism with difficulties in excreting bilirubin and bile acids. The disease ultimately leads to cirrhosis, portal hypertension, and death due to hepatic failure usually before the age of 15 years. Liver transplantation completely cures this disease, as was demonstrated in our patients.

Familial hypercholesterolemia is a hereditary disorder resulting from the absence of LDL cell membrane receptors with accumulation of lipoproteins and cholesterol in the plasma. Patients ultimately die of myocardial infarction before the age of 20 years because of severe atherosclerosis. Because of the extrahepatic manifestation of this disease, combined heart–liver transplantation might be necessary to cure these patients (7,10,26–28).

In inborn errors of metabolism with extrahepatic manifestations, usually involving the kidney, that have no life-threatening consequences, liver transplantation may significantly improve the patient's condition. Glycogen storage disease type I is a hereditary disorder with glucose-6-phosphatase deficiency (4,7,29). In patients in
whom metabolic acidosis does not respond adequately to medical treatment, liver transplantation may be considered (4,7,12,13,29). One of our patients with a glycogenosis type I benefited well from liver transplantation. In glycogenosis types III and VI, liver transplantation would only be indicated in case of concomitant liver tumor. Another group of metabolic disorders that could significantly benefit from liver transplantation are those in which toxic metabolites could be removed by the grafted liver. Examples are methioninemia, homocystinuria, and maple syrup urine disease. So far, however, no cases of liver transplantation have been described for these indications. Finally, there is a group of inborn errors for which liver transplantation could be beneficial but would not be curative because the disorder affects organs other than the liver. Glycogenosis type IV is a branching enzyme deficiency affecting other organs such as muscle, including the heart, brain, and leukocytes (12, 15,30). One of our patients with a glycogenosis type IV initially benefited from liver transplantation but later died from cardiac failure. Hyperoxaluria type I is a hereditary disorder of the glyoxylate metabolism and patients ultimately die from renal failure. Watts et al. (31) described a successful combined hepatorenal transplantation in a patient with hyperoxaluria type I. The role of liver transplantation in protoporphyria is uncertain. This is a highly variable autosomal disorder characterized by photosensitivity and elevated levels of protoporphyrin in erythrocytes, plasma, and feces. When jaundice complicates the liver disease, death is probable within a few months. Successful liver transplantation was described in the short term, but it is uncertain whether excessive protoporphyrin will be deposited in the grafted liver and cause progressive liver damage (4,32,33).

CONCLUSION

In conclusion, with a 76% actuarial survival rate, liver transplantation has become an accepted mode of therapy in a number of inborn errors of metabolism. In metabolic disorders in which the liver is the primary affected organ, complete cure can be obtained. Otherwise, prognosis is determined by the extrahepatic extension of the disease. Timing of liver transplantation should, if possible, be elective. However, when patients present with symptoms of fulminant hepatitis or acute liver failure, rapid decision making is obligatory.

With improved prognosis in liver transplantation, new indications come to light. With the development of alternative techniques, such as auxiliary liver transplantation, perhaps in the future other modes of treatment for some inborn errors of metabolism will become available.

REFERENCES

DISCUSSION

Dr. Mowat: Concerning the number of children who die very early in life, who have metabolic disorders with disastrous effects in the first week of life, do you see any possibility of liver transplantation in newborn infants?

Dr. Otte: From the technical point of view we would easily perform a transplant in a patient with metabolic disease. An operation on a child with Crigler-Najjar is an easy operation technically, although we have to use a sophisticated technique. So from the technical point of view that is possible. Surgeons must be trained in pediatric surgery, and in microvascular surgery. The second question is: How easily do these small children tolerate surgery, and how easily do they tolerate the post-transplantation period? I must confess that at the beginning, when we started the program, I was not convinced myself that very small children should be transplanted. Basil Zitelli of Pittsburgh (USA) was one of the pediatricians who convinced me that I had to change my mind, and that small children did well. This has turned out to be true. The main problem is the donor, since very small donors are extremely scarce. We don't use donors less than 1 month of age because the liver is not mature. Therefore, we often have to use a reduced-size liver from an older donor. There is an increased incidence of thrombosis if the donor is very young. In conclusion my answer is yes, but these very small children should be taken care of by extremely specialized teams having experience with such children.

Dr. Casaer: When you have a child with Crigler-Najjar syndrome on the waiting list and you would like to have a neurological variable to assess any bilirubin toxicity that might still be reversible, I would suggest that you do regular brain stem evoked responses. Bilirubin toxicity for the eight cranial nerve and its brain stem nuclei has been well established in young infants; it could therefore be useful in these children, especially since you ask for a variable that could almost predict the moment at which damage to nervous system tissue occurs.

Dr. Otte: I am not the right person to answer the question, except that as a clinician I am only interested in some way of predicting the time when brain damage is going to develop. When the first child with Crigler-Najjar and brain damage was put on the waiting list, we had a lot of discussion and some people hypothesized that the damage might be reversible, but it is not since it is caused by necrosis. We have not been presented since then with another child having encephalopathy. I don't know what I would do. We would discuss it with the parents. But the other children had no encephalopathy. The transplantation was successful in the first child, but he has neurologic sequelae and the quality of his life has not been improved as much as we hoped. I think that liver transplantation is a too major a procedure to be offered to a child as a palliation. It should be curative. So if the child has complications of his disease which are not reversible after liver transplantation, the balance between the advantages and the disadvantages is doubtful.

Dr. Odievre: In the Crigler-Najjar disease, the problem is relatively simple. We can maintain patients in good condition for many years by controlling the index of bilirubin saturation of albumin and thus adjust the daily duration of phototherapy in order to maintain this index under 60%. The problem is when these patients develop acute infectious disease; the investigations then have to be repeated several times a week because the index may increase to 70 or 80%.
necessitating 14 or 15 h of phototherapy each day instead of 12 h. Because of these problems, the patients should be transplanted when they are 5 years of age or sometimes earlier.

*Dr. Otte:* Maybe this is an aspect of importance. You have to choose the age when the transplantation has to be performed. I think it should be done before the age of 6, when the child enters school.

*Dr. Mowat:* It is also very important for us as pediatricians to make sure that the parents of potential donors have the opportunity of providing organs for transplantation.