Liver Transplantation for Inborn Errors of Metabolism

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During recent years, liver transplantation has become a realistic alternative for the treatment of usually fatal types of liver disease. The list of diseases for which it has been performed has become extensive. In children, biliary atresia represents the most common diagnosis; metabolic disorders form the next largest category. Table 1 illustrates the metabolic diseases for which transplantation has been performed. The number of children who have been treated for this group of diseases at the University of Pittsburgh is shown in Table 2, indicating the relative frequency of such diseases among the first 1,000 adult and pediatric cases transplanted (1). For the most part, candidates for transplantation have cirrhosis, liver failure, and risk of developing hepatoma. Replacement of the liver cures the severely affected organ and also corrects the enzyme deficiency. Other candidates include children in whom the metabolic disorder is not associated with hepatic injury but invariably terminates in brain damage or other types of extrahepatic complications. The experience with these rare conditions remains limited.

METABOLIC DISEASES WITH LIVER DAMAGE

α-1-Antitrypsin Deficiency

α-1-Antitrypsin, the principal serum protease inhibitor, is a glycoprotein produced in the hepatocyte and secreted at a rate that maintains serum concentrations of 150–200 mg/dl. This molecule shows a remarkable degree of genetic heterogeneity and at least 75 variants have been identified by isoelectric focusing and other techniques. The most common form is type M; the best studied variant is type Z. Individuals with the PiZZ state have α-1-antitrypsin levels that are 10–15% of normal.

Incidence

Deficiency of α-1-antitrypsin is relatively common, occurring as an autosomal recessive inherited disorder in 1 in 1,500 to 1 in 4,000 live births (2).
TABLE 1. Disorders of metabolism for which liver transplantation has been carried out

<table>
<thead>
<tr>
<th>With liver damage</th>
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<tbody>
<tr>
<td>α-1-Antitrypsin deficiency</td>
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<tr>
<td>Wilson’s disease</td>
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<tr>
<td>Hereditary tyrosinemia</td>
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<tr>
<td>Glycogen storage diseases types 1 and 4</td>
</tr>
<tr>
<td>Protoporphyria</td>
</tr>
<tr>
<td>Galactosemia</td>
</tr>
<tr>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Without liver damage</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome type I</td>
</tr>
<tr>
<td>Hyperoxaluria, type I</td>
</tr>
<tr>
<td>Niemann-Pick disease</td>
</tr>
<tr>
<td>Sea blue histiocyte syndrome</td>
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<tr>
<td>Familial hypercholesterolemia type II</td>
</tr>
<tr>
<td>Urea cycle</td>
</tr>
<tr>
<td>Protein C deficiency</td>
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<tr>
<td>Hemophilia</td>
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<tr>
<td>Cystinosis</td>
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</table>

* Three patients treated by combined hepatic and renal transplantation.
* One patient treated by combined hepatic and renal transplantation.
* One patient treated by combined hepatic and heart transplantation.

Natural History

The natural history of α-1-antitrypsin deficiency is highly variable. A profound serum deficiency is associated with the development of emphysema in the fourth to fifth decades of life. A small percentage (10–20%) of homozygous ZZ individuals develops neonatal cholestasis which is indistinguishable from that of other forms of

TABLE 2. Number of children under 18 years of age with metabolic diseases treated with liver transplantation

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-1-Antitrypsin deficiency</td>
<td>37</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>8</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>8</td>
</tr>
<tr>
<td>Glycogen storage type I</td>
<td>1</td>
</tr>
<tr>
<td>Glycogen storage type IV</td>
<td>4</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>2</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
<td>1</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>63</strong></td>
</tr>
</tbody>
</table>

* Among the first 1,000 adult and pediatric cases transplanted at the University of Pittsburgh. From Esquivel CO, et al. (1).
hepatobiliary disease. Jaundice usually clears before the age of 6 months, but biochemical abnormalities may persist for several months or years. In some series, 30–40% of children with neonatal cholestasis developed cirrhosis during the first years of life (3). This complication is more frequent in patients in whom a paucity of interlobular bile ducts and persistence of jaundice after 6 months of age are noted (4). On the other hand, about 10% of children with cirrhosis caused by α-1-antitrypsin deficiency have no history of neonatal cholestasis.

Children with cirrhosis frequently die in childhood or early adulthood from gastrointestinal bleeding or progressive liver failure. In some cases an unpredictable and unexplained fulminant hepatic failure occurs. An increased risk for hepatocarcinoma has been described in adults (5). The validity of the association between cirrhosis and the phenotypes MZ and SZ has been questioned, and even in PiZZ individuals the mechanisms responsible for hepatic complications are not defined.

Candidates for Transplantation

At the present time, α-1-antitrypsin deficiency is the second most common indication for liver transplantation in children. Transplantation should be considered in those patients proven to have cirrhosis. Timing of the procedure remains uncertain; in our opinion, because liver disease may decompensate rapidly, transplantation should not be delayed until manifestations of end-stage liver disease develop, and a reasonable age for transplantation seems to be 4–8 years.

Long-Term Effects

Liver transplantation leads to the acquisition of the donor phenotype and normal serum α-1-antitrypsin levels; however, it remains to be shown that chronic lung disease and other rare complications of the deficiency, such as glomerulonephritis, pancreatitis, and panniculitis, will be prevented. Theoretically, the heterozygous phenotype PiMZ, found in about 5% of the population, could be a risk factor for emphysema in young adults, so that it would be better to use a liver graft from donors having not this phenotype. In fact, recent studies show that the risk for the development of emphysema is related to a serum level of α-1-antitrypsin below 80 mg/dl, a concentration that is only seen in subjects with PiSZ or ZZ (6).

Wilson’s Disease

In this condition, biliary excretion of copper and incorporation into ceruloplasmin are both severely impaired. The basic lesion underlying these two disturbances is not yet known. Defective biliary excretion leads to accumulation of copper in the liver with progressive liver damage and subsequent diffusion into the blood and accumulation in other sites, such as cerebral nervous system, kidneys, and eyes.
Incidence

Inheritance is autosomal recessive. The prevalence is about 1 in 30,000 to 100,000 live births (7).

Natural History

The clinical manifestations are highly variable but in children are predominantly hepatic. More often, the picture is that of a subacute or chronic liver disease resembling chronic active hepatitis or cirrhosis in which hepatic insufficiency slowly develops. Some patients present with fulminant liver failure with hemolysis and renal failure associated with very high mortality. In fact, the clinical heterogeneity of presentation is so large that Wilson's disease has to be suspected in all children over 7 years with any liver disease of unknown etiology (4). The demonstration of a serum ceruloplasmin concentration of less than 20 mg/dl and of corneal Kayser-Fleisher rings generally suffices to make the diagnosis in 85% of patients (7). Occasionally, the diagnosis may be missed: a 24-h urinary excretion of copper greater than 100 µg favors the diagnosis. The finding of persistent equivocal results is an indication for determining copper concentration in a liver biopsy specimen, but clotting abnormalities may preclude the biopsy. An elevated serum copper level has been shown to be useful in separating patients with fulminant hepatic failure due to Wilson's disease from others (8).

Treatment with penicillamine is effective. Long-term results are excellent but the 3- to 6-month lag before improvement occurs may be too long in patients with acute liver failure (9).

Candidates for Transplantation

Sternlieb (7) has identified three groups of patients to be considered for liver transplantation:

1. Patients presenting with fulminant hepatitis
2. Severely decompensated cirrhotic children who have failed to improve after 2 or 3 months of adequate chelation and nonspecific therapy
3. Effectively treated patients in whom severe hepatic insufficiency and hemolysis develop following noncompliance with chelation therapy. The latter candidates are perhaps less than ideal as their compliance with post-transplantation therapy may be suspect (10).

Patients with fulminant hepatic failure have to be transferred to the transplantation center as soon as possible, where intensive supportive care will sustain life until a suitable donor can be found. The problem in the patients belonging to the two other groups is to define the degree of severity of the liver disease in order to perform transplantation before irreversible manifestations develop (11).
Long-Term Effects

The plasma levels and urine excretion of copper and the ceruloplasmin level normalize following liver transplantation; kinetics of intravenously administered copper in five patients one or more years following transplantation have normalized to the values found in obligate heterozygotes for the gene (1). Transplantation prevents the neurologic dysfunction of Wilson’s disease. Reversal of severe neurological deficits has been observed (12).

Hereditary Tyrosinemia Type I

This metabolic disorder results from a deficiency of the fumarylacetoacetase which catalyzes the last step of tyrosine degradation. Due to the enzyme defect, maleylacetoacetate and fumarylacetoacetate accumulate and are metabolized to succinylacetone, which inhibits renal tubular function and porphobilinogen synthetase (13). The liver is considered to be the main organ for tyrosine metabolism.

Incidence

The disease has autosomal recessive inheritance. It has a worldwide distribution and a high prevalence in the French Canadian population of Quebec (0.8 per 100,000 births). The prevalence in Sweden and Norway is about 1 in 100,000.

Natural History

The disorder is characterized by liver disease and renal tubular dysfunction. The course of the disease may be acute or chronic. In the acute form, the patients die of liver failure in early infancy. The chronic form is dominated by rickets and progressive cirrhosis; death is caused by liver failure and/or development of hepatocellular carcinoma. Few patients survive to adulthood (13).

Although not specific for this disorder, serum tyrosine and methionine levels are generally markedly elevated. Generalized aminoaciduria, phosphaturia, glycosuria, and renal tubular acidosis occur. Intermittent extreme elevation of blood α-fetoprotein are frequent. The diagnosis of tyrosinemia can be established by determination of succinylacetone in urine or serum and by assay of fumarylacetoacetase in lymphocytes and fibroblasts. Dietary restriction of tyrosine and phenylalanine improves the renal tubular dysfunction but does not influence the liver damage.

Candidates for Transplantation

Children with onset of liver failure would most benefit from a liver transplant as soon as it is feasible. The high risk of hepatoma formation over the age of 4 years
must lead to consideration for transplantation very early in the course of the disease. The preoperative search for such a complication is mandatory in order to reduce the incidence of tumor recurrence (14). Regenerative nodules may be difficult to differentiate from hepatomas. α-Fetoprotein is not of diagnostic value in these patients, and various imaging techniques have to be used in the routine management of patients.

**Long-Term Effects**

Replacement of the liver corrects the enzyme deficiency in this organ, but the kidneys remain potentially affected. Some patients continue to have renal tubular dysfunction, while others are normal in this respect, suggesting a variable tissue distribution of enzymatic deficiency (15). A persistent succinylacetone excretion, about 20% of the preoperative level, has been observed in a patient, but no further deterioration of the tubular function was seen (13,16). Thus, the renal tubular dysfunction of variable severity may not be corrected by liver transplantation and must be carefully monitored, in particular because cyclosporin may cause nephrotoxicity (15). The possibility that a prolonged postoperative dietary restriction of tyrosine and phenylalanine corrects the persistent tubular dysfunction in these patients, as it does before liver transplantation, remains to be determined; otherwise, some of these patients could be potential candidates for later renal transplantation.

**Glycogen Storage Diseases**

These are characterized by the accumulation of glycogen mostly in the liver, muscles, and kidneys, and classified according to their specific enzyme deficiency. Types with predominant liver manifestations are IA, IIB, III, and IV (4) (Table 3).

**TABLE 3. Major types of glycogen storage diseases with liver injury**

<table>
<thead>
<tr>
<th>Type</th>
<th>Enzyme deficiency</th>
<th>Metabolic disturbances</th>
<th>Liver damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Glucose-6-phosphatase</td>
<td>Severe</td>
<td>Adenoma, adenocarcinoma</td>
</tr>
<tr>
<td>IIB</td>
<td>Glucose-6-phosphate translocase</td>
<td>Severe</td>
<td>Adenoma</td>
</tr>
<tr>
<td>III</td>
<td>Amylo-1-6-glucosidase</td>
<td>Moderate</td>
<td>Portal fibrosis, portal hypertension, adenoma</td>
</tr>
<tr>
<td>IV</td>
<td>Amylo-1,4-1,6-transglucosidase</td>
<td>No</td>
<td>Cirrhosis, portal hypertension, liver failure</td>
</tr>
</tbody>
</table>
Incidence

All these types are transmitted as an autosomal recessive trait. Among 76 patients aged more than 12 years, 19 had type 1A, three had type 1B, and 34 had type 3; no patients had type 4 (17).

Natural History

Patients affected with type 1A experience growth retardation and a variety of metabolic disturbances, including hypoglycemia and lactic acidemia with fasting, hyperlipemia, and hyperuricemia. Improvement can be obtained with frequent feedings, continuous nocturnal enteral feeding, and more recently, use of uncooked cornstarch in the diet; in some patients, the improvement is only partial and/or transient. Development of multiple hepatic adenomas is not exceptional, and there is a possibility of a malignant transformation. In addition to this symptomatology, patients with type 1B exhibit a predisposition to infection which is correlated with neutropenia.

The long-term prognosis in patients with type 3 is better, in keeping with the relatively less severe metabolic disturbances; however, myopathy, cardiomyopathy, and portal hypertension secondary to progressive portal fibrosis have been reported. Some patients also develop liver adenomas (17).

Progression to cirrhosis and liver failure is rapid in all patients with type 4, and death usually occurs before the age of 4 years.

Candidates for Transplantation

Transplantation is the only available treatment for patients with type 4 and would normally be considered at about 2 years of age. However, other affected organs, such as the heart, may further threaten life.

The indication of liver replacement in the other types depends on the response to the classical therapy. One of our patients with type 1A had undergone a portocaval shunt at 6½ years of age, and was then treated with nocturnal drip feeding until the age of 15 years; a liver transplantation was performed at that age because of persistent fasting intolerance, severe growth retardation, and very high blood cholesterol level (4.64 mmol/dl), despite good compliance with medical treatment. Two months later, cholesterolemia was 0.4 mmol/dl. Another indication for liver transplantation in this patient was prevention of malignant degeneration of the multiple adenomas present in her liver.

Miscellaneous Metabolic Diseases with Liver Injury

Protoporphyria

A relatively small fraction of afflicted patients with this disease have died in hepatic failure due to liver damage caused by protoporphyrin deposition. The biochemical
abnormality reflects deficiency in ferrochelatase activity with resultant increase in protoporphyrin in erythrocytes, plasma, and feces (18).

Photosensitivity is the major clinical manifestation and is not life threatening. However, some patients develop progressive cholestasis with subsequent decreased flow of the hepatotoxic pigment into the gut and the risk of liver failure and death within a few months.

Liver transplantation is indicated in those patients who develop cholestasis (19). In one case (20), it resulted in return to normal liver function and almost complete disappearance of skin photosensitivity manifestations. However, correction of the metabolic disorder was incomplete, perhaps because the contribution of liver in protoporphyrin overproduction is small in comparison with that of the erythropoietic tissue. The long-term consequence of the persisting disorder might be recurrent liver injury, and it might be useful to propose measures for prevention.

Hemochromatosis

Hemochromatosis is another cause of cirrhosis in adult patients. Several have successfully undergone liver transplantation (1). No progression or amelioration of the nonhepatic consequences of hemochromatosis has been noted.

Two infants with congenital hemochromatosis have also received liver replacement for cirrhosis. They were alive and well 1–2 years after surgery (1).

Galactosemia and Hereditary Fructose Intolerance

Liver transplantation has been proposed in both diseases when cirrhosis is present. It has been performed for this reason in one patient with galactosemia. Early diagnosis is important in these conditions, so that the patients can be established on specific restricted diets to avoid such long-term complications.

Other Genetic Disorders

Byler's disease and cystic fibrosis are considered by some authors as metabolic in origin. Liver transplantation can be the only available treatment of cirrhosis accompanying these diseases. Several patients with Byler's disease have received a liver graft (21). The indication of transplantation in patients with cystic fibrosis is more difficult to define because the association of chronically infected pulmonary disease. A combined transplantation of liver, heart, and lungs should be considered in those patients with cirrhosis.

METABOLIC DISEASES WITHOUT LIVER DAMAGE

Crigler-Najjar Syndrome Type I

This is caused by a complete deficiency in the hepatic bilirubin-UDP-glucuronyl transferase activity.
Incidence

The syndrome is inherited in an autosomal recessive pattern. It is rare: only about 100 cases have been reported in the world literature.

Natural History

Patients with this syndrome have unconjugated serum bilirubin concentrations ranging from 20 to 40 mg/dl. As distinct from patients with type II, they do not respond to enzyme induction with phenobarbital, and severe or lethal kernicterus is a constant risk even after the neonatal period: some patients have been reported in whom irreversible neurologic damage was observed only in adolescence.

Treatment is only palliative and restricted largely to life-long phototherapy and cholestyramine in hospital and at home (22,23). Intercurrent infections are associated with further increase in unconjugated hyperbilirubinemia which may precipitate the neurologic injury, at any age.

Candidates for Liver Transplantation

Considering that the risk for neurologic impairment is permanent, all patients with Crigler-Najjar type I are potential candidates for transplantation (24). The latter should be performed when phototherapy ceases to be effective or practical, and clearly prior to the development of kernicterus.

Long-Term Effects

The serum bilirubin concentration falls postoperatively and remains thereafter normal, indicating the marked capacity of normal liver to take up bilirubin.

Familial Hypercholesterolemia Type II

A 6-year-old girl with severe hypercholesterolemia and atherosclerosis has successfully undergone combined liver–heart transplantation (25). She experienced a marked diminution in serum cholesterol to levels which, although not normal, may be compatible with long-term, complication-free survival. Another patient has undergone a liver transplantation 3 weeks after heart transplantation (26). Liver transplantation should be considered only for those patients who are unable to produce any functional LDL receptors and do not respond to other forms of therapy (27).

Hyperoxaluria Type I

In this disease the abnormal glyoxylate metabolism leads to diffuse oxalate deposits in many organs, but mainly the kidney. Liver transplantation corrects the
enzyme deficiency and should be proposed in young patients before advanced renal and systemic damage. A combined hepatic and renal transplantation has been performed in patients with renal failure (28).

Miscellaneous Disorders

A child with homozygous protein C deficiency has been treated at age 20 months by liver transplantation; there was a complete postoperative reconstitution of protein C activity and resolution of the thrombotic condition (29).

Several patients with hemophilia have been transplanted for postnecrotic cirrhosis and liver failure due to replacement therapy with clotting factors. The survival patients were well 3 years after transplantation without any clinical evidence of residual clotting dysfunction (30).

Liver transplantation should be considered in several other metabolic diseases, such as some aminoacidopathies and various disorders of the urea cycle; unfortunately, these disorders are almost invariably responsible for severe and irreversible brain damage in the first days of life, too early to be amenable to transplantation. However, one child aged 20 months with carbamylphosphate synthetase (CPS) deficiency has been transplanted; there was a complete correction of hyperammonemia, but plasma citrulline remained low, suggesting that citrulline originates from the gut rather than the liver (31). It would be necessary to continue citrulline supplementation after liver transplantation for CPS and ornithine transcarbamylase deficiency. In another group of metabolic diseases, in particular lysosomal and peroxisomal diseases, extrahepatic organs are involved and liver transplantation may not affect the extrahepatic dysfunction.

CONCLUSION

In conclusion, hepatic transplantation for metabolic diseases of the liver produces a definitive cure of the liver disease and also cures the underlying metabolic abnormalities of the genetic disease. It is indicated not only for patients with evident liver damage but also for those in whom the deficiency is based exclusively within the liver. Several recent reports indicate that replacement of the liver is not always followed by complete cure of the metabolic disease in those patients in whom the deficiency is also present in extrahepatic tissues. In any case, the recipient will remain an obligate carrier of the disease and will transmit the trait to all offspring.

REFERENCES

DISCUSSION

Dr. Hobbs: Has any center transplanted patients with the nul-gene defect? The ZZ is ideal to transplant, since it is a single amino acid defect and there is already some protein present, so I don’t think you will get antibodies. But for the nul-gene I think you would certainly get antibodies.

Dr. Odièvre: I do not know whether any nul-gene defect patients have been transplanted but I think that the number of children with this type of phenotype in the world is very low.

Dr. Van Hoof: The ZZ phenotype of α-1-antitrypsin deficiency corresponds to an anomaly of the glycan content of the protein. The abnormal protein accumulates in the cis-ternae of the endoplasmic reticulum, and this causes liver damage. Most probably nul-gene will not raise the same problem and will therefore not be classified among disorders with liver damage. May I ask Dr. Odièvre the reason for classifying the diseases according to the fact that they are or are not accompanied by liver damage. A more logical classification would have been to separate the generalized enzyme deficiencies from the group in which the missing enzymatic step is located completely or predominantly in the liver. Only in the latter group could a complete correction of the disease be expected.

Dr. Odièvre: In the first group with liver damage there is no discussion about the necessity of a transplantation because if we don’t perform it the child will die. Concerning the group without liver damage we are obliged to discuss the risk of surgical procedure in a child who is apparently in a good condition. From the physiological or pathogenic point of view you are right.

Dr. Sokal: I have a question about the tyrosinemia. You pointed out that these patients still excrete succinylacetone and all patients have high levels of urinary δ-aminolevulinic acid after transplantation. So would it be necessary to give to these patients detoxifying compounds as was suggested during Dr. Duran’s presentation? Is there any evidence that this may be responsible for malignancies in these patients?

Dr. Otte: I think this classification is quite useful in the clinical situation for several reasons. The main reason you mentioned is regarding the balance between the risk of dying for the child and the risk of liver transplantation: you mentioned 15 to 20%. So you should balance that against the risk of dying from the disease. When the patient is going to die within a matter of weeks or days, there is not much of an ethical problem. So I think this classification is quite useful in day-to-day practice. But there is another reason why it will be useful in the future. This concerns the technique. So far we have unfortunately to do an orthotopic transplantation with removal of the native liver. There is, of course, a technique of heterotopic partial liver transplantation but at present this technique does not work particularly well, especially when the recipient liver is normal. You know maybe that the team of Rotterdam has started doing heterotopic partial liver transplantation again and they have obtained quite good results in adult patients with cirrhosis. But when they have used the technique for fulminant hepatitis, for example, they have been unable to obtain a success. From experimental studies one might extrapolate that it is unlikely that heterotopic liver transplants would work when normal recipient liver remains because there is some kind of competition. So in the future surgeons have to do a better job. Experiments are continuing to try to find a way eventually to replace only
part of the liver by transplant. But for the time being there is no successful technique and the only way we have is to replace the whole liver.

Dr. Odière: In tyrosinemia the phenylalanine- and tyrosine-restricted diet results in disappearance of tubulopathy, while the liver disease is hardly influenced at all. Perhaps it would be interesting to continue the diet therapy after liver transplantation in those patients who have persistent urinary excretion of succinylacetone in order to see if the excretion improves, and with the hope of avoiding a further renal transplantation.

Dr. Saudubray: This raises the more general question as to whether we have to restrict this type of therapy to inborn errors that are mainly or completely restricted to the liver, or whether we can extend the therapy to inborn errors affecting not only liver but other tissues as well. I shall give two examples. In propionic and methylmalonic acidemia, we know that the enzyme defect is present in every tissue. But we also know from physiological studies and from the C13 turnover of propionate and methylmalonate that the main site of production of the toxic compound is muscles, while the main site for their catabolism is the liver. Although I don’t often recommend performing liver transplantation in propionic aciduria, I would like to emphasize that from a metabolic point of view liver transplantation could be a therapeutic procedure for this kind of disorder, because the liver may well be able to clear every toxic metabolite. This is one example. On the other hand, the principal concern is for glycogenosis type 1B. In this disease you have two main sites for the defect. One is the liver, giving all the classical clinical symptoms due to glycogenosis type 1, but in addition you have defective transport of glucose-6-phosphate within leukocytes, leading to the other group of symptoms, namely recurrent infections. Is liver transplantation a suitable procedure for the therapy of glycogenosis type 1B?

Dr. Odière: Recurrent infections in type 1B glycogen storage disease with granulopenia are classical but not constant. I am personally following six patients with this type of disease and only one has problems with infections.

Dr. Mowat: I think one of the problems is the heterogeneity of all these disorders. A good example of this is type 4 glycogen storage disease, where recently a patient has been reported with as much as 10% of normal activity for the deficient enzyme and with no progression of the liver disease over a period of follow-up of 5 years. I think we need to know much more about many of these conditions before we make generalized statements.

Dr. Brodehl: I think the indication for a liver transplantation in glycogen storage disease type 1 is not enzyme replacement but the development of adenomas which become malignant. At least this was the reason for performing a transplantation in one case in our institute. The same is true for tyrosinemas, which have a high rate of malignancy in the later stage. This should be another indication for liver transplantation in these patients.

Dr. Odière: In tyrosinemia the risk of hepatoma is so high that we propose liver transplantation for all patients at about 2 years of age. In glycogen storage type 1A, 1B, and type 3 many patients develop liver adenoma. It has been claimed that the adenoma can disappear with nocturnal enteral nutrition; it is not my experience. Malignant transformation of liver adenomata is rare during childhood; this risk, however, justifies repeated evaluation of α-1-fetoprotein in blood.

Dr. Schaub: I would like to put a question concerning the long-term results in the transplanted liver. Is it clearly demonstrated that, for instance, in Wilson’s disease the transplanted liver is free of copper deposit and free of fibrosis or will storage of copper and fibrosis in the transplanted liver again develop?

Dr. Brodehl: Our experience in Wilson’s disease is only very limited. I would not expect the copper to accumulate again because the defect is located in the liver. Of course, initially you
have a high storage of copper within the body and there could be a mobilization and spillover into the liver, but later, as far as I know from the literature, there is no further accumulation of copper in transplanted Wilson's disease. The story with cystinosis is different. The transplanted kidney accumulates cystine again but in a different fashion from the original kidneys. Cystine comes from the macrophages and leukocytes from the blood, which invade the transplanted kidney, although the cells of the transplanted organ do not accumulate cystine because they possess the lysosomal transport system, which is missing in cystinosis.

Dr. Mowat: Just to add a little bit to that: in adult patients the Kayser Fleischer rings clear gradually after transplantation. It takes about 2 years for them to disappear.

Dr. Otte: Regarding α-1-antitrypsin deficiency you remind us that the risk of death from emphysema is related to the α-1-antitrypsin concentration in the plasma. Can we be sure that the normalization of the α-1-antitrypsin will protect the patient against the risk of death from emphysema in the very long term?

Dr. Odièvre: The α-1-antitrypsin deficiency represents only one of the risk factors for emphysema: smoking and living in a dusty environment are other factors. Adult specialists claim that a level of circulating α-1-antitrypsin above 150 mg per 100 ml protects the individuals.

Dr. Mowat: I would like to comment on that. Ten percent of our children with liver disease who are asymptomatic have large lung volumes and all the lung function studies suggest they have emphysema. We don’t know for certain that they have emphysema because we have not biopsied the lungs. However, this raises the consideration that some patients are already on the way to developing emphysema before you transplant them. It is true that α-1-antitrypsin is also produced in monocytes and macrophages. It may be that the tissue concentration of is more important in inhibiting tissue-damaging proteases than the serum concentration. I have reservations about whether our patients who are transplanted will avoid emphysema. We should also remember that the lungs of most patients with liver transplantation may be a very stressful time in the intensive care unit, which may well aggravate or initiate lung damage.

Dr. Hobbs: I did, in fact, suggest that there might be enough α-1-antitrypsin synthesized in white cells for a bone marrow transplant to work. In fact, that has been tested and it does not work. We have tested the Pi-types in our transplant patients and I can assure you that although we have transferred marrows with different Pi-type, the patients practically never get a reasonable serum level of the donor Pi-antitrypsin.