In this report, we propose to show how liver transplantation has been used to treat a number of inborn errors of metabolism. Such procedures have not only been of considerable benefit to the patients, but also have shed light upon some basic pathophysiological mechanisms of the metabolic defects involved. In the future, additional information about other hepatic-based inborn errors should emerge with this approach.

The broad topic of orthotopic liver transplantation, or liver replacement, has been discussed by Professor Roy Calne of Cambridge elsewhere in this volume. The scope of this article will therefore be limited to the application of this procedure to the treatment of metabolic disorders.

METABOLIC SPECIFICITY OF THE DONOR LIVER

The potential curability by liver transplantation of hepatic-based inborn errors of metabolism was established in the mid and late 1960s by observations involving analysis of serum haptoglobin phenotypes of recipients before and after transplantation. Earlier, Smithies had demonstrated that three phenotypes of haptoglobin could be identified on the basis of their different electrophoretic mobilities in starch gel. In those cases in which the donor and recipient phenotypes differed, the recipient always adopted the donor type after transplantation, as in Figure 1. This conversion was permanent. Moreover, similar substitutions of donor for recipient phenotype were also seen when

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Figure 1 The effect of orthotopic liver transplantation on serum haptoglobin phenotype. Preoperatively, the recipient was classified as Smithies type 2–1 by starch gel electrophoresis; the liver donor was type 2–2. Postoperatively, only the donor type was detectable in the recipient’s serum (by permission of W. B. Saunders Co. 1969).

group specific component (another alpha globulin) and the C’3 component of complement were analyzed. Thus, the case was made that the liver retained its metabolic specificity after its transplantation into a new environment.

**ALPHA-ANTITRYPSIN DEFICIENCY**

From these observations of haptoglobin and other serum proteins, the cure of alpha-antitrypsin deficiency by liver transplantation could be predicted.

Alpha-antitrypsin, the chief component of the alpha,-globulin fraction of human plasma, is an inhibitor of proteolytic enzymes such as trypsin, chymotrypsin and collagenase. As with haptoglobin and group-specific component, there are identifiable phenotypes of which at least 17 have been described so far, using discontinuous acid starch gel electrophoresis. In alpha-antitrypsin deficiency, the presence of the abnormal phenotype PiZZ (the most common phenotype is PiMM) is accompanied by alpha-antitrypsin concentrations approximately 10% of normal. Twenty to 30% of children with this phenotype will develop infantile cirrhosis; the condition also predisposes in adults to cirrhosis or pulmonary emphysema of early onset and, rarely, both hepatic and pulmonary disease, either in childhood or adult life. The homozygous PiZZ phenotype is encountered in about one in 2500 live births.

In November 1973, we treated by liver transplantation a 16-year-old girl with cirrhosis caused by homozygous alpha-antitrypsin deficiency. Chronic rejection eventually caused failure of the graft and she was retransplanted 2½ years after the first operation. She died 5 weeks later, after a total survival of 2 years, 4 months.

Multiple donor and recipient serum samples were examined by Drs Allan G. Redeker and Robert L. Peters of Los Angeles (Table 1). Preoperatively, the
LIVER TRANSPLANTATION FOR METABOLIC ERRORS

Table 1  Alpha-1-antitrypsin phenotype and concentration before and after transplantation

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Pretransplant</th>
<th>First donor</th>
<th>Post-transplant</th>
<th>Second donor</th>
<th>After retransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration mg/%</td>
<td>ZZ</td>
<td>MM</td>
<td>18 mo.</td>
<td>26 mo.</td>
<td>MM</td>
</tr>
<tr>
<td>(normal 140-470)</td>
<td>55</td>
<td>—</td>
<td>264</td>
<td>256</td>
<td>176</td>
</tr>
</tbody>
</table>

recipient's serum contained only 55 mg/% of alpha-1-antitrypsin; the phenotype was PiZZ. The donor of the first liver graft had the normal PiMM phenotype. After liver replacement, the recipient's alpha-1-antitrypsin concentration increased to normal levels and had the donor's PiMM phenotype. By coincidence, the second homograft was from a donor with the heterozygous PiMZ phenotype. (In heterozygotes, the alpha-1-antitrypsin concentration is about 60% of normal but there does not appear to be any predisposition to liver disease.) After the second transplant, the recipient again adopted the donor's phenotype, this time PiMZ.

Histological examination of both hepatic homografts was performed by Professor K. A. Porter of London and Dr Robert L. Peters of Los Angeles. With the periodic acid Schiff and the peroxidase-labeled antibody methods, both of which are specific techniques for identifying the telltale alpha-1-antitrypsin granules in the liver, no evidence of glycoprotein deposition could be found.

From this experience, and from observations reported by Sharp and his associates of two children with alpha-1-antitrypsin deficiency who survived for about 1 month after liver transplantation at the University of Minnesota, it has been established that the liver is the sole source of the deficient alphaglobulin. Furthermore, the provision of a new liver not having the abnormal PiZZ phenotype is curative of the hepatic disease and, presumably, is also protective of other organs such as the lung which are adversely affected by antitrypsin deficiency.

WILSON'S DISEASE

Much the same conclusion can be drawn from our observations in two patients treated with liver replacement for Wilson's disease. In this inborn error of metabolism, there is progressive accumulation of copper in the body. The characteristic Kayser–Fleischer rings, which represent discoloration of the corneas with copper, may be detected by slit-lamp examination. More importantly, deposition of the metal in the liver and the brain may cause subsequent degenerative changes. The biochemical abnormalities associated with the disease include elevation of the albumin-bound serum copper concentration, increased urinary excretion of copper, very low levels of the
copper-containing serum protein ceruloplasmin, and a low total serum copper concentration.

We have transplanted two children with hepatic cirrhosis caused by Wilson's disease. The first was an 11-year-old boy, who survived 6 years after liver replacement; the cause of death was a partial biliary obstruction unrelieved by late reoperation. Postoperatively, repeated liver biopsies showed that there was no tendency to accumulate copper within the new organ. A prolonged cupriuresis after operation substantially reduced the total body copper content. Moreover, copper excretion after penicillamine showed a normal response.

This patient was studied in collaboration with Sternlieb and Scheinberg of New York. Certain features of the case were atypical — the serum ceruloplasmin was in the low normal range and there were no Kayser-Fleischer rings — but the very high copper concentration in the native liver left little doubt about the diagnosis. Nonetheless, the potential usefulness of the metabolic observations in this case was diminished by the atypical biochemical findings.

Such reservations did not apply to the second recipient, who had all the classical features (including Kayser-Fleischer rings) of Wilson's disease. He was first diagnosed at the age of 11 years. Within 3 years he had signs of progressive deterioration of hepatic function, including ascites. However, the recommendation for transplantation was based more on the seriousness of his progressive neurological impairment than because of liver failure. The neurological symptoms included dystonia, dysarthria and choreoathetosis. Symptomatically and biochemically, he was unresponsive to D-penicillamine and triethyltetramine dihydrochloride.

In March 1971, orthotopic hepatic transplantation was performed. Postoperatively, immunosuppression was with cyclophosphamide (for which azathioprine was later substituted), prednisone and a 3-month course of heterologous antilymphocyte globulin. At present, his liver function is normal (Figure 2), 5½ years post-transplantation.

His own liver removed at the time of transplantation had a markedly increased copper content. However, biopsies of the homograft at 1, 1½ and 3½ years postoperatively showed tissue copper levels of 30, 45 and 27 mg/g wet weight, respectively — values only slightly above normal. Histologically, the biopsies appeared normal. The Kayser-Fleischer rings gradually reabsorbed and had disappeared entirely by the third postoperative year. The biochemical abnormalities similarly were gradually corrected (Figure 2). Most importantly, the neurological abnormalities have completely resolved.

NIEMANN- PICK DISEASE

The list of inborn errors of metabolism effectively treated with liver transplantation will undoubtedly lengthen. Daloze and Corman and their
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Figure 2 The postoperative course and biochemical findings for the first 17 months after liver transplantation in our second patient treated for Wilson's disease. After liver replacement, the serum ceruloplasmin, which was virtually absent preoperatively, rapidly increased to normal; the total serum copper showed a similar trend. Urinary copper excretion, which was elevated preoperatively, eventually declined. Moreover, the response to penicillamine was normal (by permission of Transplant. Proc. (1973), 5, 829).

associates have treated a 2-year-old child with Niemann–Pick disease, in whom the liver had been severely damaged by deposits of sphingomyelin within it. After transplantation, the homograft showed no tendency to accumulate sphingomyelin; sphingomyelinase, the deficient enzyme in this disorder, was found in normal concentrations in the peripheral blood, urine, cerebrospinal fluid and the graft itself. Unfortunately, the severe neurological impairment already present preoperatively did not improve and in fact contributed to the death of the child from aspergillus pneumonia almost 2 years after transplantation. At autopsy, sphingomyelinase activity was also detectable in the cerebral tissue.

TYROSINEMIA

Finally, we recently performed liver replacement in a 10-year-old child with tyrosinemia. A multifocal hepatoma had also developed within the severely cirrhotic liver. During the first 2 postoperative months, the serum and urine tyrosine concentrations rapidly became normal. Urinary excretion of p-hydroxyphenylpyruvic acid products also declined to nearly normal levels. These findings suggest that this inborn error is correctable by transplantation.
LIVER AND BILE

Detailed metabolic studies now in progress should shed further light upon the pathophysiological mechanisms of this disorder.

INBORN ERRORS OF METABOLISM AND THE TOTAL TRANSPLANT EXPERIENCE

It is worthwhile noting that these recipients of liver grafts for inborn errors constitute only a small proportion of our experience with liver transplantation (Table 2). Of the first 114 patients, 63 were in the pediatric age range. Out of

<table>
<thead>
<tr>
<th>Recipients</th>
<th>114</th>
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<tbody>
<tr>
<td>Adult</td>
<td>51</td>
</tr>
<tr>
<td>Pediatric</td>
<td>63</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>52</td>
</tr>
<tr>
<td>Other liver diseases</td>
<td>7</td>
</tr>
<tr>
<td>Metabolic diseases</td>
<td>4</td>
</tr>
</tbody>
</table>

63 children 52 were transplanted for biliary atresia; only four were treated for metabolic diseases. Two of the four have lived more than 5 years after operation and three have lived more than 2 years. Two are still alive, one after 2 months and the other after nearly 5½ years.

References