

**CHANGING CONCEPTS:  
LIVER REPLACEMENT FOR  
HEREDITARY TYROSINEMIA  
AND HEPATOMA**

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## *Changing concepts: Liver replacement for hereditary tyrosinemia and hepatoma*

IN RECENT YEARS there has been increased use of hepatic transplantation for the treatment of liver-based inborn errors of metabolism.<sup>1,2</sup> In 1976, a 9-year-old girl with chronic hereditary tyrosinemia who had developed a 15-cm hepatoma in her cirrhotic liver underwent liver replacement with immunosuppression therapy with azathioprine,

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prednisone, and antilymphocyte globulin. The abnormal metabolic profile of tyrosinemia was promptly and completely corrected, but a pulmonary metastasis from the hepatoma was discovered shortly afterward. The new liver was rejected in 3 months, and the patient died during a second attempt at transplantation.<sup>3</sup>

We have had subsequent experience with four additional patients with the same diagnoses, in whom immunosuppression therapy after liver replacement was with cyclosporine and prednisone. These four recipients are well and

**Table.** Clinical features

| Patient | Age (yr) | Date of transplantation | Preoperative $\alpha$ -fetoprotein* (ng/ml) | Liver function                |                        |         | Hepatoma(s) in specimen from transplantation    | Referral source  |
|---------|----------|-------------------------|---|-------------------------------|------------------------|---------|---|--|
|         |          |                         |   | Total serum bilirubin (mg/dl) | Prothrombin time (sec) |         |   |  |
|         |          |                         |   |                               | Patient                | Control |   |  |
| 1       | 21       | 3/20/83                 | 2,740†                                      | 2.9                           | 17.0                   | 11.6    | None; tumor removed by previous right lobectomy | University of Cincinnati<br>William Balistreri, M.D.     |
| 2       | 2½       | 11/14/81<br>5/13/83     | >25,000                                     | 1.8                           | 15.0                   | 12.5    | Multiple  | Cornell University<br>Maria New, M.D.                    |
| 3       | 3½       | 1/25/84                 | 4,600                                       | 1.8                           | 17.0                   | 12.0    | Multiple  | University of Chicago<br>Lawrence Gartner, M.D.          |
| 4       | 3        | 5/28/84                 | 13,560                                      | 3.7                           | 15.0                   | 11.5    | Multiple  | Children's Hospital of<br>Dayton<br>Stephan Newman, M.D. |

\*Normal <20.

†Before right hepatic lobectomy, 1/1983 (see text).

metabolically normal 3 months to almost 3 years after transplantation and have no evidence of recurrent tumor. These observations suggest the desirability of liver transplantation earlier in the course of this disease. The point has been supported by experience with a fifth candidate whose proposed transplantation was interdicted by metastases to the diaphragm, which were discovered at the time of operation. This 4-year-old girl died 1½ months later.

The four recipients, who received treatment in the cyclosporine era, were 2½ to 21 years of age. Each had cirrhosis and multiple abnormalities of liver function, including prolonged prothrombin time and low-grade hyperbilirubinemia (Table). The diagnosis had been made early in life by the demonstration at established metabolic centers of hypertyrosinemia, tyrosinuria, and marked excretion of tyrosine metabolites in the urine, which were managed with a diet low in tyrosine and phenylalanine.

In three of the patients, elevations of  $\alpha$ -fetoprotein (Table) originally aroused suspicion of hepatoma development. However, a definite mass was detectable with computed tomography and other radiographic techniques only in the oldest (patient 1). This patient underwent a right hepatic lobectomy at another hospital, at which time the main portal vein was accidentally tied off; the hepatoma was thought to be cleanly removed. After the right-sided lobectomy, she developed very severe liver failure and was bedridden until the time of transplantation 2 months later. There was no residual tumor in the hepatic remnant. In patient 2 the diagnosis of hepatoma had been suspected after a routine ultrasound examination, and was confirmed by open liver biopsy.

Patients 2, 3, and 4 had multiple small hepatomas in all

parts of the excised livers. However, the surgical margins were free of tumor.

Although the livers were cirrhotic, they were relatively soft. The transplantation procedures were by well-standardized techniques,<sup>1,4</sup> except in the child who had undergone right hepatic lobectomy, whose portal vein was thrombosed from the site of surgical ligature back to the confluence of the splenic and superior mesenteric veins. In this recipient a cloaca was fashioned at the superior mesenteric-splenic venous junction, to which a free inferior vena caval graft from the liver donor was anastomosed. The donor portal vein was anastomosed, in turn, to the proximal end of this graft.<sup>5</sup>

Cyclosporine and prednisone were given intravenously or orally from the time of operation, with rapid weaning from prednisone to maintenance doses, presently 2.5 to 7.5 mg/day. Despite therapy, one of the recipients (patient 2) slowly rejected the graft, and retransplantation was carried out without incident 18 months after the primary procedure. She is well 15½ months after retransplantation. The other three recipients also are well after 3, 7, and 17 months, respectively.

The  $\alpha$ -fetoprotein levels, which ranged from 4600 to 25,000 ng/ml before liver replacement (or before hepatic resection in patient 1) fell to within the normal range within a few days or weeks, and have remained normal. There has been no evidence of recurrent hepatoma in any patient, and all four now have normal liver function. The metabolic abnormalities characteristic of tyrosinemia were normalized immediately after transplantation, even though the patients were given a regular diet.

Detailed studies of amino acid metabolism have been or are being carried out in the referring centers (Table) and

will be described separately. It is now thought that hereditary tyrosinemia is caused by fumarylacetoacetate hydrolase deficiency.<sup>6,8</sup> In other liver-based inborn errors of metabolism with or without a specific and identifiable enzyme defect, the metabolic phenotype of the graft has remained permanently that of the donor.<sup>1,2</sup> Thus the metabolic amelioration in our patients with tyrosinemia should be for the lifetime of the grafts.

The use of liver transplantation for "metabolic engineering" has been a tantalizing prospect for a number of years, but the poor results with liver replacement discouraged the wide application of this approach until recently. With the advent of immunosuppression therapy with cyclosporine and steroids, the prognosis after liver replacement has improved so dramatically, particularly in pediatric recipients, that reluctance to go forward with this aggressive therapy has diminished.<sup>1</sup> Furthermore, the increasingly recognized risk of hepatoma formation<sup>9</sup> is an additional and potent reason to consider liver transplantation at an earlier time and under semiselective conditions.

In the early days of liver transplantation, efforts to treat hepatomas that could not be excised by conventional techniques resulted in an incidence of tumor recurrence so high that the potential value of the operation was vitiated.<sup>1,4</sup> With better patient selection in more recent times, this incidence of recurrence has been reduced,<sup>1</sup> and in patients with hepatomas incidental to tyrosinemia,  $\alpha_1$ -antitrypsin deficiency, sea-blue histiocyte syndrome, or biliary atresia, the incidence of recurrence has been zero. Thus, the threat of late metastases in the four surviving patients with tyrosinemia is not as great as might have been predicted from the older literature.

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