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Xenotransplantation of Hamster Liver Into Gunn Rats Reverses Congenital Hyperbilirubinemia

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THE Gunn rat is an animal model for Crigler-Najar syndrome, a rare form of congenital unconjugated nonhemolytic hyperbilirubinemia due to the absence of glucuronyl transferase.^{1,2} It leads to deposition of bilirubin in the basal ganglia, culminating in precocious death of the patient. Because the uptake, conjugation, and excretion of bilirubin by hepatocytes involves specific carriers and enzymes, this animal model provides a unique opportunity to investigate the interactions between proteins of donor origin with those of the recipient.³ In this study we have assessed whether liver xenotransplantation can reverse the congenital hyperbilirubinemia in the Gunn rat.

MATERIALS AND METHODS

Homozygous (jj, jaundiced) female Gunn rats (n = 11) received orthotopic liver transplants from normal hamsters. The recipients were immunosuppressed with tacrolimus (1 mg/kg/d × 15 days IM) and cyclophosphamide (8 mg/kg/d IP × 7 days). Blood samples were taken every 6 days for determination of serum bilirubin levels. The presence of bilirubin conjugates was also analyzed in the bile. Controls included Gunn rats that received immunosuppression alone without liver xenotransplantation (n = 2).

RESULTS AND DISCUSSION

A short course of immunosuppression prolonged liver xenograft survival in Gunn rat recipients from 7 days (untreated) to a mean of 31 days. As shown in Fig 1, no change in serum bilirubin levels was observed in the control animals, whereas Gunn rats transplanted with hamster livers exhibited a precipitous decrease in their serum bilirubin levels, which reached normal within 7 days posttransplantation and remained so throughout the observation period. This decrease in serum bilirubin was accompanied by a concomitant increase in the levels of conjugated bilirubin in the bile, suggesting that the uptake, conjugations, and secretion of bilirubin in Gunn rats who received hamster liver was proceeding normally. Taken together, the results of these experiments suggest that despite their species-specificity, hamster xenoproteins were capable of transporting and conjugating rat bilirubin, leading to resolution of hyperbilirubinemia in the Gunn rat, and prompting us to speculate that inborn errors of metabolism may also be corrected by concordant liver xenotransplantation.

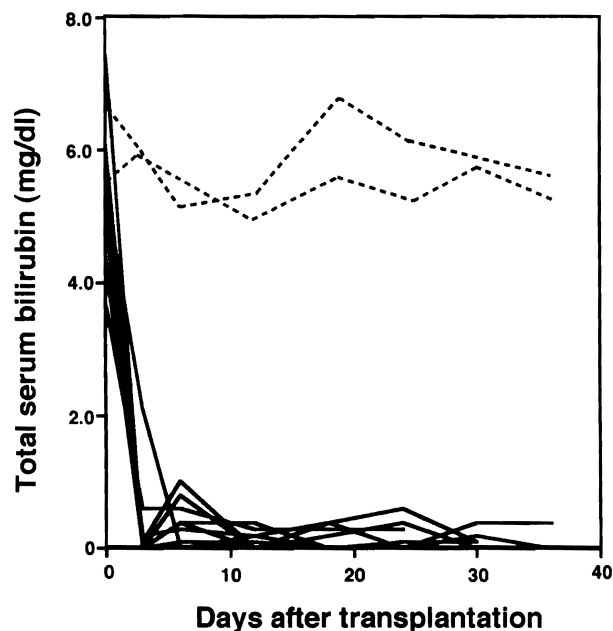


Fig 1. Bilirubin levels in Gunn rats after hamster liver xenotransplantation. Total serum bilirubin levels decreased precipitously after xenotransplantation, reaching normal within 7 days (solid line). In contrast, levels in control animals remained elevated (broken line).

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Aided by project grant no. DK29961 from the National Institutes of Health, Bethesda, MD.

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0041-1345/96/\$3.00/+0