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Indications for Orthotopic Liver Transplantation: With Particular Reference to Hepatomas, Biliary Atresia, Cirrhosis, Wilson's Disease and Serum Hepatitis

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HEPATIC TRANSPLANTATION has passed through the feasibility stage of development since survival of humans for as long as 2½ years has been achieved following removal of the liver and its replacement (orthotopic transplantation) with a cadaveric homograft. Consequently, the position will be taken that liver transplantation is a legitimate albeit imperfect form of treatment. With this attitude, there is not a question about the propriety of clinical hepatic transplantation but only about the circumstances under which it should be considered. The opinions to be developed will be based primarily upon our own experience with orthotopic transplantation,¹ although the reader is also referred to the important observations of Calne,² Fortner et al.,³ and Birtch and Moore.⁴

Methods

Thirty-three consecutive orthotopic liver recipients, aged 11 months to 68 years, were treated from March 1963 to January 1970 by techniques described elsewhere.¹ The first 25 cases were thoroughly documented in a recent book;¹ the last eight have not been previously reported. In addition, a more recently treated patient will be mentioned briefly because of the specially interesting circumstances of treatment in the presence of Australia antigenemia. Immunosuppression of the first seven recipients was with azathioprine and prednisone. All subsequent patients were also given heterologous antilymphocyte globulin (ALG).

Results

Hepatoma

The preoperative diagnosis of hepatoma was the reason for proceeding with the liver replacement of 12 of the 33 patients including six of the first eight. Six of these 12 recipients had underlying cirrhosis of the Laennec, postnecrotic and biliary varieties in three, two and one instances, respectively. The biliary cirrhosis was in a 10-year-old child with biliary atresia. An additional unsuspected small hepatoma was found in the liver of another child treated for intrahepatic biliary atresia, making a total of 13 cases available for observation.

Early deaths—Seven of the 12 patients with prospectively diagnosed primary cancer of the liver died from 6½ to 39 days after orthotopic hepatic homotransplantation. Five of these cases were among the first seven in our experience; an important contributory cause of failure was the invariable use of livers that had been badly damaged by ischemia.¹ The other two patients who were treated at a later time died of technical accidents with subphrenic abscesses and bile peritonitis respectively.

At autopsy, an exhaustive search was made to determine if any metastases had been missed with the preoperative survey and the operative examination. No residual tumor was found in 6 of the 7 recipients. In the other patients who died 7½ days after transplantation, there had been previously unsuspected spread to a lumbar vertebra.

Prolonged survival—The other six recipients, including the one with an incidental hepatoma, lived through the immediate effects of the operation and became available for longer term studies. In all six, hepatic cell carcinoma (hepatoma) was the histologic diagnosis. Five of the patients died 76, 143, 339, 400, and 432 days after operation (Table 1). Recurrent neoplasm was responsible for the death of four of the recipients. The fifth (OT 26) died of other causes but had developed a metastasis to the left lung. The most common sites of spread (Table 1) were the lungs and the liver homografts (four examples each).

The only patient with hepatoma still surviving is the 4-year-old girl with biliary atresia whose tumor was not known in advance to be present. In this case sera were examined by Dr. Elliot Alpert of the Peter Bent Brigham Hospital, Boston, for the presence of the fetoprotein which when found essentially always signifies the diagnosis of hepatoma.⁵ Fetoglobulin was found in the preoperative sample. After transplantation, the abnormal protein persisted for more than 5 months, but in diminishing quantities until it finally disappeared. The child is in excellent condition 9 months postoperative with no evidence of recurrence.

Biliary Atresia

There were 15 patients, aged 11 months to 5 years, with biliary atresia (13 extrahepatic and two intrahepatic), including the child whose excised liver was later discovered to contain a small hepatoma.

Early deaths—There were six deaths within the first 40 postoperative days. These were caused by hepatic necrosis probably due to postmortem donor ischemia (two examples), thrombosis of the hepatic artery or portal vein (one example each), nonthrombotic occlusion of the hepatic artery (one example), and generalized infection and pneumonia associated with partial biliary tract obstruction and cholangitis.

Apart from the small size of the structures that had to be anastomosed, the atresia patients presented problems caused by a high incidence of anomalies. Three of the six early deaths listed above were due to technical accidents in patients who had anatomic variations including a hypoplastic portal vein, a fan-like hepatic arterial supply of diminutive host vessels too tiny to permit anastomosis, and a peculiar malrotation in which the portal vein passed anterior to the duodenum. These and other anomalies which constitute a special hazard in recipients with biliary atresia have been described elsewhere.¹

Later deaths—Four of the nine patients who lived beyond 40 days died after 61, 105, 133 and 186 days. All four deaths were caused by regional hepatic gangrene of which the essential cause was apparently too little immunosuppression. With the correction of this defect in treatment and with attention to fixation of the liver to prevent distortion of the blood vessels,¹ the complication of septic hepatic infarction was eliminated and has not been observed since November 1967.

Three of the other five recipients are still alive after 9, 12, and 26 months. The two other children died after 13½ and 30 months. The original homograft of both of these patients underwent slow rejection. In the first case, retransplantation was carried out after 68 days. The second transplant then supported life for a year before failing. The other child died 2½ years after a first orthotopic transplantation and 2½ weeks after regrafting. The second transplantation was greatly

complicated by the fact that the portal and superior mesenteric veins had thrombosed and undergone cavernous transformation. The immediate cause of death was bacterial peritonitis.

Cirrhosis

Six patients were treated, with the disappointing record of five early deaths. Reasons for the heavy acute mortality included the wretched condition of the recipients at the time of operation, major hemorrhage due to portal hypertension and the depression of normal coagulation, and technical or metabolic mishaps.

Alcoholic cirrhosis—Three patients aged 33, 39, and 50 years died 10, 13 and 3 days respectively after operation. Obstruction of the homograft biliary drainage system had been accidentally produced in one recipient. The second developed bile peritonitis after disruption of a choledochocholedochostomy. The third suddenly became unconscious a few hours post-transplantation and never awakened; the cause for the neurologic calamity was not evident at autopsy.

Postnecrotic cirrhosis—The two recipients, aged 8 and 15, had evidence after transplantation of massive liver necrosis. They failed to wake from anesthesia and died after ½ and 9 days.

Wilson's disease—The 11-year-old child was admitted in hepatic precoma. After liver replacement, he had a grave rejection crisis, the most severe one we have ever seen with recovery. His bilirubin rose to 48.6 mg. per cent but eventually the process was reversed, so that now he has completely normal liver function 14 months later. A number of special studies are being reported by DuBois and his associates.⁶ Briefly, the copper content of the excised liver was 216 μ /Gm. wet tissue weight (normal less than 15 μ g.). The preoperative ceruloplasmin was 30 mg. per cent (low normal) and the urine copper 50 μ g./24 hours.

After transplantation the ceruloplasmin rose to 40 mg. per cent. The urine copper increased to more than 300 μ g./24 hours, before slowly returning to normal (less than 30 μ g./day) in the ensuing weeks. After 6 months, a homograft biopsy was obtained. The copper content was less than 15 μ g./Gm. wet tissue.

The Question of Hepatitis

Another case will now be recorded in addition to the 33 consecutive ones compiled 9 months or longer ago. On August 8, 1970, a 28-year-old woman with chronic active hepatitis was treated with orthotopic liver transplantation. For at least 2 years before operation and even on the day of liver replacement, immunodiffusion tests for the Australia antigen⁷ had been positive. On the morning after operation, the Australia antigen had disappeared and it has not since been found in any of the subsequent blood specimens. One month after operation, the patient has not had a rejection and is in excellent condition.

DISCUSSION

The main objective of this paper was to review the indications for orthotopic liver transplantation. Because of the high rate of recurrent carcinoma in our own experience, it has become policy in cases of hepatoma to consider liver replacement only under the most exceptional circumstances. This does not mean that some recipients with hepatoma cannot be cured nor does it imply criticism of other transplantation groups who persist in similar therapeutic efforts. In fact, one of our recipients and one of Calne's have no evidence at all of tumor recurrence and have probably been cured.

Whatever the virtues and faults of liver replacement for hepatoma, by far the more desirable candidates for the procedures are those without neoplasms. On the average, the performance of orthotopic transplantation for benign disease is more difficult since the patients tend to be sicker and to have more advanced portal hypertension. Moreover, if the diagnosis is biliary atresia, an increased incidence of vascular anomalies can be anticipated.¹ Nevertheless, the longest survivors in the world after liver transplantation are patients who had biliary atresia.

So far there have been few patients with cirrhosis who have benefited from liver transplantation. A reluctance to recommend such drastic therapy except in the agonal stages of the disease probably has been the main reason. Now that long-term survival and rehabilitation have been shown to be feasible, transplantation should be considered at an earlier time, particularly in cases of postnecrotic cirrhosis in which the maximum value of medical management and of abstinence from alcohol has already been realized.

However, an important question must be answered in a number of such candidates concerning the cause for the progression of the hepatic disease. In the last 2 years, many patients with "chronic aggressive hepatitis" leading to fatal cirrhosis have had demonstrated in their serum the "hepatitis-associated" or Australia antigen. The existing evidence suggests that the Australia antigen is the actual serum hepatitis virus.⁷ If this were true, antirejection therapy could be predicted to perpetuate and even aggravate the systemic virus infection by reducing host immunologic reactivity.

The course of the patient whose Australia antigen test promptly became negative after liver replacement was decidedly against such pessimism, even though a follow-up is available for only a month. The immediate disappearance of the Australia antigen provided striking evidence for an essentially exclusive hepatic source of the antigenic factor, at least in the patient under discussion, whether this was the actual virus or something manufactured by the liver after induction by the virus.

Observations of the child with Wilson's disease for 14 months after liver replacement provided another example of the important ancillary information that has come from transplantation research. Insofar as can be determined in this recipient, an inborn error of copper metabolism was cured by provision of a new liver. It is possible that further study of this and similar cases will permit identification of the basic defect in Wilson's disease and resolution of the controversies⁸ about its etiology.

SUMMARY

Orthotopic liver transplantation has led to prolongation of useful life. Among the first 33 recipients at the University of Colorado, there were eight who survived a year or longer, as well as a ninth who is in perfect health after nine months. The prime indication for orthotopic liver transplantation is nonneoplastic hepatic disease. Treatment of hepatomas by liver replacement has been followed by a high incidence of tumor recurrence.

As of November 16, 1970 the patient whose Au antigen became negative after transplantation had no difficulty for 2½ months. Then, the Au antigen became positive again and within a few days she developed clinical and laboratory evidence of acute hepatitis from which she is now recovering.

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Table 1
 Fate of Six Patients Who Received Liver Replacement for Indication of Hepatoma and Lived Long Enough After Operation to Permit Observations About Course of Malignancy

Patient Number	Metastases First Detected (days postop.)	Location First Metastases	Treatment of Metastases	Metastases to Homograft	Organs Ultimately Involved	Cause of Death & Time
OT 8	90	Lungs	Vincristine sulfate; 5 FU; surgical excision of intra abdominal masses; local Xray therapy to pelvis	Yes	Brain, lungs, liver, other abdominal organs	Carcinomatosis, 400 days
OT 14	380	Diaphragm, liver, retroperitoneal space	-	Yes	Mediastinum, pleural cavity, diaphragm, retroperitoneal space, liver, pancreas, other abdominal organs	Carcinomatosis; disrupted cholecysto-duodenostomy, 432 days*
OT 15	60	Lungs	-	Yes	Lungs, liver, diaphragm	Carcinomatosis, 339 days
OT 23	29	Lungs	-	Yes	Brain, lungs, liver retroperitoneal space	Carcinomatosis, 143 days
OT 26	59	Lungs	-	No	Lungs	Gastrointestinal hemorrhage, 76 days
OT 33 [†]	-	None found	-	-	-	Alive, 9 months

* Retransplantation had been carried out at 380 days, at which time the first metastases were discovered. By the time of death 52 days later, the extension of the metastases was pronounced.

[†]The diagnosis was an incidental finding in the liver specimen which had been removed because of biliary atresia.