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ORTHOTOPIC LIVER TRANSPLANTATION IN HUMANS

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In the interval from March, 1963 until May, 1967, 9 attempts were known to have been made at orthotopic transplantation of the human liver, 7 by us (Starzl *et al.*, 1968*a*; 1963; 1964), and one each by Moore (Moore *et al.*, 1964) and Demirleau (Demirleau

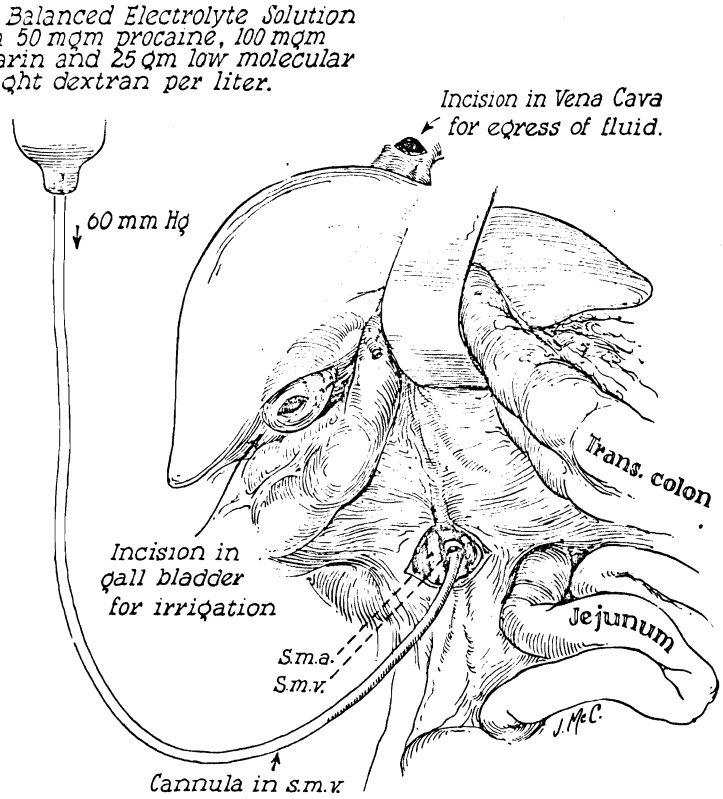

Fig. 1. Core cooling of cadaveric liver used for infant donors. Immediately after entering the abdomen, the cannula is placed into the readily accessible superior mesenteric vein. This vessel is far enough away from the portal triad so that the portal vein, which will ultimately be used for anastomosis, is not in danger of injury. Egress of the perfusion fluid is provided by the venotomy in the suprahepatic inferior vena cava. Bile is washed from the gallbladder through the cholecystotomy. (By kind permission of the publishers of *Annals of Surgery*.)

et al., 1964). Two of these patients died during or immediately after operation (Demirleau *et al.*, 1964; Starzl *et al.*, 1963); the other 7 succumbed after 6 to 23 days.

Since July 1967, we have performed 9 additional such operations with still imperfect but distinctly encouraging results. Five of these patients are still alive 2 weeks, 2 months, 3 months, 4 months and 10½ months later. The other 4 died after 2, 3½, 4½ and 6 months. Detailed reports of the first 7 cases have already been published (Starzl *et al.*, 1968*b*; 1968*c*).

In the following remarks, attention will be focused primarily on the unsuccessfully treated cases, since the complication that directly or indirectly killed these patients has also recently been seen at other centers including UCLA (Fonkalsrud, 1968), and is peculiar to man, as well as being probably completely avoidable.

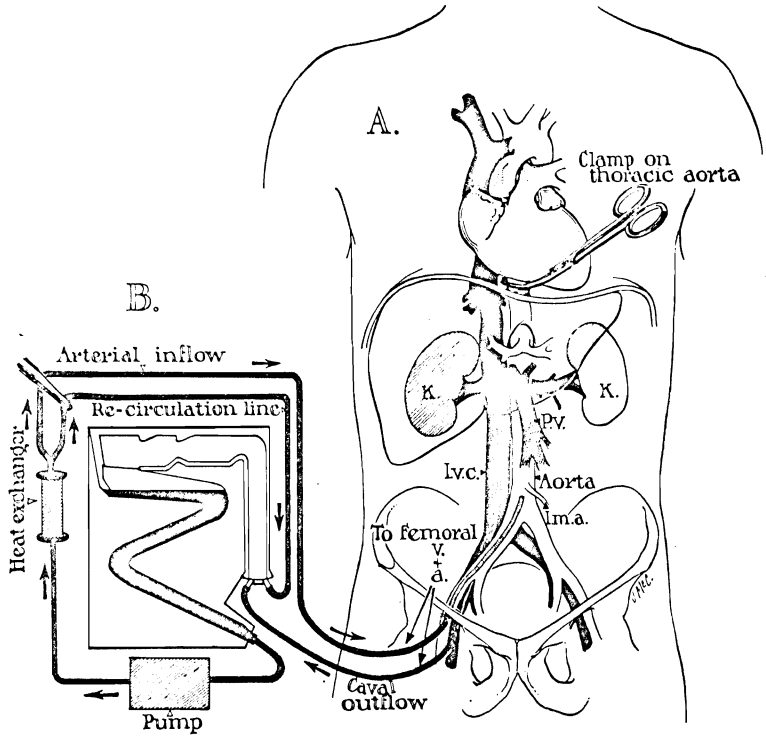

Fig. 2. Technique of extracorporeal cadaver perfusion. Catheters are inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. The extracorporeal circuit is primed with heparinized glucose or electrolyte solution to which procaine is added. The cadaver is anticoagulated with first surge of the pump. Temperature control is provided by the heat exchanger. (By kind permission of the W. B. Saunders Company, Philadelphia.)

METHODS

In the infant cadaveric donors, the organs were cooled as rapidly as possible after death by infusion of a cold solution through the superior mesenteric vein (Fig. 1). The accessibility of this vessel and the ease with which it could be isolated permitted

cooling to be instituted with the loss of only a minute or two. The adult cadavers were cooled by post mortem extracorporeal perfusion with an artificial heart-lung machine that included a heat exchanger (Fig. 2). The aorta was removed in continuity with the hepatic arterial supply of the infant livers.

The excised organs were then conserved with a technique (Brettschneider *et al.*, 1968) that involves low-flow perfusion of the liver with diluted blood (6 ml/g tissue/hr.), hyperbaric oxygenation (40 PSIG), and hypothermia (4°C). The times from donor

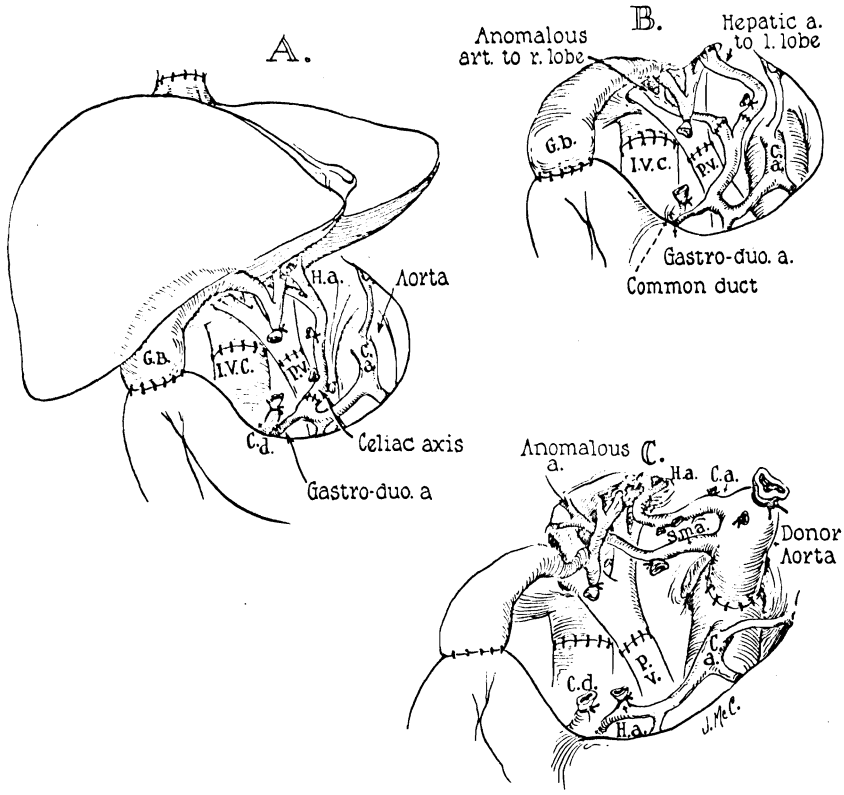

Fig. 3. Recipient operations. Cholecystoduodenostomy was performed in all 9 cases.
A. The kind of arterial anastomosis used in Cases 1, 3, 4, and 6–8. The homograft coeliac axis or common hepatic artery was attached to the proper or common hepatic artery.
B. Arterial anastomoses in Case 2. The right hepatic originated from the superior mesenteric artery.
C. Anastomosis of the homograft aorta to the recipient aorta (Case 5). This technique was used because of the double arterial supply.
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death to homograft revascularization in the recipient ranged from 4 to 8 hrs. In one case, the donor died while the eventual recipient was still at the O'Hare Airport in Chicago, trying to get onto a plane to make the thousand mile trip to Denver.

Recipients were selected who had a reasonable histocompatibility match with the donors as determined by prospective studies of the peripheral lymphocytes by Dr. Paul Terasaki (1967) of Los Angeles and in our laboratories. A superb match was obtained

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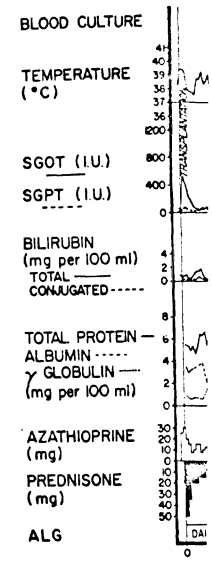

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Seven of the 9 recipients were infants aged 13 to 24 months; 6 had a diagnosis of extrahepatic biliary atresia and the other 3 had hepatomas. The adults, aged 16 and 43 years, had hepatomas. In 7 of the 9 cases, there was moderate or severe portal hypertension which made recipient hepatectomy difficult.

In principle, the operation of orthotopic liver transplantation is a simple one, involving first the reconstruction of vascular structures entering and leaving the new liver (Fig. 3). Unfortunately, two of the children received homografts that had anomalous right hepatic arteries originating from the superior mesenteric artery. In one, the hepatic branches were anastomosed individually (Fig. 3B). In the other, the vessels were left in continuity with the aorta which in turn was attached to the recipient aorta (Fig. 3C). Direct hepatic artery anastomosis was performed in the other 7 (Fig. 3A). Biliary drainage for the new livers was with cholecystoduodenostomy.

Postoperatively, immunosuppressive therapy was with azathioprine, prednisone, and heterologous antilymphocyte globulin (ALG) raised in the horse. The doses and interrelationships of these agents in 4 of the cases are shown graphically in Figs. 4, 5, 6 and 9.

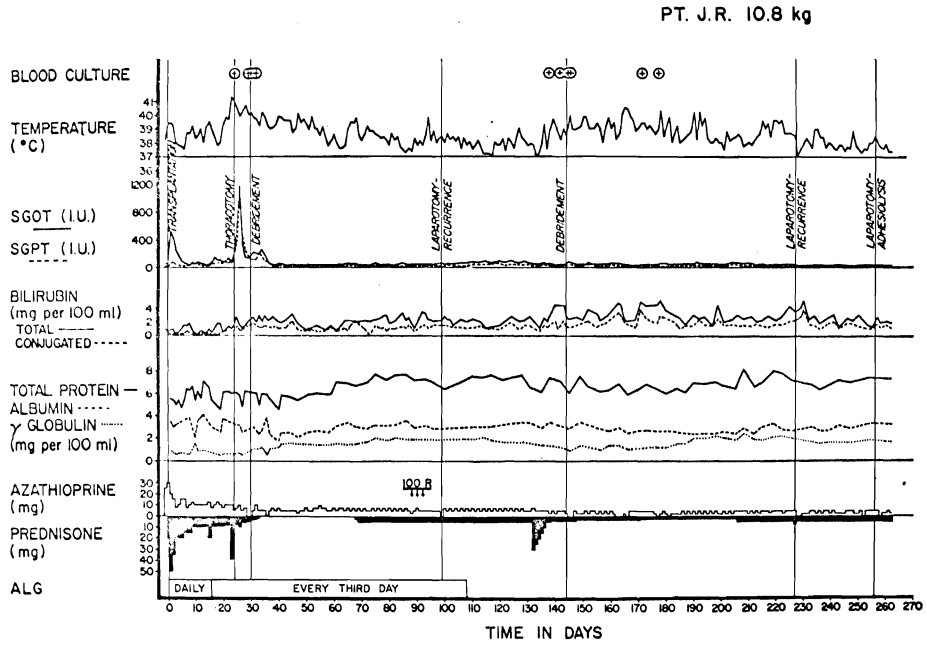

Fig. 4. Course in Case 1 for the first 9 months after orthotopic liver transplantation; she is still alive after 10½ months and has been discharged from the hospital. The indication for operation was hepatoma. Note the high rises in SGOT and SGPT, and the bacteremia which occurred at the time of the initial liver infarction. The later septicemia developed when the patient became leukopenic during treatment with vincristine for tumor metastases. The thoracotomy was for removal of an unexpanded right upper lung lobe. The first 2 laparotomies were for excision of tumor recurrences. Liver function has been stable for 8 months. 100 R – Depth dose of local homograft irradiation. The temperatures are the highest for each day.
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RESULTS

In all 9 cases, the homografts provided good early function as was learned in the first patient, an 18-month-old girl with hepatoma (Fig. 4). She was not jaundiced before operation and has not become clinically so, in the 10½ months since. Her total proteins, albumin, alkaline phosphatase, and BSP excretion have been normal for months.

Nevertheless, she suffered the calamitous complication alluded to in our introductory remarks. Three weeks after transplantation, she developed high rises in her serum transaminases at the time other liver function tests were little changed (Fig.4). The picture was completed by the appearance of gram-negative septicemia.

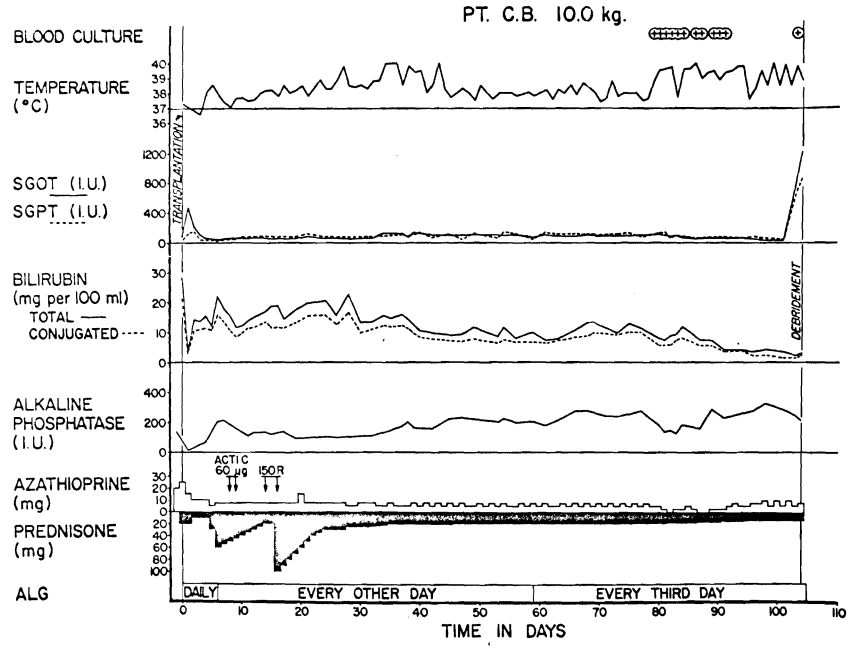

Fig. 5. Course in Case 5 after orthotopic liver transplantation for extrahepatic biliary atresia. A vigorous and protracted rejection began within a few days postoperatively which was not reversed for 10 weeks. Function was improving when persistent gram-negative septicemia presaged liver sepsis. Complete right lobar infarction finally occurred causing death within 48 hrs. At autopsy, the right hepatic artery was thrombosed. Acti C – Intravenous actinomycin C in micrograms. 150 R – Homograft irradiation.

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Liver scans at that time showed a filling defect in the right lobe. This part of the liver was found at operation to be infarcted. After the infected necrotic tissue was debrided, regeneration occurred. However, it required 8 months for the filling in to be complete.

The same complication occurred in each of the first 5 patients, and was followed shortly after by death in 2 patients. In Fig. 5 is shown the course of one of these patients who had passed through a difficult but reversible rejection (as can most readily be appreciated by the secondary rise and fall of serum bilirubin) only to die 3½ months post-

operatively of a septic hepatic infarction of the right lobe which was presaged by gram-negative septicemia and ultimately signalled by the typical high rises in transaminases.

Finally, 2 other patients survived regional hepatic gangrene which was treated by right lobectomy or debridement, but died 4 and 5½ months later respectively with deepening jaundice and other evidence of chronic liver failure (Fig. 6). In these 2 cases, there was initial evidence of hepatic regeneration but ultimately the homografts began to shrink as could be demonstrated with serial liver scans (Fig. 7).

The autopsy examination in each of the 4 children who died, either soon after or at some time following the onset of partial or complete right lobar gangrene, revealed

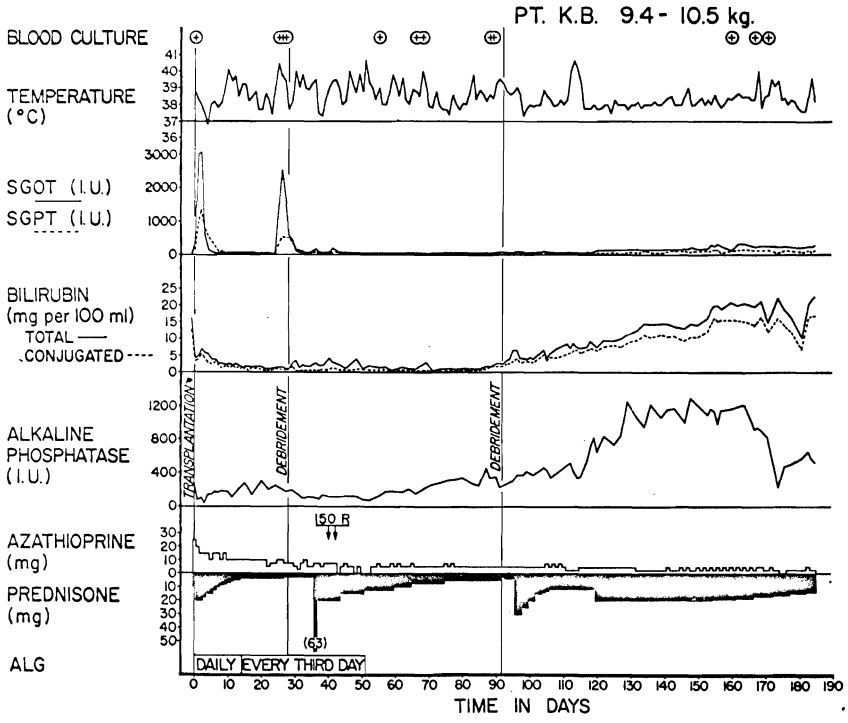

Fig. 6. Course in Case 3 after orthotopic liver transplantation for extrahepatic biliary atresia. Hepatic function was excellent during the first 3 months despite infarctions of large portions of the central and right liver which were treated with debridement. Thereafter, liver failure was progressive. Note the late parallel increases in alkaline phosphatase and bilirubin. The immediate cause of death was intraperitoneal rupture of an undrained residual abscess. Survival was 6 months. Liver irradiation was with 150 R depth dose at each arrow. The temperatures are the daily maximums. (By kind permission of the publishers of *Annals of Surgery*.)

a common finding. There was selective thrombosis of the right hepatic artery. Apparently the events of this distressing syndrome were initiated by regional hepatic dearterialization, followed by bacterial invasion of the necrotic tissue with enteric organisms, and then septicemia.

A fuller explanation for these disasters was sought by angiographic studies in fresh infant and adult cadavers. Dye was injected in the common hepatic artery. The right

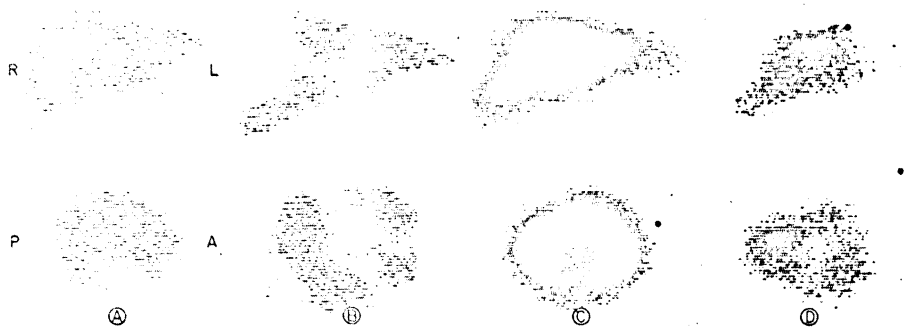

Fig. 7. Radioisotope liver scans in Case 3.
A. Normal scan 10 days post-transplantation.
B. Non-opacifying areas in the right and central parts of the liver 27 days postoperatively. Septicemia had developed.
C. The necrotic areas were debrided. There was evidence of regeneration 84 days post-transplantation. Liver function was still excellent.
D. Liver shrinkage and diminished isotope uptake 176 days after transplantation. The child died 10 days later when an abscess in the left lobe ruptured into the peritoneal cavity.
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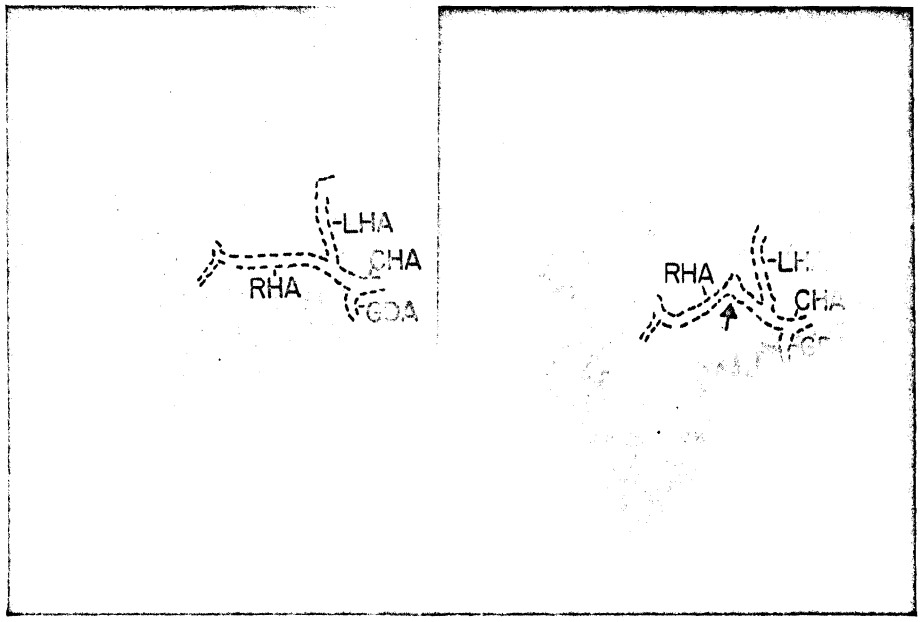

Fig. 8. Angiographic studies performed in a 5-year-old child immediately after her death from head injuries. Dye was injected into the common hepatic artery (CHA) proximal to the gastroduodenal artery (GDA). Left. Initial injection. Note the smooth course of the right hepatic artery (RHA). Right. The restraining ligaments of the liver have been incised, a cholecystoduodenostomy performed, and the head of the X-ray table elevated to 60°. The right lobe of the liver has rotated down and medially. The course of the left hepatic artery is undisturbed. However, the right hepatic artery (RHA) is now severely kinked where it passes beneath the common duct (see discussion.)
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branch was long and straight (Fig. 8, Left). The ligaments of the liver were then incised and a simulated transplantation performed. Now, when the X-ray table was elevated to 60°, the right liver lobe rotated down and medially, and in some instances (but not all) there was distortion and kinking of the right hepatic artery. Even in the most extreme cases, however, there was not occlusion (Fig. 8, Right). It was concluded that a mechanical element such as this slight liver torsion could have been contributory to the dearterialization and that the reduced blood flow and organ swelling which occurred during rejection might have been additional factors (Starzl *et al.*, 1968*c*).

In the last 4 cases, the liver ligaments of the homografts have been reattached, pinning the organ into the normal location. Septic liver infarction has not occurred as exemplified by a recent patient with biliary atresia who cleared his bilirubin from 30 mg% to almost normal within a few days (Fig. 9). He has not subsequently had

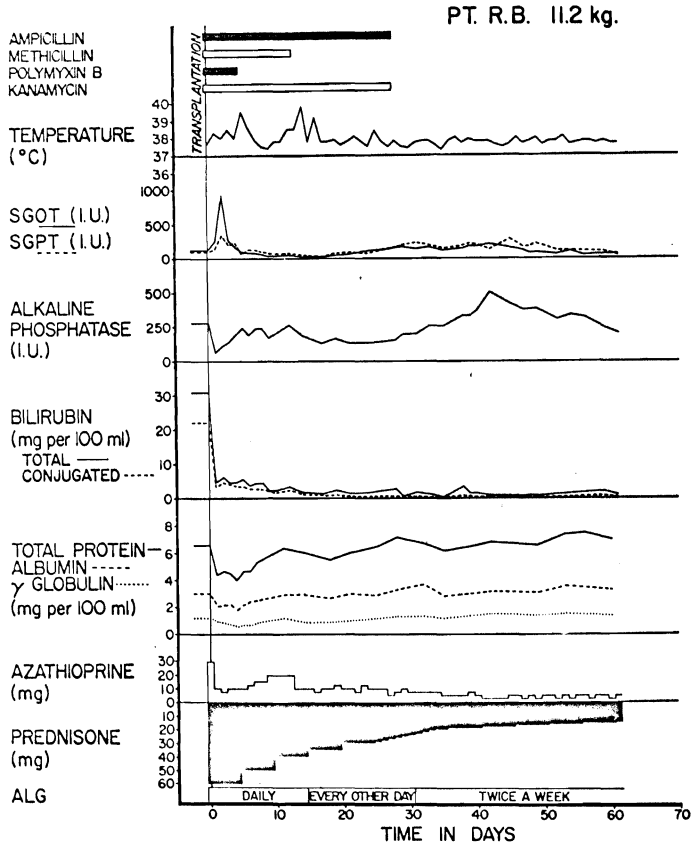

Fig. 9. The first 2 months of the course in Case 6; the child is now 4 months postoperative and has been discharged from the hospital. The operation was for extrahepatic biliary atresia. The homograft was immobilized by suturing its ligaments. Jaundice has not recurred, although rejection was diagnosed from the third to seventh postoperative weeks because of the rises in alkaline phosphatase, SGOT, and SGPT; these changes have receded. By 4 weeks, all antibiotic therapy was stopped. The child has since been afebrile. The temperatures are the maximums for each day. An equally benign course has been observed in Case 7.
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overt rejection, and has been discharged from the hospital; he has now survived for 4 months.

Liver tissue from uninfarcted areas was obtained from 2 to 6 months after transplantation in each of the first 5 cases, either from biopsy (Case 1) or autopsy (Cases 2–5). In none was there evidence of active rejection. Histopathologically, the organs ranged from nearly normal, to the presence of mild fibrosis in the portal tracts, through moderate fibrosis in the same location, and, in one case severe enough fibrosis after 4½ months to warrant the designation of cirrhosis. These changes were thought to represent chiefly repair of an earlier rejection. The extent of the abnormalities was roughly related to the degree of histocompatibility previously shown to exist between donors and recipients.

SUMMARY

Nine patients were treated with orthotopic homotransplantation of the liver. Five of these patients are alive from 2 weeks to 10½ months postoperatively. The encouraging results compared to those in the past are probably due to attempts at histocompatibility matching, the utilization of better preservation techniques, and improved immunosuppression.

The septic liver infarctions which killed 2 patients and contributed to the deaths of 2 others appear to have had an at least partially mechanical etiology which is partly based on man's (or a child's) determination to assume an erect posture. The complication appears to be preventable by effective fixation of the transplanted liver in its natural position and by the provision of more stringent immunosuppression in the early postoperative period.

ACKNOWLEDGEMENT

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