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LIVER REPLACEMENT IN CHILDREN*

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In the 10½ years between the spring of 1963 and the fall of 1974, liver transplantation was attempted in 93 patients by removing the diseased native liver and replacing it with a cadaveric homograft in the natural (orthotopic) location. Fifty-six of the liver recipients were 18 years old or younger; the other 37 were adults.

The following report will be concerned with the 56 pediatric patients, of whom 40 carried the diagnosis of biliary atresia. Attention will be directed to the need in the treatment of biliary atresia to develop a unified philosophy in which the porticoenterostomy of Kasai and liver transplantation are perceived to be complementary rather than competitive components of the continuum of care.

CASE MATERIAL

The indication for operation was something other than biliary atresia in only 16 of the 56 pediatric recipients. The mean age of these 16 patients at the time of transplantation was 12.9±4.6 (S.D.) years (range 1 to 18 years). Nine of the 16 patients had some variant of chronic aggressive hepatitis without HB_sAg antigenemia (table 1). Three more had hepatomas for which conventional partial hepatectomy was not feasible. Two had Wilson's disease. There was one example each of congenital biliary cirrhosis and cirrhosis associated with homozygous alpha-1-antitrypsin deficiency of the PiZZ phenotype.

The 40 patients who had biliary atresia were 42.0±37.7 (S.D.) months old (range 3 to 191 months) at the time of transplantation. The four oldest

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Table 1. Pediatric patients with diagnosis other than biliary atresia.

	Number	Survival > 8 months	Alive now**
Chronic aggressive hepatitis	9*	3 (33%)	2 (2/3, 1½ years)
Hepatoma	3	2 (67%)	0
Wilson's disease	2	2 (100%)	2 (4¼, 6 years)
Congenital biliary cirrhosis	1	1 (100%)	1 (3 years)
Alpha-1-antitrypsin deficiency	1	1 (100%)	1 (1½ years)

* None of these 9 patients was HBsAg positive.

** The three late deaths were after 13, 14 and 26 months (see text and table 4 for causes).

children, who were 7, 11, 11 and 15 years old (OT 80, 26, 67 and 43*), were diagnosed as having intrahepatic atresia largely because of their long survival. Histopathologically, these 4 livers showed a micronodular biliary cirrhosis compatible with congenital intrahepatic biliary atresia. Two of the 4 livers also contained liver cell carcinomas (hepatomas); only one such malignancy was found in the other 36 patients suffering from extrahepatic biliary atresia.

Excluding the four oldest children, the collective age of the other 36 patients with biliary atresia was 31.3 ± 15.7 (S.D.) months (range 3 to 67 months).

Although they will not be considered in this report, it is worth mentioning that the 37 adult patients treated during this same time were 39.0 ± 11.1 (S.D.) years old (range 21 to 68 years). Their most frequent diagnoses were primary hepatic malignancy, chronic aggressive hepatitis and alcoholic cirrhosis.

MANAGEMENT PRINCIPLES

Most aspects of the care of these patients have been described (7). Here, a few details will be mentioned.

In recent years, only stable brain dead donors have been accepted. Preliminary arteriography has been routinely performed. Complicated preservation devices are no longer used for the grafts. With almost all infant and

* These orthotopic transplant (OT) numbers are frequently given so the reader may follow given patients through different publications from our center. This method of identification has been used since 1969 (7).

child donors, the only preservation used has been perfusion with a chilled electrolyte solution through the portal vein just before and after liver removal. To protect the larger livers of adolescents and adults, these donors are often placed on cardiopulmonary bypass and cooled by means of a heat exchanger preparatory to a final infusion with cold electrolyte solution (7).

HL-A typing was obtained on all donors and recipients since 1964, but the match was not used as an instrument of donor-recipient matching. In 51 of the 54 pediatric cases in which typing data were obtained (table 2), major

Table 2. HL-A typing of primary grafts in 56 pediatric cases.

Match*	No.	Survival >8 months	Alive now
A	1**	1 (100%)	0
B	2	1 (50%)	0
C	8	3 (38%)	2 (25%)
D	16	3 (19%)	2 (13%)
E	25	11 (44%)	9 (36%)
F	2	0	0
Not done	2	1 (50%)	0
Total	56	20 (36%)	13 (23%)

* A-Match: HL-A identity between recipient and donor.
B-Match: Compatibility between donor and recipient, but fewer antigens determined in the donor.
C-Match: One antigen incompatible.
D-Match: Two antigens incompatible.
E-Match: Three or four antigens incompatible.
F-Match: ABO violation or positive cytotoxic crossmatch.
** Retransplanted after 68 days with C-match graft. Thus the extended survival reflects the result with the second or less well matched graft.

incompatibilities were present. The presence and severity of incompatibilities did not seem to influence the outcome, although the force of such a conclusion was weakened by the fact that good matches were a rarity.

Preformed anti-red cell isoagglutinins and leukocyte cytotoxins are apparently less injurious for liver grafts as compared to kidneys. These antibodies, which immediately destroy many renal homografts that are transplanted in violation of a 'positive crossmatch' (4, 7) do not usually cause a comparable hyperacute rejection of the liver (5). In two patients of the pediatric series, liver transplantation was carried out in confrontation of such preformed antibodies (table 2).

One significant change has been made in the technique of transplantation.

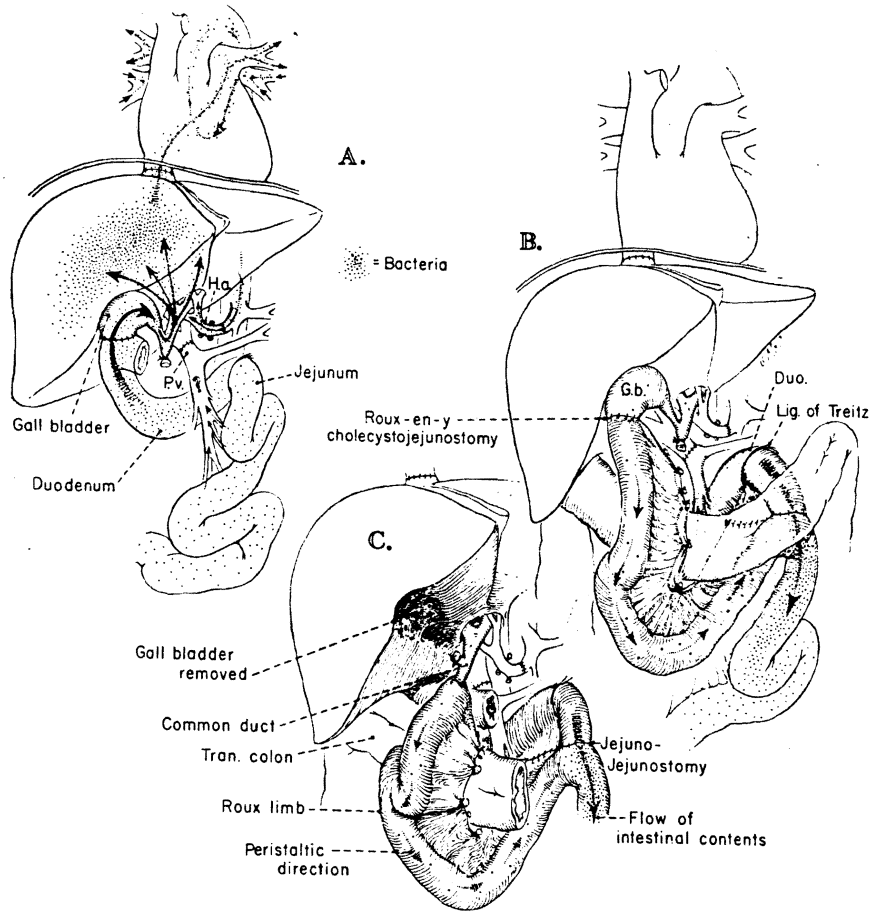

Fig. 1. Commonly used methods of biliary reconstruction. (A) Cholecystoduodenostomy. This extremely simple operation probably carries the greatest risk of graft infection. (B) Roux-en-Y cholecystojejunostomy. This operation protects from hepatic sepsis by placing the new liver outside the main gastrointestinal stream. The isoperistaltic limb is made at least 18 inches long. (C) Roux-en-Y choledochojejunostomy. The end-to-end duct-to-bowel anastomosis is simple if the duct is dilated, as would be the case if a conversion became necessary from B to C because of biliary obstruction. If the common duct is not dilated, the end of the Roux limb is closed and the common duct is anastomosed to the side of the jejunum an inch or so from the tip. (By permission of *Transplant. Proc. 6*: 129, 1974.)

Provision for graft biliary drainage in most of our early experience was with cholecystoduodenostomy after ligation of the common duct (fig. 1A). Since November 1973, the gall bladder usually has been anastomosed to the je-

junum by the Roux-en-Y technique (fig. 1B), thus placing the transplant outside the main continuity of the gastrointestinal tract. In a few cases, choledochojejunostomy (fig. 1C) or choledochocholedochostomy with T-tube splinting has been used instead after removal of the gall bladder.

Splenectomy was carried out at the time of transplantation or had been performed previously (3 cases) in 42 of the first 51 pediatric patients, being omitted only if it seemed excessively dangerous. In the last five cases of this report, splenectomy was omitted.

Triple agent immunosuppression with azathioprine, prednisone and horse antilymphocyte globulin (ALG) has been standard treatment for most cases since 1966 (7). If hepatotoxicity with azathioprine is suspected, cyclophosphamide may be substituted with the expectation of a comparable therapeutic effect (8).

RESULTS IN PEDIATRIC CASES

Other than Biliary Atresia

Mortality in the first half year. Seven of the 16 patients died from one to 188 days after operation (table 3). The longest survivor amongst the early deaths was a 15 year old girl (OT 65). She developed inexorable rejection of her first graft. After 157 days, retransplantation was carried out. She died one month later with a multiplicity of complications including intra-abdominal infection, pneumonitis and pulmonary insufficiency. Total survival was 188 days. Histopathologic analysis of the successive grafts showed that the first transplant was severely damaged by rejection while the only damage to the second graft was chronic venous congestion. By 37 days the first graft was undergoing cellular rejection and the portal tracts were densely infiltrated by lymphoid cells, about 20 per cent of which had pyroninophilic cytoplasm. By 147 days there was loss of bile ductules and obstruction of hepatic arterioles and small arteries by fibrous intimal thickening. When the graft was removed at 157 days there was marked centrilobular cholestasis and frequent scattered areas of old ischemic damage and recent infarction. At autopsy, the second graft had no evidence of rejection.

The second longest survivor amongst those who died early was a 15 year old boy whose homograft was eventually invaded and destroyed in 143 days by metastases from the hepatoma which had been the original disease in the excised native liver (OT 23).

Omitting the foregoing recipients with survivals of 188 and 143 days, the

Table 3. Transplantation for indications other than biliary atresia. Causes of death in the first half year after transplantation.

OT No.	Age at operation (years)	Survival (days)	Last bilirubin (mg%)	Clinician's opinion** of cause of death	Pathologist's opinion
65	15	188	1.5	First homograft rejected and replaced after 157 days; died of abdominal sepsis and pulmonary insufficiency 31 days later.	First graft: Loss of bile ductules and obliterative intimal thickening in small arteries following rejection. Second graft: Chronic venous congestion. No evidence of rejection.
23	15	143	40	Carcinomatosis	Multiple metastases of liver cell carcinoma. Severe centrilobular cholestasis. Rejection not definite.*
7	16	64	3.0	Intra-abdominal sepsis following perforation of right colon diverticulum.	Few tiny focal necroses associated with sepsis. No evidence of rejection.
41	16	61	13	Systemic sepsis and hepatic abscesses after delayed correction of partial biliary obstruction (cholecystoduodenostomy to choledochoduodenostomy).	Slight bile retention and evidence of partial bile duct obstruction. No evidence of rejection. No obvious liver abscesses seen.
44	11	34	14	Partial biliary obstruction and dilated intrahepatic duct communicating with ruptured hepatic abscess (diagnosed at autopsy).	Partial biliary duct obstruction. Ruptured hepatic abscess and cholangitis. Widespread fatty infiltration. No evidence of rejection.
31	15	9	30	Massive hepatic necrosis; possible arterial insufficiency of graft.	Acute cellular rejection.

Table 3. (continued).

OT No.	Age at operation (years)	Survival (days)	Last bilirubin (mg%)	Clinician's opinion** of cause of death	Pathologist's opinion
20	8	1	too soon	Massive hepatic necrosis; probable arterial insufficiency of graft.	Extensive hepatic necrosis. No rejection.

* In all the tables, the phrase 'rejection not definite' was used in an equivocating sense. The classical findings of cell-mediated rejection were not present, but abnormalities such as intrahepatic cholestasis cannot yet be excluded as manifestations of the rejection process, either early or late after transplantation (see reference 7 for full description of histopathology of rejection).

** The clinician's opinions in this and the other tables were reached after the gross autopsy findings were known, but without knowledge of the histopathology of the grafts.

five other patients shown in table 3 died 33.8±28.9 (S.D.) days postoperatively (OT 20 1 day; OT 31 9 days; OT 41 61 days; OT 44 34 days; and OT 57 64 days). Graft rejection accounted for only one of these failures. Technical complications accounted for three more fatalities. The fifth death after 64 days resulted from perforation of a posterior diverticulum in the ascending colon.

The two earliest deaths were of patients who had massive necrosis of the liver at autopsy, one (OT 20) and nine days (OT 31) postoperatively. Although the hepatic artery of one of these patients (OT 20) was patent at autopsy, it was thought that it had been distorted or kinked with consequent poor flow. Alternatively, the transplant may have sustained unrecognized damage from ischemia before, during or just after its removal from the donor and during implantation. The graft of the other patient (OT 31) was found at autopsy to be undergoing uncontrolled cellular rejection (fig. 2).

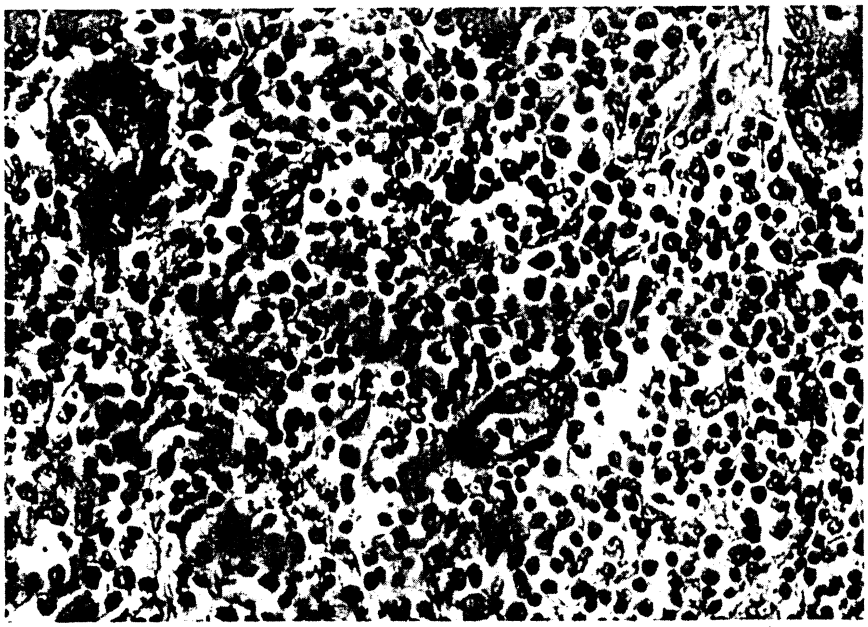

Fig. 2. Acute cell-mediated rejection (OT 31). The portal tract is diffusely infiltrated with lymphoid cells. Hematoxylin and eosin. (× 300)

Two of the patients died 61 and 34 days after transplantation (table 3) as a consequence of partial obstruction of the homograft cystic duct following cholecystoduodenostomy. The results were dilatation of the intrahepatic

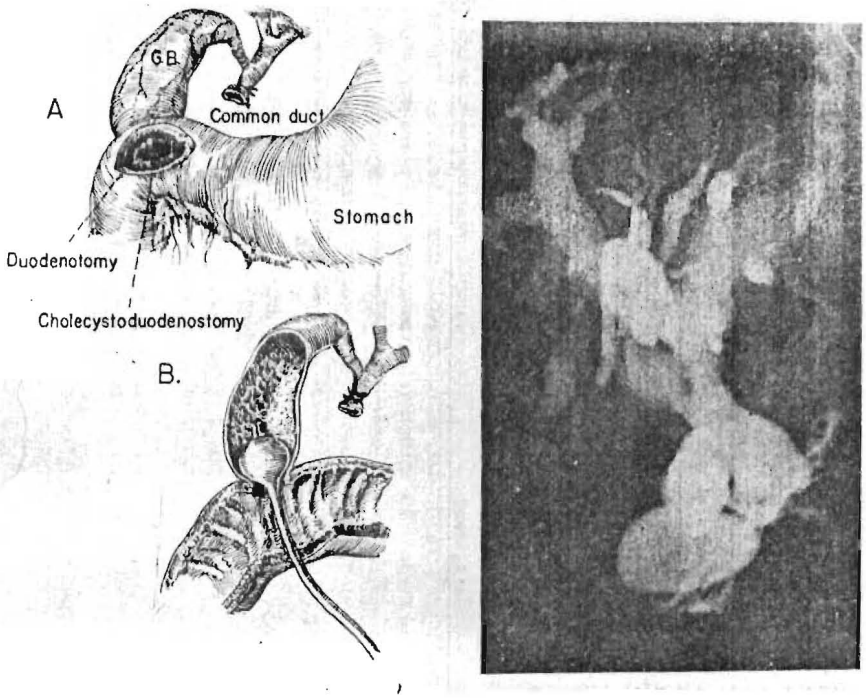

Fig. 3. Cholangiography of hepatic homograft. (A) and (B). Technique of dye injection through a duodenotomy and through the anastomosis. Right ... the obstructed duct system in patient OT 43. Operative and radiographic findings were almost identical in patient OT 41. In both cases cytomegalovirus of the cystic duct was present and may have been partially responsible for the complication. (By permission of *Surgery 72*: 604, 1972.)

biliary tree similar to that shown in figure 3, and bacteremia that presumably originated from the liver. The complication was diagnosed at autopsy in one case after a right hepatic duct had ruptured first into an abscess and then into the subphrenic space (OT 44). The diagnosis in the other recipient (OT 41) was made at reoperation. Secondary conversion to choledochoduodenostomy was carried out, but too late. The grafts of these patients at autopsy had no evidence of rejection.

Late mortality. Nine of the 16 recipients had long survival (tables 1 and 4). Eight lived for at least a year and since a ninth child has reached the eight month mark with normal liver function, the one year survival is almost certain to be 56 per cent. Of the nine children who lived for a long time, six are still alive (table 4).

Two late deaths at 13 and 14 months were caused, at least in part, by

Table 4. Liver transplantation for indications other than biliary atresia. Ultimate fate of the nine patients who had prolonged survival.

OT No.	Age at operation (years)	Survival (months)	Last bilirubin (mg%)	Clinician's opinion of cause of death	Pathologist's opinion
8	1½	13	15	Carcinomatosis from original hepatoma	Recurrence of liver cell carcinoma. Chronic cholangitis and obstruction of biliary tree by inspissated bile. Thrombosis of both branches of hepatic artery. Arterial collateral from right phrenic artery.
14	16	14	5	Carcinomatosis; first graft rejected and removed after 379 days; died 57 days after second graft (with disrupted cholecystoduodenostomy)	First graft: Micronodular cirrhosis and cholangitis. Narrowing of small hepatic artery branches probably as a result of chronic rejection. Second graft: Widespread fatty infiltration. No evidence of rejection or bile duct obstruction.
27	11	72	20	Alive	Biopsy at 4 years 10 months shows slight increase in amount of connective tissue in portal tracts. Liver copper levels normal. No evidence of rejection.
42	16	51	0.5	Alive	Biopsy at 3½ years showed normal liver. Liver copper levels normal. No evidence of rejection.
55	6	26	30	Undiagnosed main bile duct obstruction	At necropsy biliary tree dilated and blocked by inspissated bile due to stricture at choledochocholedochostomy.

Table 4. (continued).

OT No.	Age at operation (years)	Survival (months)	Last bilirubin (mg%)	Clinician's opinion of cause of death	Pathologist's opinion
56	18	37	2.5	Alive	Biopsy at 5 months showed early evidence of bile duct obstruction. Two months later cholecystoduodenostomy converted to choledochoduodenostomy.
74	16	19	10.0	Alive	Biopsy at 133 days showed some centrilobular cholestasis with bile thrombi following a rejection episode.* No evidence of bile duct obstruction or recurrence of alpha-1-antitrypsin enzyme deficiency hepatic changes.
77	16	17	0.5	Alive	Never biopsied.
92	11	8	1.0	Alive	Biopsy at 90 days showed changes consistent with acute viral hepatitis. No evidence of rejection or large bile duct obstruction.

* By 1 year 5 months rebiopsy showed no cholestasis, but slight cellular infiltration of portal tracts and swelling of hepatocytes suggestive of some drug toxicity.

metastases from the hepatomas for which the transplantation had been originally performed (OT 8 and OT 14).

A third child whose original disease was chronic aggressive hepatitis died 2 years and 2 months after transplantation (OT 55). At autopsy, which was performed by Dr. Fred Germuth of St. Louis, Missouri, the total intra- and extrahepatic duct systems were crammed with chalk-like sludge. The complication was apparently caused by an underlying stricture at the choledocho-choledochostomy that had been constructed more than two years earlier without T-tube drainage. The diagnosis was not made premortem in spite of two attempts to perform transhepatic cholangiography. Failure to enter the intrahepatic ducts was incorrectly taken as assurance against duct obstruction.

The liver in this tragic case had little evidence of rejection. The predominant findings were those of bile stasis. All the bile ductules were dilated and many lacked lining epithelium and were blocked by inspissated bile (fig. 4).

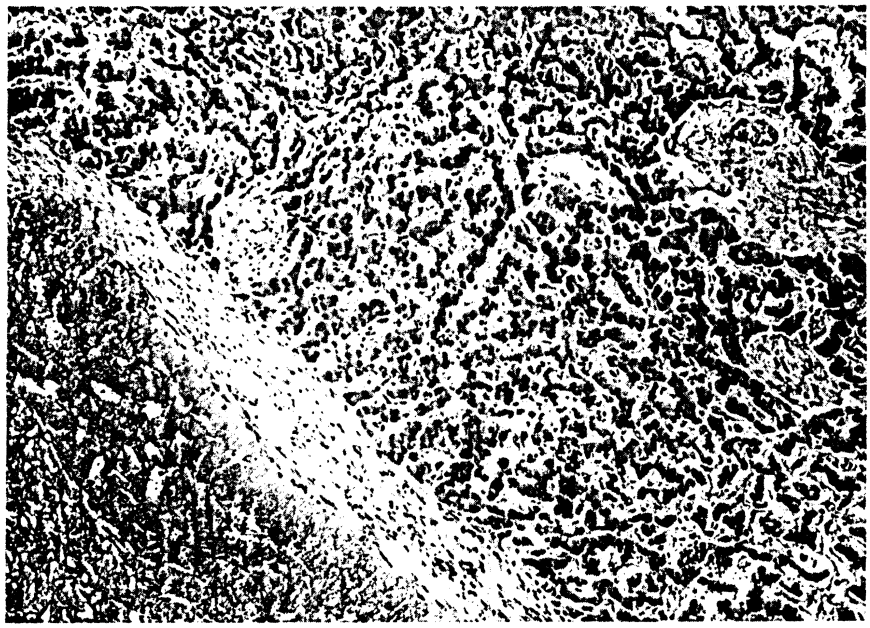

Fig. 4. Biliary obstruction caused by a stricture at the common duct anastomosis (OT 55). In the lower left of the picture, a greatly dilated bile ductule is filled with inspissated bile. Hematoxylin and eosin. (× 120)

Some ductules had ruptured with extravasation of bile and subsequent focal fibrosis and calcification. There was also great narrowing of many of the hepatic artery branches by intimal thickening composed of smooth muscle cells and connective tissue. In several of the arteries the internal elastic lamina was ruptured. This arterial narrowing seemed to be mainly endarteritis caused by proximity to bile extravasation and cholangitis but chronic rejection may have contributed in part to the vascular obliterative changes.

Cases of biliary atresia

Mortality in the first half year. Twenty-nine of the 40 patients died early after transplantation (intraoperatively to 188 days). The mortality occurred in progressive waves to which specific etiologic factors selectively contributed at successive times.

Ten patients died 4.9±6.3 (S.D.) days postoperatively (range intraoperatively to 20 days) because of failure to obtain a satisfactory technical result, or in one case because of a mistake in management (table 5). The most common accident was inability to arterialize the new liver, either because of hepatic artery thrombosis (three cases) or because of nonthrombotic occlusion of this vessel by compression or twisting (two cases). Operative and postoperative hemorrhage killed two more recipients and contributed to the death of a third. Portal vein thrombosis, obstruction of the venous outflow from the liver (caused by excessive cuff lengths of the vena caval anastomosis at the diaphragm) and blood volume mismanagement accounted for the other three failures.

hepatic artery thrombosis and wound hemorrhage, respectively) were of patients who were undergoing retransplantation after the first grafts had failed after 85 and 33 days for reasons that may not have involved rejection (see table 5). The primary graft of one patient (OT 70) appeared to have been irreversibly damaged by viral infection. The other primary graft (OT 52) was obtained from an anencephalic monster. It provided excellent function except for the persistence of jaundice. When the graft was removed after 85 days, intrahepatic ducts could not be found. It was considered possible that the donor had unrecognized intrahepatic biliary atresia.

A second group of five early deaths occurred 21.8±11.9 (S.D.) days (range 7 to 36 days) after transplantation because of what the clinicians diagnosed as an inability to control rejection. Jaundice (table 6) and other perturbations of liver function tests showed hepatic failure but infections elsewhere were almost invariably present as a contributory cause of mortality. In one of the cases, a chimpanzee heterograft was used to replace a failed homograft after

Table 5. Biliary atresia. Early deaths from faulty technique or management (excluding duct problems).

OT No.	Age (years)	Time to death or graft loss (days)	Main complication	Pathologist's opinion
1	3	0	Bleeding	Massive necrosis of hepatocytes of allograft due to ischemic damage before transplantation.
18	1	4	Hepatic artery clot	Homograft completely necrotic except for single layer of surviving liver cells beneath capsule.
21	2	1	Portal vein clot	Necrosis of hepatocytes in central and middle zones of lobules and fat accumulation in liver cells in peripheral lobular zones of homograft.
24*	3	11	Liver necrosis from arterial insufficiency	Necrosis of hepatocytes in central and middle zones of homograft. No evidence of rejection.
34*	2	7	Outflow obstruction	Homograft completely necrotic.
38	3	20	Hepatic artery clot	Necrosis of hepatocytes in central zones of lobules of homograft. No evidence of rejection.
48	2	2	Liver necrosis from arterial insufficiency; bleeding	Massive necrosis of hepatocytes of allograft.
52	¼	85 (first graft)	Rejection	First graft: Marked cholestasis due to congenital intrahepatic biliary atresia. Little evidence of rejection.
		1 (second graft)	Hepatic artery clot	Second graft: Massive necrosis of hepatocytes.

Table 5. (continued).

OT No.	Age (years)	Time to death or graft loss (days)	Main complication	Pathologist's opinion
76	2	33 (first graft)	Rejection	First graft: Massive necrosis of hepatocytes in central and middle zones of lobules of homograft due to extensive viral infection of unknown kind. No evidence of rejection.
		2 (second graft)	Bleeding	Second graft: Normal-looking liver homograft.
80	7	1	Hypovolemia from inadequate fluid replacement	Normal-looking liver homograft.

*. A complex of anomalies was present consisting of an absent retrohepatic inferior vena cava, hepatic artery originating from superior mesenteric artery, preduodenal portal vein and intestinal rotation (3, 7).

Table 6. Biliary atresia. Early deaths from rejection.

OT No.	Age (years)	Time to death or graft loss (days)	Complication	Last bilirubin (mg%)	Pathologist's opinion
7	11/12	7	Rejection; liver failure	15	Acute cellular rejection
35	2	36	Rejection; liver failure; infection	17.5	No rejection. Liver failure possibly secondary to infection.
50	1	31	Rejection; liver failure	12.6	Acute cellular rejection
71	2	10 (first graft)	Rejection; liver failure		First graft: Acute rejection of mixed cellular and humoral type.
		14 (second graft; chimp)	Rejection; liver failure	14.7	Second graft: (xenograft): No evidence of rejection.? liver failure secondary to pulmonary insufficiency.
86	3	21	Rejection; liver failure; partial duct obstruction repaired after 10 days.	29	Acute cellular rejection

Table 7. Biliary atresia. Delayed deaths after technical complications.

OT No.	Age (years)	Time to death (days)	Complication	Last bilirubin (mg%)	Pathologist's opinion
26	11	76	Late intra-abdominal bleed; pancreatitis; gastrointestinal bleed; infections	10	Necrosis of centrilobular hepatocytes due probably to hypotension. No evidence of rejection, obstruction or cholangitis. No fungal invasion of liver.
30	11/12	37	Partial duct obstruction; infections	22	Virus infection of unknown kind (not cytomegalovirus) causing bile ductule obstruction and focal liver necrosis (see fig. 5). No evidence of rejection.
43	15	47	Partial duct obstruction*; liver abscesses	7.4	Marked evidence of partial large duct obstruction and cholangitis. No evidence of rejection.
47	3	81	Bile fistula; intra-abdominal abscesses	5.0	Evidence of infection of graft with cytomegalovirus. No evidence of rejection or cholangitis.
49	2	73	Partial duct obstruction and fistula*; gastrointestinal haemorrhage	2.9	Evidence of infection of graft with cytomegalovirus. No evidence of rejection or cholangitis.
68	5	28	Disrupted cholecystoduodenostomy*; multiple abdominal abscesses; bowel perforation	10.4	Necrosis of most of centrilobular and midzonal hepatocytes due probably to hypotension. No evidence of rejection or cholangitis.
84	2½	84	Partial duct obstruction; infection	11.0	Partial duct obstruction of large bile ducts. No evidence of rejection.

* Attempted secondary duct reconstruction. In the cases in which obstruction was relieved, the final histopathologic picture at autopsy did not always clearly reflect the earlier complication.

rejection of the first organ in 10 days. The chimpanzee liver was much less severely damaged than the homograft (table 6).

The histopathology of the transplants in these five cases is summarized in table 6. The diagnosis of cell mediated rejection was usually confirmed but in case OT 35, the histopathologic findings were not compatible with rejection by customary criteria of diagnosis. In the other cases which had typical rejections there were large numbers of lymphoid cells infiltrating the portal tracts, and the areas around the central veins. The findings were like those shown in figure 2. Lymphocytes were present in smaller numbers in and around the sinusoids. Many of the lymphoid cells were large with pyroninophilic cytoplasm and mitoses were common. The portal tracts were oedematous and there was necrosis of hepatocytes in the central and middle zones of the lobules. The reticulin framework of the liver retained a lobular pattern but there was collapse of reticulin around the central veins. Cholestasis with bile 'thrombi' in the canaliculi was not a dominant feature.

Seven additional patients passed through the first few postoperative weeks in spite of very serious and eventually lethal technical complications (table 7). Six of the seven had defective biliary reconstructions, four with the kind of cystic duct obstruction shown in figure 3 after cholecystoenterostomy. Two other patients had bile fistulas, and in one of these cases there was also a delayed bowel perforation at the site where the intestine had been mobilized from its adhesion to the portal structures of the native liver. Only one of the seven patients, an 11 year old girl (OT 26), had a complication not related to the biliary tract of the homograft. In this case, an injury of the pancreatic tail apparently occurred during splenectomy. Later, this general area became the site of intra-abdominal hemorrhage and an invasive retroperitoneal fungal infection. Shortly after, gastrointestinal hemorrhage also occurred.

The histopathology of the homografts after 60.9 ± 22.9 (S.D.) days (range 28 to 84 days) in these mechanically flawed seven cases is summarized in table 7. Histopathologic evidence of partial obstruction of the large biliary ducts was the main feature in three of the seven liver allografts. In one of these cases (OT 30) the cause was a massive viral infection of the epithelial cells lining the biliary tree causing swelling, necrosis and shedding of the infected cells to form obstructing casts (fig. 5). Obstruction in the other two livers (OT 43 and OT 84) was due to the same cystic duct lesion shown in figure 3. Two of the livers were severely infected with cytomegalovirus. Hypotension, associated with the patient's terminal illness, appeared to be the cause of the predominantly centrilobular necrosis in two other grafts. There was no evidence of rejection in any of these hepatic transplants.

Fig. 5. Biliary obstruction caused by virus infection of the lining epithelium of the biliary ductules (OT 30). A portal tract containing a greatly narrowed bile ductule is in the upper right of the picture. Some of the lining epithelial cells are necrotic and others contain viral inclusions. Hematoxylin and eosin. (× 120)

The final wave of seven deaths came after 110±56.3 (S.D.) days (range 51 to 186). All but one of these patients had abnormal liver function but the final event in each of their lives was uncontrolled infection with bacteria, fungi or viruses (table 8). Four of these seven delayed deaths were of patients who had a complication that has been called 'septic hepatic infarction' (7). Portions of the liver became necrotic and were invaded with bacteria from the intestinal tract. The four patients were tided over the immediate effects of the partial liver infarction, but they all eventually died with local plus systemic sepsis. Septic hepatic infarction is now thought to be due at least in part to under-immunosuppression and thus to be a manifestation of rejection. Mechanical factors such as twisting of the fragile hepatic arterial branches of these tiny recipients could contribute (7).

The livers from patients OT 37, 59 and 67 did not have regional infarctions; these patients had overwhelming systemic infections (table 8).

Table 8. Biliary atresia. Complex delayed deaths.

OT No.	Age (years)	Time to death (days)	Complication	Last bilirubin (mg%)	Pathologist's opinion
9	1	133	Septic hepatic infarctions	5	Micronodular cirrhosis, cholestasis, and obliterative intimal thickening in small arteries due to chronic rejection. Also multiple small septic infarcts due to thrombosis of hepatic artery branches. Bile duct obstruction not definite***.
10	1	186	Septic hepatic infarctions; general sepsis	23	Hepatic fibrosis, cholestasis, and obliterative intimal thickening in small arteries due to chronic rejection. Also multiple small septic infarcts due to thrombosis of hepatic artery branches. Bile duct obstruction not definite.***
11	1	61	Septic hepatic infarctions; general sepsis	12	Micronodular cirrhosis and cholestasis due to chronic rejection. Also multiple small septic infarcts due to thrombosis of right hepatic artery. Bile duct obstruction not definite.***
12*	1	105	Septic hepatic infarctions; general sepsis	3	Biliary tree dilated and blocked by inspissated bile due to kink at junction of cystic and common duct. Also multiple small septic infarcts due to thrombosis of right hepatic artery. No evidence of rejection.
37	3	51	Nocardia and Candida sepsis	4.9	Marked non-specific fatty infiltration of hepatocytes in homograft. No evidence of rejection or bile duct obstruction.

Table 8. (continued).

OT No.	Age (years)	Time to death (days)	Complication	Last bilirubin (mg%)	Pathologist's opinion
59**	11/12	175	? septicemia	normal	Arterial and arteriolar narrowing as a result of past rejection. No evidence of bile duct obstruction at autopsy. No infection found to account for sudden death following brief fever.
67	11	59	Pneumonia (? herpes)	4.2	Marked fatty infiltration of hepatocytes in homograft. No evidence of rejection or bile duct obstruction.

* Also probably had partial biliary obstruction.
** Had apparently successful reconstruction of partially obstructed duct four months previously. Death occurred suddenly after an illness of a few hours.
*** The term 'bile duct obstruction not definite' means that an opinion was not possible about the cause of the cholestasis. Obstruction was considered unlikely but it could not be ruled out. The same term is used in table 9.

Table 9. Biliary atresia. The ultimate fate of the 11 patients who had extended survival.

OT No.	Age at operation (months)	Survival (months)	Last bilirubin (mg%)	Clinician's opinion of cause of death	Histopathology of graft	
13	25	30	52	First homograft chronically rejected and removed after 881 days; died 20 days later with rejection.	First graft:	Narrowing of small arterial branches and infiltration of large lymphoid cells due to chronic rejection. Severe cholestasis. Bile duct obstruction not definite.**
					Second graft:	Massive necrosis of hepatocytes in central and middle zones of lobules. The necrotic areas contain aspergillus. This liver was only given an arterial supply. No evidence of rejection.
16	23	13½	9.7	First homograft subacutely rejected and removed after 65 days; died 339 days later with chronic rejection	First graft:	Severe narrowing of small arterial branches and infiltration by large lymphoid cells due to chronic rejection. Some cholestasis. Multiple old and new infarcts.
					Second graft:	Chronic rejection with severe arterial narrowing and lymphoid cell infiltration. Focal areas of old ischemic atrophy and recent infarction. No cholestasis.

Table 9. (continued).

OT No.	Age at operation (months)	Survival (months)	Last bilirubin (mg%)	Clinician's opinion of cause of death	Histopathology of graft
19	52	41	23	Liver injury following hemophilus septicemia; ? chronic rejection	Severe narrowing of small arterial branches due to chronic rejection. Marked cholestasis. Bile duct obstruction ruled out by cholangiography. CMV in gall bladder mucosa at autopsy. Lungs contained CMV, aspergillus and pneumocystis.
29	67	12½	15	? hepatitis; ? chronic rejection	Viral hepatitis. No evidence of rejection or bile duct obstruction.
33	46	65	normal	Alive	Never biopsied.
46	46	47	normal	Alive	Biopsy at 9 months showed cellular infiltration of portal tracts probably representing mild homograft rejection. No evidence of persistence or progression of viral hepatitis. No evidence of bile duct obstruction.
53	20	40	normal	Alive	Never biopsied.
64	36	28	normal	Alive	Never biopsied.
73	58	20	normal	Alive	Never biopsied.
89	45	10	normal	Alive	Never biopsied.
91	38	8	normal	Alive	Biopsy at 42 days at time of acute clinical rejection episode showed dense lymphoid cell infiltration including lymphoblasts and cells in mitosis. No evidence of bile duct obstruction.

* Autopsy report has been published (6).
** See table 8 footnote for definition of statement about obstruction.

The histopathologic appearance of the seven livers recovered from 51 to 186 days postoperative is summarized in table 8. Some evidence of chronic rejection was present in four of the seven livers and in three of these cases it was accompanied by obliterative intimal thickening of the small hepatic arteries (fig. 6). In one homograft kinking at the junction of the cystic and

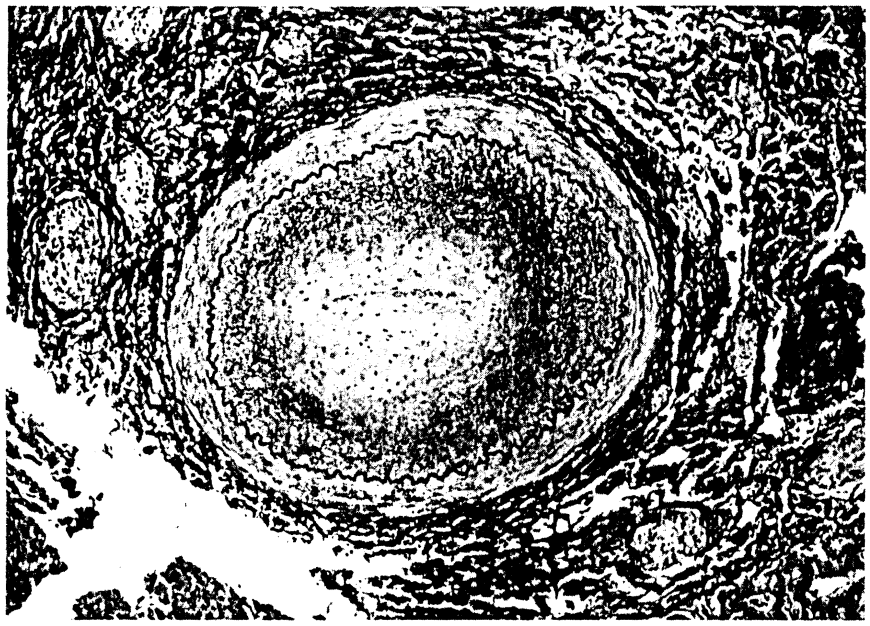

Fig. 6. Chronic rejection of a liver homograft (OT 19) almost 3½ years after transplantation. The small hepatic artery branch in a portal tract is completely occluded by a massively thickened intima. The internal elastic lamina is preserved. Elastic stain. (× 120)

common duct had caused the biliary tree to become dilated and blocked by inspissated bile. The other two livers showed only marked fatty infiltration secondary to infection.

Late mortality. Of the 11 patients who lived for more than a half year, four subsequently died between 12½ and 41 (mean 24.2) months postoperatively for the reasons listed in table 9. All four children became jaundiced, but the reasons for this were probably multiple (table 9).

These four children were given a total of 6 grafts, since 2 of the recipients had retransplantation. The histopathologic findings in the six transplants are shown in table 9. The most important pathologic findings in 4 of the 5

homografts that functioned for the longest time ($2\frac{1}{3}$ to 41 months) were chronic rejection with narrowing of the small arterial branches (fig. 6) and infiltration by lymphoid cells. The fifth chronically functioning liver (OT 29) showed the changes of viral hepatitis with no evidence of rejection or bile duct obstruction after more than a year. The second graft of patient OT 13 was given only an arterial supply. At 20 days after retransplantation it showed massive necrosis of hepatocytes in the central and middle zones of the lobules and infection by aspergillus.

The other seven patients are still alive (table 9) from 8 to 68 months postoperatively (mean 31.1 months). It is of interest that all seven survivors have normal bilirubins and that their liver function tests are normal in other measurable dimensions.

Graft biopsies were obtained early in the course of two of the seven patients who are still living. These showed cellular rejection, mild in one case and marked in the other. Both patients are well, 7 months and $3\frac{1}{4}$ years later (OT 91 and 46) and after total survivals of 8 and 47 months respectively.

EFFECT OF ORIGINAL DISEASE

The only unequivocal effect of the original disease upon the transplant recipient was recurrence of the hepatomas in three cases. The patients with Wilson's disease were relieved of their excessive copper storage in extrahepatic tissues, and there has been no tendency for the homograft to accumulate copper (table 10). The pediatric victims of chronic agressive hepatitis,

Table 10. Biochemical findings pre- and posttransplantation in a patient with classical Wilson's disease.

	Normal values	Pre-Op	3 months	17 months	24 months
Liver copper	(<20 μg/gm)	184	—	45	27
Ceruloplasmin	(22-49 mg/100 ml)	1.0- 1.7	74	48	32
Urine copper	(<30 μg/24 hours)	540	119	80	87
SGOT	(3-27 Iu./L)	25	70	25	15
Bilirubin	(<1.0 mg/100 ml)	2.9	.4	.64	.5

HB_sAg negative, have not had an obvious recapitulation of the disease in their grafts although this has probably occurred in one adult who was HB_sAg positive (2).

In an earlier report on immunosuppressed kidney and liver recipients, the appearance of HB_sAg in the serum seemed to be a permanent and consequently sinister finding (9). Therefore the observations on the course of post-transplantation HB_sAg antigenemia which developed postoperatively for the first time in 5 of the chronic survivors were of great interest. Four (OT 29, 42, 55 and 77) of the patients had clinically apparent bouts of HB_sAg-associated hepatitis. A fifth patient (OT 46) had positive sera but had no associated alterations in liver function or clinical symptoms. Three of the 5 patients had subsequent clearing of the virus marker. One of the exceptions (OT 77) is shown in figure 7; although he recovered clinically he is now a carrier.

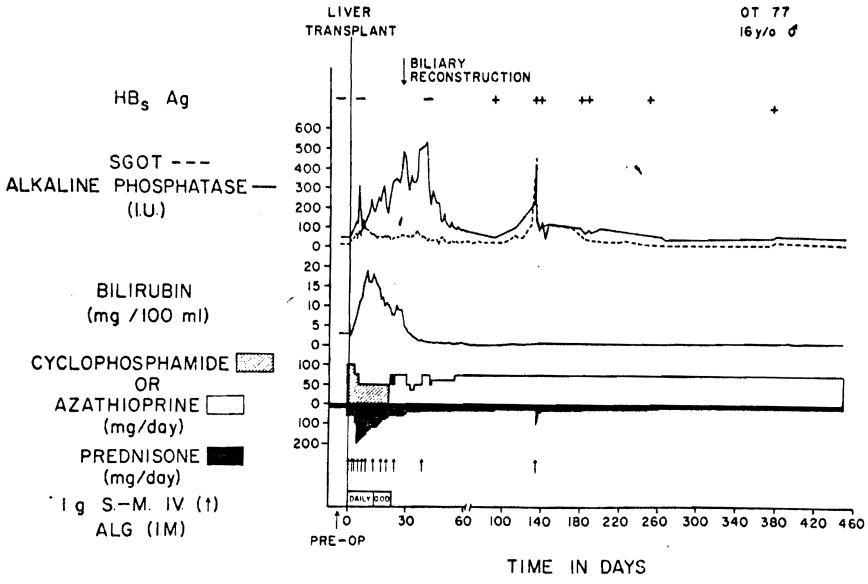

Fig. 7. Recovery after liver replacement for the indication of chronic aggressive hepatitis. The patient (OT 77) is the one whose postoperative transhepatic cholangiogram is shown in 8B. Jaundice persisted until the duct system was relieved of its obstruction by converting the initial Roux-enY cholecystojejunostomy to a choledochojejunostomy at the time indicated by the arrow. Note also that a bout of serum hepatitis complicated the recovery after about 2½ months. The patient recovered but became an HBsAg carrier.

The other patient (OT 29) with persistent HB_sAg died after 12½ months and had findings of hepatitis in his graft (see table 9).

The poor results in 40 patients with biliary atresia, projected at a one year survival of 28%, are in contrast to the 56% figure in pediatric recipients with

other preoperative diagnoses. Although atresia patients have other anomalies of which some may jeopardize the transplantation (3, 7) the presence of anomalies is not the main explanation for the difference in outcome between the two groups. Probably, the principal adverse factor has been the small size of the structures to be reconstructed in the younger and smaller population of the atresia subgroup, and a consequent increase in technical errors.

PROSPECTS OF IMPROVEMENT

The statistics given earlier showed that technical and mechanical complications were the main cause of early or late death in 22 cases, or the majority of all patients who have died. In an effort to ameliorate this situation, a number of changes were instituted in the autumn of 1973.

In an effort to minimize vascular accidents, microvascular techniques were used with increasing frequency for the portal venous and hepatic arterial anastomoses. Of even greater importance, techniques were upgraded to diagnose biliary obstruction and manage it effectively by reoperation according to the strategy outlined in an earlier publication (5).

Any patient who becomes jaundiced after transplantation or who develops unexplained bacteremia is now suspected of having biliary obstruction. Transhepatic cholangiography is performed, sometimes on multiple occasions (figs 8 and 9). The yield has been high since this aggressive and consistent policy was instituted. Of the last ten pediatric patients, three have required early conversion of Roux-en-Y cholecystojejunostomy to choledochojejunostomy because of the kind of partial or complete obstruction shown in figures 3 and 8B. All have survived and with prompt relief of jaundice. A fourth patient, who had the same complication plus a bile leak from the ligated common duct (fig. 8C), died before reoperation was possible (table 7, OT 84). Six (60%) of the last ten pediatric recipients are still alive after 8 to 20 months. Without aggressive reintervention this figure would have been 30%.

Even if all the technical problems are solved, it now seems to us that between one and two of every ten liver homografts is going to be rejected early in spite of the best immunosuppression available today. In such cases, early retransplantation will have to be considered after the differential diagnosis of duct obstruction is ruled out, and providing other etiologic factors such as hepatitis or drug hepatotoxicity are not implicated.

The indolent pattern of an inexorably rejecting graft is shown in figure 9,

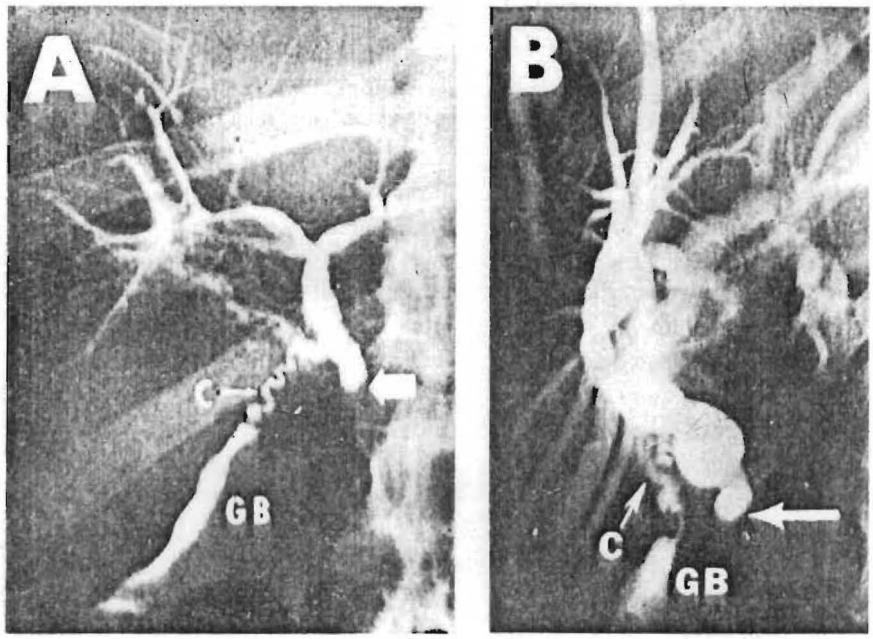

Fig. 8. Transhepatic cholangiography in 3 patients: (A) The demonstration of a nondilated duct system prompted intensification of steroid therapy. Arrow – ligated common bile duct. (B) partially obstructed duct system. The patient was reoperated and the cholecystojejunostomy (see fig. 1B) was converted to the cholcdochojejunostomy shown in figure 1C. The ultimate result was perfect (see fig. 7). (C) Obstructed cystic duct syndrome plus bile extravasation near distal ligated common bile duct (arrows). This child died of generalized sepsis before reoperation could be carried out. C: cystic duct; GB: gallbladder.

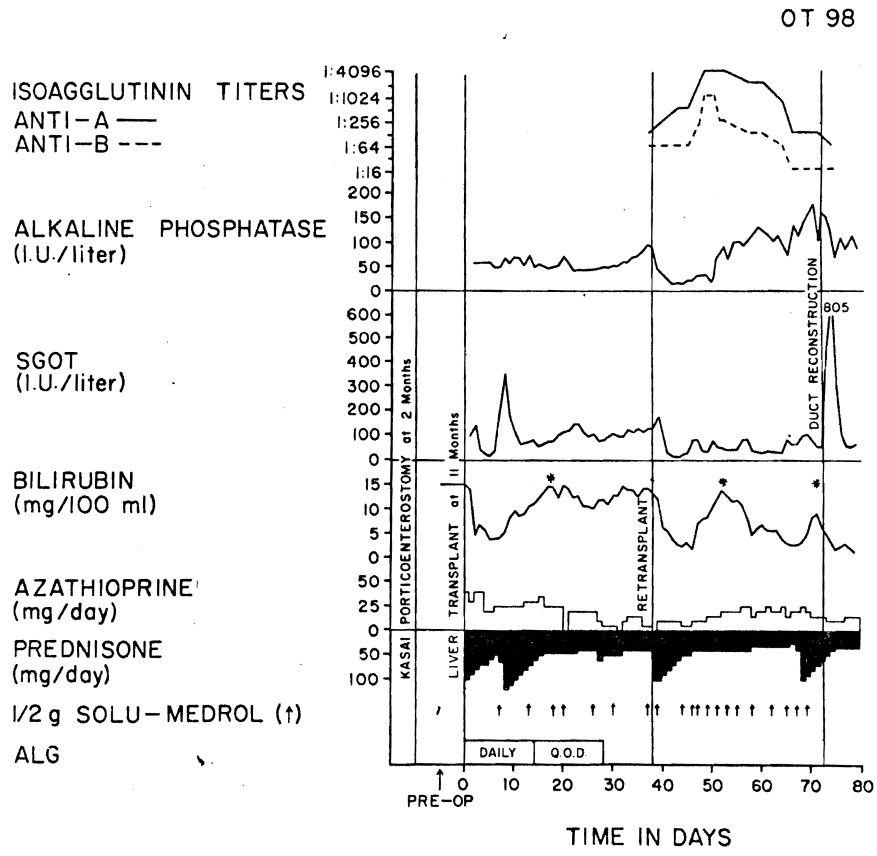

Fig. 9. Uncontrolled rejection after orthopic liver transplantation (OT 98) in a 9 month old child who had had an unsuccessful porticoenterostomy at the age of 2 months. The rejected primary transplant was removed after 38 days and replaced with another liver. The recipient was O blood type as was the first donor. The second donor was A blood type. Note the prodigious increase in the anti-A isoagglutinins which did not have an obvious adverse effect. The duct system of the second graft became obstructed, and was relieved by converting the cholecystojejunostomy to choledochojejunostomy. The asterisks indicate the performance of transhepatic cholangiograms. The first two were normal but the third revealed obstruction.

with jaundice that is predominantly obstructive and with serum transaminases that are modestly elevated. If the biliary reconstruction is proved sound, there can be little doubt of the diagnosis, and reexploration must be performed as soon as a liver becomes available. In the case depicted (fig. 9) the graft weighed more than 500 grams, an estimated fivefold increase from

its weight at its insertion a month earlier. The second graft for this O recipient was from an A donor. In spite of this red blood group mismatch, the organ functioned much better than the red blood group compatible first organ.

Since cadaveric organ donors may not be available at times of desperate need, cautious exploration of chimpanzee liver heterotransplantation is going to be necessary as a possible way out of what otherwise rapidly becomes a hopeless situation. Three liver heterotransplantations have been performed (5, 7) with maximum survival of only two weeks, but with encouragingly minor histopathologic findings in the grafts (for example, see table 6, OT 71).

PORTICO-ENTEROSTOMY AND TRANSPLANTATION IN BILIARY ATRESIA

Some of the patients with biliary atresia whom we have recently seen have had earlier portico-enterostomy procedures that failed. The prior performance of the Kasai operation has not jeopardized transplantation. In three cases of our experience the previous construction of an isolated Roux-en-Y jejunal segment has proved to be a significant advantage since the Roux limb has been used to accept the graft biliary drainage (figs. 9 and 10).

Although the Kasai procedure apparently alters the natural history of biliary atresia in some cases, the operation will be curative only rarely. Altman and Lilly have shown that progressive cirrhosis is almost invariable, even in those patients whose jaundice has been completely relieved by porticoenterostomy (1). Although some of these children probably will have their lives prolonged, eventually almost all will become candidates for transplantation.

Thus, porticoenterostomy and liver transplantation are not competitive procedures. They should be viewed as complementary in the continuum of care that is slowly evolving for children with biliary atresia. If it is to be effective, porticoenterostomy has been urged by its proponents before the age of three months when liver transplantation is not yet a good possibility. Liver replacement is reserved for a later time. Examples of this approach are shown in figures 9 and 10.

In our three patients who had liver transplantation after previous Kasai procedures, one died in less than a month and the other two are still alive after 3 and 20 postoperative months.

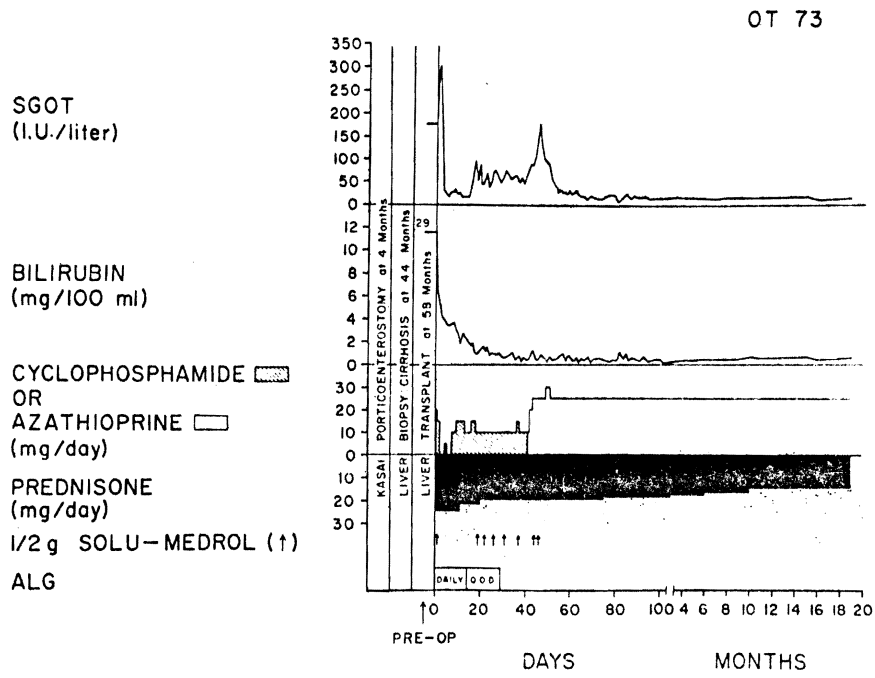

Fig. 10. The course of a child who had a failed Kasai operation but who ultimately was effectively treated with liver replacement. The successive use of the porticoenterostomy and liver transplant is also illustrated in figure 9.

SUMMARY

In the decade ending in the fall of 1974, liver replacement was attempted in 93 patients of whom 56 were 18 years old or younger. Twenty of the 56 pediatric recipients had survival of eight months or more, 17 lived for at least a year and 13 are still alive. The longest survival is now six years.

The results with biliary atresia were poorer than if the original disease was something other than atresia. In both subgroups, the greatest cause for the high failure rate was a variety of technical misadventures of which complications of bile duct reconstruction headed the list. Failure to control rejection was a far less common cause of death. Suggestions to improve the results were made.

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