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Liver Transplantation

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What I would like to do in this first paper is to give a general survey of liver transplantation but omit the overriding issue of liver sepsis, as this relates to biliary duct reconstruction. I will focus specifically on this problem of liver sepsis in a second report.

Varieties of Liver Transplantation

There are two fundamentally different kinds of hepatic transplantation procedures. In one, a second organ is placed in some abnormal location such as the paravertebral gutter, the splenic fossa or the pelvis. If an auxiliary graft is to succeed, I believe it should be revascularized according to the principles I discussed in connection with the hepatotrophic factors in my Judd Lecture (Fig. 1). Note in Figure 1 that the splanchnic blood perfuses the auxiliary liver through a mesenteric-portal anastomosis, that the hepatic artery is attached to the aorta and that the outflow is to the vena cava.

The results with auxiliary transplantation in patients (and for that matter in animals) have been so discouraging that I have not done one for about six years. However, Dr. Joseph Fortner of New York has an auxiliary graft recipient going now more than a year after the exact operation shown in Figure 1 for the indication of biliary atresia. This is a very important case which will certainly bear watching.

Incidentally, some of the most interesting possibilities for auxiliary transplantation are certain inborn errors of metabolism, of which I will mention just two. One is the Crigler-Najjar syndrome in which the function of the native liver is quite normal except for the inability to conjugate bilirubin due to the absence of glucuronyl transferase. The

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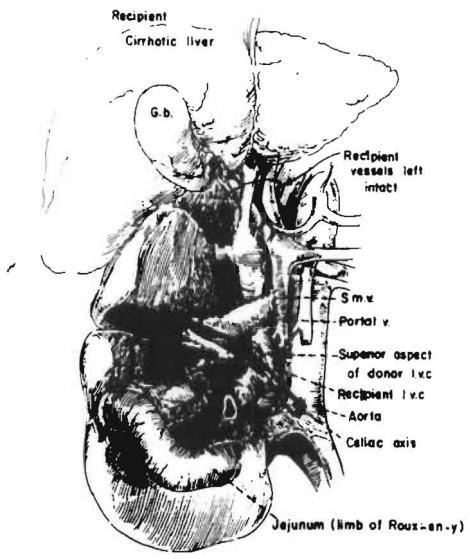

FIG. 1. Auxiliary liver transplantation as carried out clinically. Note that transplant was given a double blood supply and that the venous component was from nonhepatic splanchnic bed. Technique was almost identical to that developed in dogs. Biliary drainage should be with a Roux-en-Y cholecystojejunostomy. (By permission of W. B. Saunders Company, 1969.)

second possibility is juvenile Gaucher's disease. Here the missing enzyme is Beta glucosidase. The resulting cramming of the reticuloendothelial system may actually lead to liver failure. With either of these disorders, an auxiliary liver should be curative; in the Crigler-Najjar syndrome simply by clearing bilirubin and in the Gaucher's patient by providing the enzyme which would probably reverse the hepatic lesion and cause removal of the deposits of glucosyl ceramide elsewhere.

Orthotopic Transplantation

The rest of my remarks will deal with orthotopic liver transplantation, that is, about liver replacement. The diseased native liver is removed and revascularization of the graft is performed in as anatomically normal a way as possible – anastomosing the portal vein and hepatic artery end-to-end and reconstructing the vena cava above and below the liver. In most of our early cases, we have anastomosed the gallbladder to the duodenum after ligating the distal common duct (Fig. 2). I will be outlining the hazards of this approach in my second report.

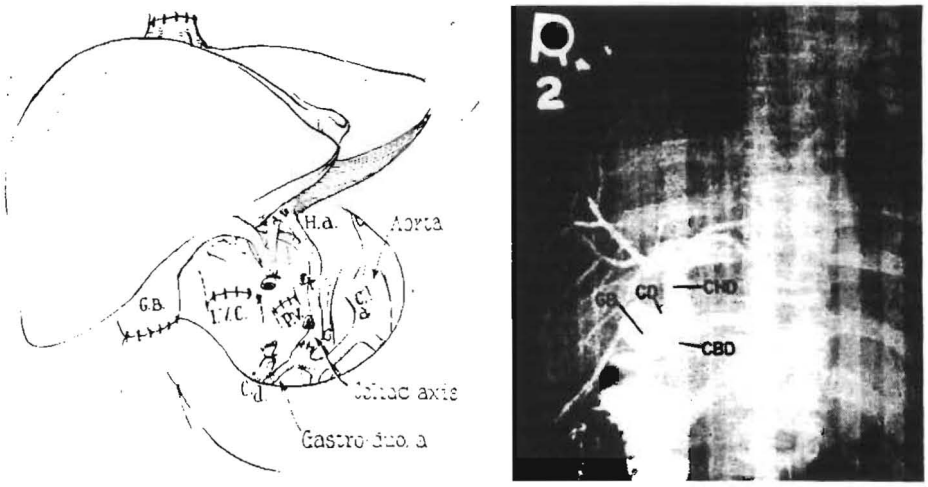

FIG. 2. Orthotopic liver transplantation with biliary duct reconstruction by cholecystoduodenostomy. The cholangiogram on right was obtained at reoperation by inserting a Foley catheter into gallbladder. There was no evidence of obstruction. CBD – common bile duct; CD – cystic duct; CHD – common hepatic duct; GB – gallbladder. (By permission of *Surgery*, 72:604, 1972.)

Indications for Operation

With these preliminary remarks I will now turn to the question about the indications for operation. At the beginning, we thought that the ideal reason for liver replacement would be primary hepatic malignancies, including hepatoma. Our enthusiasm was quickly dampened by the kind of experience which I will illustrate for you with a single case.

In Figure 3 are chest x-rays of a 15-year-old boy. A few weeks after "successful" orthotopic liver transplantation for a gigantic hepatoma, there was already a small pulmonary metastasis. He died 143 days after operation with his lungs almost replaced by metastases.

During the same interval, his new liver was similarly invaded as could be followed with serial scans (Fig. 4). There was evidence of metastases at all times after three months. He finally died of combined hepatic and pulmonary insufficiency. At autopsy, his lungs were a mass of tumor (Fig. 5). The same was true of his liver to an extent that only a tiny remnant of normal hepatic tissue remained (Fig. 6).

We have had a half a dozen other so-called successful liver transplantations with subsequent widespread metastases of hepatomas and one similar experience with a hemangioendotheliosarcoma. Three of the patients died beyond one year posttransplantation of tumor spread.

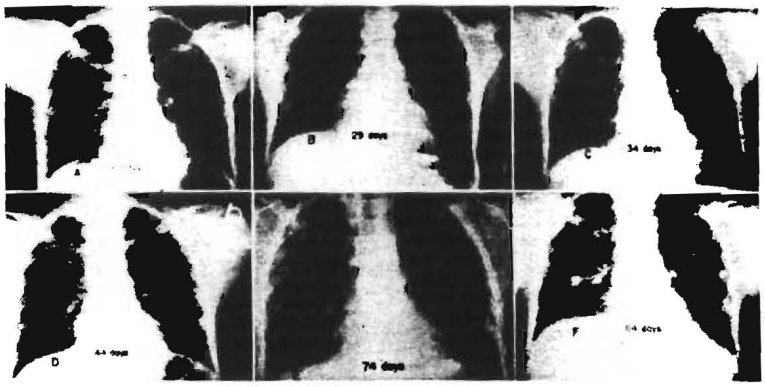

FIG. 3. The extremely rapid development of pulmonary metastases. (*A*) The chest is clear 6 days after liver replacement for indication of hepatoma; (*B*) 29 days postoperative. Two metastases are visible in left lower lung field (*arrows*); (*C*) 5 days later the tumor deposits previously seen have grown in size (*horizontal arrows*) and a third focus is now present in right upper lobe (*vertical arrow*); (*D*) 44 days. Only ten days have elapsed since last examination. Metastatic growths are scattered throughout lungs (*arrows*); (*E*) 74 days postoperative; (*F*) four months after operation. Transient dyspnea was first noticed a few days later. Patient died of pulmonary and hepatic insufficiency 143 days after transplantation. (By permission of W. B. Saunders Company, 1969.)

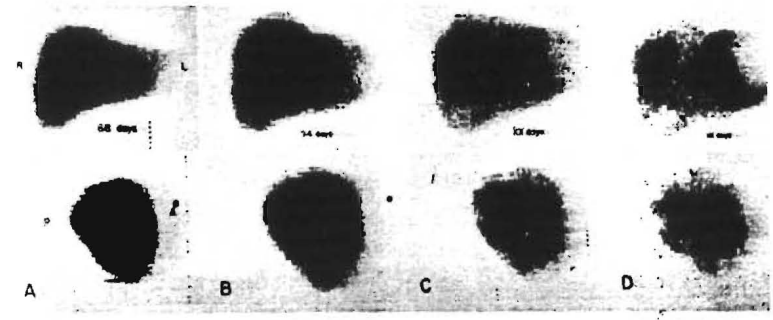

FIG. 4. Destruction of the homograft in the same patient as Figure 3 by tumor recurrence. Postero-anterior and lateral liver scans were obtained with 99m technetium. (*A*) 68 days; (*B*) 94 days: patient had become jaundiced; hepatomegaly is evident; (*C*) 101 days: multiple areas of poor isotope concentration are now visible; (*D*) 111 days: process has continued its rapid progression. By the time of death one month later, the homograft was almost completely replaced with carcinoma. (By permission of W. B. Saunders Company, 1969.)

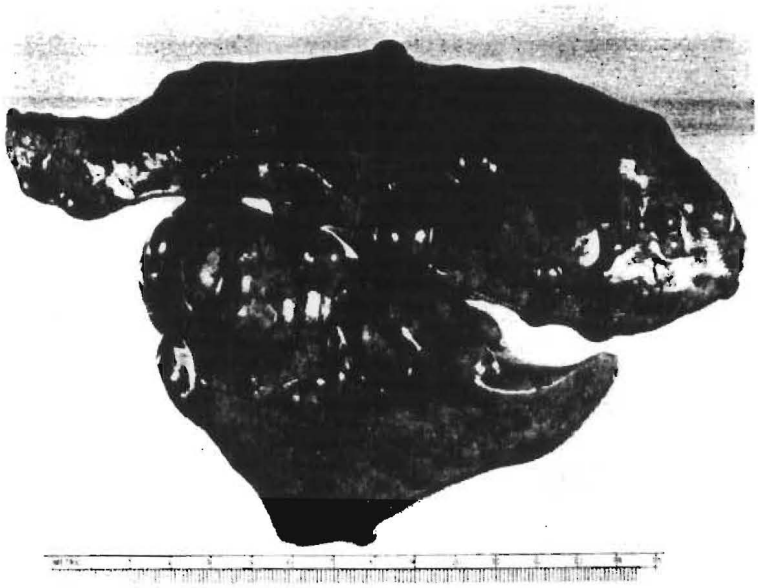

FIG. 5. Extensive pulmonary metastases in same patient as in Figures 3, 4 and 6.

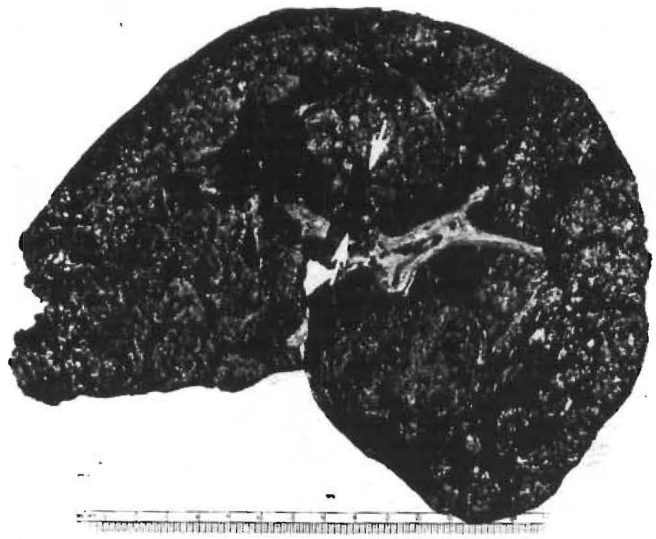

FIG. 6. Metastases in patient shown in Figures 3, 4 and 5. 143 days after orthotopic liver transplantation, liver homograft has been replaced by tumor except for a very small residual area of hepatic parenchyma (*arrows*). (By permission of W. B. Saunders Company, 1969.)

It would be inaccurate to say that liver transplantation can never be used to cure hepatoma, as can also be illustrated by another case. In Figure 7 is the liver of a child with biliary atresia in which was found a 2 cm hepatoma as an incidental pathologic feature. The alpha-fetoprotein that was present in her serum disappeared (Fig. 8) and has never returned. The child has a perfect result without evidence of tumor recurrence 4½ years later. Long survival after liver replacement for hepatoma has also been reported by Calne and Williams of Cambridge and a former fellow of ours, Daloze of Montreal. Nevertheless, I personally would prefer not to do more hepatomas at this time since the high incidence of metastases (exceeding 80% in our hands) has beclouded the kind of conclusions that must be reached in evaluating any new procedure.

It has seemed possible that the outlook might be less gloomy if the malignant tumor were some kind other than a hepatoma. For example, some of the slow growing proximal duct cell carcinomas might be worth treating. This is an example, which was diagnosed with transhepatic cholangiography, by Alan Redeker of Los Angeles (Fig. 9). Liver replacement was carried out in early February with a perfect result. The small tumor was not seen until after its removal.

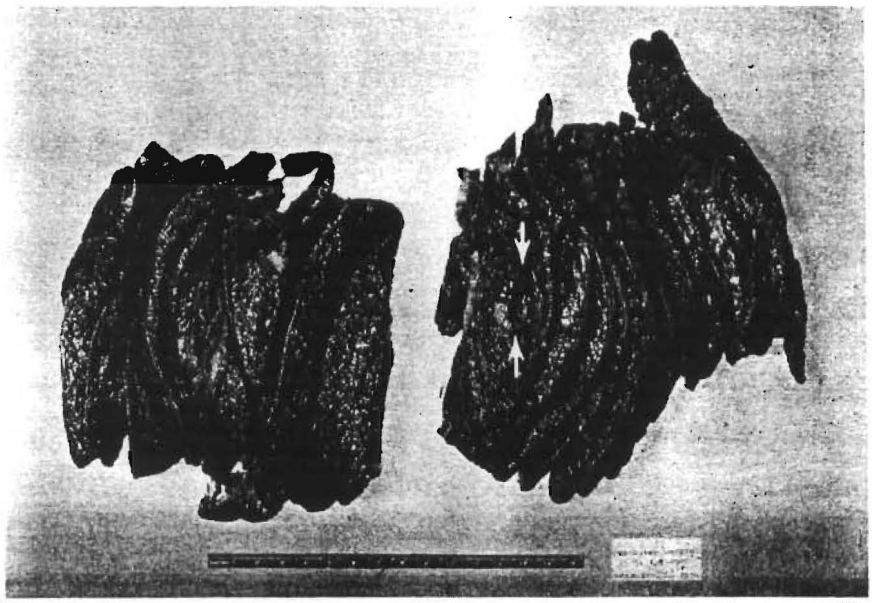

FIG. 7. Two centimeter hepatoma (*arrows*) in the liver of a 4-year-old child whose primary diagnosis was biliary atresia.

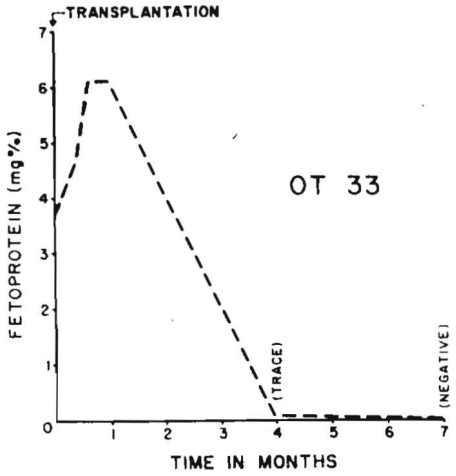

FIG. 8. Alpha-feto protein posttransplantation in child whose native liver is shown in Figure 7. (By permission of *Gastroenterology*, 61:144-148, 1971.)

FIG. 9. The diagnosis of an intrahepatic duct carcinoma by preoperative transhepatic cholangiography. Procedure performed by Dr. Alan Redeker of Los Angeles.

Table 1. Criteria for Selection for Liver Transplantation

1. Are less than 40
2. Have a hopeless prognosis*
3. Do not have cancer
4. Do not have infection

*How is this known?

In any event, the important future of hepatic transplantation is for the treatment of *benign* hepatic disease. The most common diagnoses would be chronic aggressive hepatitis, biliary atresia and alcoholic cirrhosis. In all these situations, we would like to meet the criteria shown in Table 1. Of these criteria, the second one is the most difficult since the determination of "hopelessness" may be impossible until a few hours before death. Yet, if one waits this long, there will be no transplantations.

If liver transplantation is to be prosecuted successfully, case selection must be carried out by different doctors in widely separated cities on a national basis. In doing this, the dominating role of donor availability has to be recognized. Another key condition is a trustworthy system of prior evaluation *by experts* of any prospective patient. Then if a suitable donor is found, say in Denver, a recipient who has been judged otherwise hopeless can be transported to Colorado.

FIG. 10. Postmortem arteriogram of a liver homograft that had supported life for 3½ years. Note narrowed areas in some of the smaller vessels. (By permission of the *New England Journal of Medicine*, 289:82-84, 1973.)

The indication of biliary atresia for liver transplantation is perhaps the clearest one of all, since these children require a blind-end social input with no prospect of their getting better or of growing up. With successful transplantation they can become quite normal. The little girl, whose liver was shown in Figure 7, is now 4½ years posttransplantation and attending public school in Illinois. The boy, Jimmy Grund, who was well known to the Minnesota faculty, was well for 3½ years until his sudden death was precipitated by a *Hemophilus* septicemia. Incidentally, the arterial supply of his liver homograft was patent although it contained constrictions (Fig. 10) which were apparently due to the same kind of obliterative lesions which are so familiar in kidney transplants.

We have had two patients who underwent liver replacement for Wilson's disease, a disorder in which copper deposition in the tissues leads to neurologic, hepatic and other manifestations. The first patient had profound liver failure. The second patient recipient was treated because of uncontrolled neurologic manifestations despite conventional penicillamine therapy. Both of these patients are alive and very well after 5 and 3½ years, respectively. After operation, they underwent a massive cupriuresis (Fig. 11). As the copper was being mobilized, the Kayser-Fleischer (or copper) rings and the neurologic manifestations regressed. Repeated

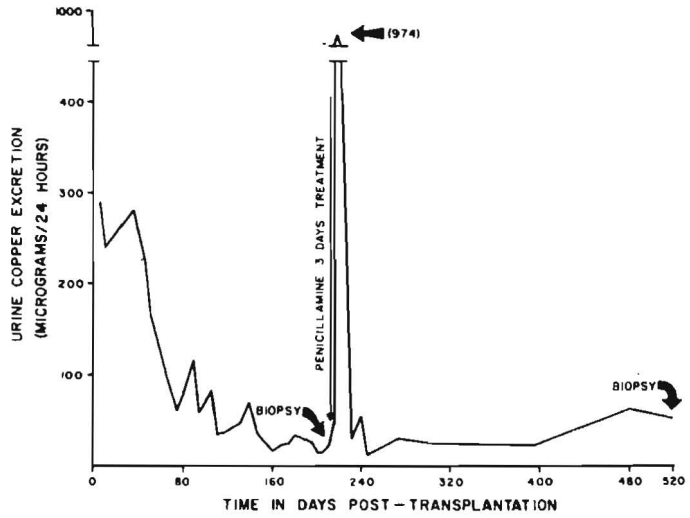

FIG. 11. Postoperative cupriuresis after liver replacement in a child who had Wilson's disease. Even after six months, note striking response to penicillamine. Child is still alive five years postoperative. (By permission of *Lancet*, March 13, 1971, pp. 505-508.)

biopsies of these livers have shown little or no reaccumulation of hepatic copper. The preoperative serum ceruloplasmin of the second child was zero. It promptly rose to normal.

Clinical Results

By showing you these pictures of healthy looking postoperative patients, I do not wish to give a false impression of the results that have been obtained. According to the April 1974 American College of Surgeons report on liver transplantation, about 200 patients have had liver replacement throughout the world. Since 1963, we have contributed 82 to this total, at a rate since 1967 ranging from 6% to 13% per year (Table 2). We have had 18 and 9 recipients, respectively, who have lived for more than one and two years. Thirteen recipients are still alive from eight weeks to almost five years postoperative. The four longest survivors are four years, 11 months; four years, 5 months; four years; and three years, 4 months.

There have been ten late deaths from 12 to 41 months postoperatively, and for the reasons listed in Table 3. The latest mortality at three years, five months was Jimmy Grund, the Minnesota child whom I mentioned previously.

With only 18 one-year survivors, it is obvious that the operation is presently unsafe. The single most important factor in the high acute failure rate has been a multiplicity of technical misadventures of which complications of biliary duct reconstruction usually with lethal sepsis lead the list. I will be devoting all of my later talk to this topic. It is surprising

Table 2. Cases of Orthotopic Liver Transplantation Treated in Denver

		Lived		
	Number	*1 year*	*2 years*	*Alive Now*
1963-1966	6	0	0	0
1967	6	1	0	0
1968	12	5	2	0
1969	6	2	1	1
1970	10	2	1	1
1971	11	2	2	2
1972	11	5	3	3
1973	13	1	0	3
1974 (To April 1)	7	0	0	3
	82	18	9	13

Table 3. The Present Status of 18 One-Year Survivors After Orthotopic Liver Transplantation. Eight are Still Alive From 14 to 58 Months. The Other 10 Eventually Died From the Causes Listed Below.

OT Number	*Time of Death (Months)*	*Causes of Death*
15	12	Recurrent cancer
29	12	Serum hepatitis and liver failure
8	13	Recurrent cancer
58	13½	? Chronic rejection ? Recurrent hepatitis
16	13½	Rejection and liver failure
14	14	Recurrent cancer
54	19	Multiple liver abscesses necessitating retransplantation
36	20	Systemic *Nocardia* infection and chronic aggressive hepatitis
13	30	Rejection and liver failure following retransplantation
19	41	*Hemophilus* septicemia and secondary liver and renal failure

how uncommonly failure to control rejection has been responsible for death.

One of the great unanswered questions about liver transplantation is whether chronic alcoholics are suitable candidates. First, cirrhotic patients have a predictably higher operative risk, in part due to the frequency of pulmonary and other infectious complications. Second, for all but those patients with clearly terminal esophageal variceal hemorrhage, hepatic coma or advanced secondary renal failure uncertainty about the natural course of the disease usually leads to a decision against transplantation until such time as the patient's condition becomes patently hopeless. Many then expire before a suitable liver becomes available; the few who are transplanted enter the operating room in a moribund state.

In Table 4, our experience with alcoholics has been separated out. Of the 82 consecutive recipients of hepatic homografts, one was treated for alcoholic hepatitis and nine carried the diagnosis of Laennec's cirrhosis without concurrent hepatoma. Nine of the ten patients have died, from 3 to 121 (mean 29) days posttransplantation; the only surviving recipient is in good condition six weeks postoperative. In contrast, 12 of the 72 patients transplanted for nonalcoholic liver disease are still alive from a few weeks to nearly five years later. The mean survival of the patients in the nonalcoholic group who have died is more than four times that of the

Table 4. Alcoholic vs. Nonalcoholic Liver Disease Treated by Orthotopic Hepatic Transplantation

	Alcoholic	*Nonalcoholic*	*Total*
No. of patients	10	72	82
Alive	1*	12	13
Dead	9	60	69
Mean survival of those who died	29 days	136 days	122 days

*Six weeks posttransplantation

alcoholic recipients. The causes of death among the alcoholics are shown in Table 5. If liver transplantation is to succeed in patients with alcoholic cirrhosis, potential recipients must be selected earlier, treated aggressively to prevent or correct infectious, pulmonary and other complications and transplanted before their condition has markedly deteriorated to the extent of coma, hepatorenal syndrome and other similar end points. In fact, no matter what the indication, I believe that operation needs to be considered earlier than we or our medical colleagues have been willing to recommend.

Table 5. Duration of Survival and Cause of Death in Ten Alcoholic Recipients of Hepatic Homografts

OT Number	*Age (Years)*	*Survival (Days)*	*Cause of Death*
22	33	10	Biliary obstruction
28	39	13	Disruption of choledochoduodenostomy; bile peritonitis
32	46	3	Unexplained coma
39	47	26	Unrelieved pre-existing coma
40	44	32	Rejection; pneumonitis; petechial hemorrhages of CNS
62	44	121	Rejection and liver failure; pulmonary emboli
70	40	34	Pneumonitis
75	48	8	Rejection and liver failure
81	47	15	*Aspergillus* pneumonitis with dissemination
82	37	Alive (6 weeks)	–

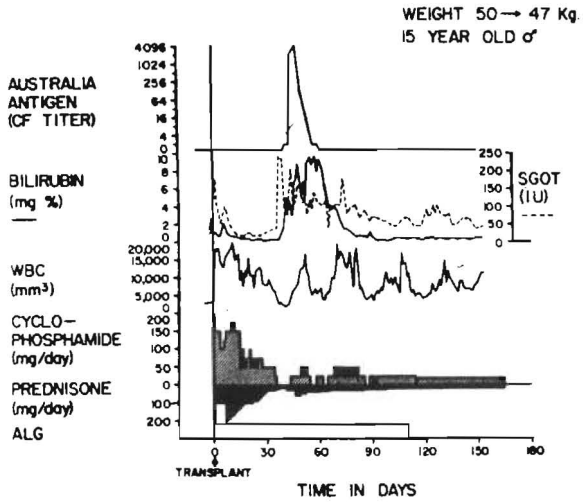

FIG. 12. The course of a teenaged boy who had liver replacement for indication of Wilson's disease. Acute derangements of liver function in second postoperative month were associated with development of Australia antigenemia. Thus, diagnosis was probably serum hepatitis, rather than rejection. After transplantation, the serum ceruloplasmin rose from zero to normal values.

The Question of Hepatitis

A few final thoughts may be in order. We still believe that under propitious circumstances, people with Australia antigenemia need not be arbitrarily eliminated from candidacy. We treated a former heroin addict under these circumstances who lived for almost two subsequent years, most of it with her family, although eventually she recapitulated her original disease.

I already mentioned (Table 3) that in patients who are Australia antigen *negative*, we have seen posttransplantation hepatitis. In Figure 12 is an example. During this flare-up of hepatic malfunction, the Australia antigen tests had turned positive. Then, the differential diagnosis of serum hepatitis versus rejection may be practically impossible.

Incidentally, I have said very little about the details of immunosuppressive treatment, since this is such a highly specialized area. We start out treating our patients with cyclophosphamide, steroids and ALG, later changing to azathioprine.

Summary

I would like to summarize now by making three brief statements. First, the prime indication for liver replacement is non-neoplastic hepatic disease. Second, it has been proved that patients can be restored to good health with liver transplantation, as evidenced by survival for as long as half a decade. Third, the greatest deterrent to improved results and, therefore, wider application is biliary duct reconstruction and hepatic sepsis, a combined subject which I will discuss later.

The work was supported by research grants from the Veterans Administration; by grants AI-AM-08898 and AM-07772 of the National Institutes of Health; by grants RR-00051 and RR-00069 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.