Liver transplantation at the University of Colorado

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In this paper, we will try to cover three questions about orthotopic liver transplantation, that is to say about liver *replacement*. The first question is what are the indications for hepatic transplantation ? Second, what have been the results ? Third, what are the prospects for future improvement ?

In Figure 1 is depicted a reminder of what exactly *is* orthotopic liver transplantation. With this operation the diseased native liver is removed, creating a space into which to accommodate the cadaveric graft. Orthotopic liver transplantation is often difficult, mainly because of the liver pathology that essentially always creates severe portal hypertension and extensive venous collaterals. Thus, removal of the native liver may be an extremely formidable undertaking. 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.

By far the most unsatisfactory aspect of this operation has been biliary duct reconstruction. In most of our cases, we have anastomosed the gall-bladder to the duodenum after ligating the distal common duct. This method has real advantages under conditions of immunosuppression because it can be performed without stents and drains. However, there have been a number of lethal complications with these cholecystoduodenostomies, a point to which we will return later.

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This work was supported by research grants from the Veterans Administration, by grants RR-00051 and RR-00069 from the general clinical research centers program of the Division of Research Resources, National Institutes of Health, and by grants AI-10176-01, AI-AM-08898, AM-07772, and HE-09110 of the United States Public Health Service.

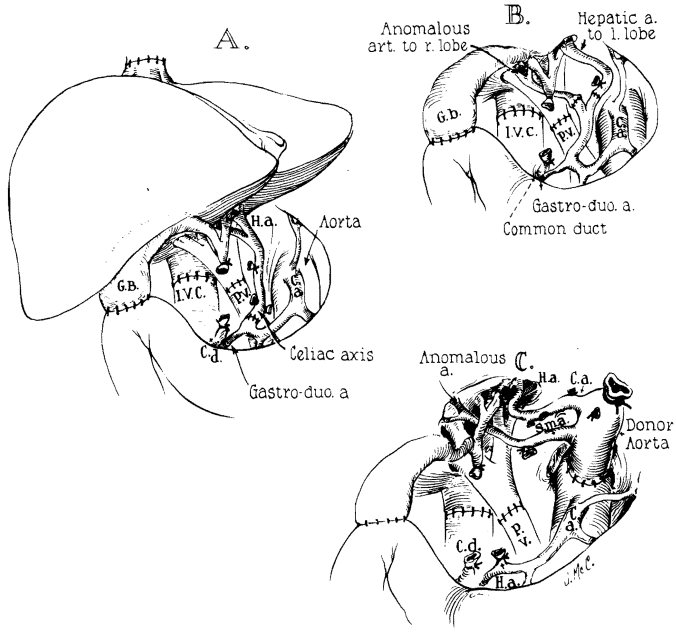

Fig. 1. — Orthotopic liver transplantation;the recipient operation. In most recent cases, cholecystoduodenostomy has been performed for biliary drainage as shown. C.a. = celiac axis ; C.d. = common duct ; G.B. - gall-bladder ; H.a. = hepatic artery ; I.V.C. = inferior vena cava ; P.V. = portal vein ; S.m.a. = superior mesenteric artery. A. The kind of arterial anastomosis most commonly used. The homograft celiac axis or common hepatic artery is attached to the proper or common hepatic artery of the recipient. B. Arterial reconstruction of two homograft arteries. The vessels are individually anastomosed to the branches of the recipient proper hepatic artery. C. Anastomosis of the homograft aorta to the recipient aorta. The variation was used in a 16-month old recipient because of the double arterial supply to the transplanted liver. (By permission of Ann. Surg. 168 : 392, 1968.)

INDICATIONS FOR ORTHOTOPIC TRANSPLANTATION

Hepatic Malignancy

With these preliminary remarks we will now turn to the first question,that about the indications for operation. At the beginning, we thought that the ideal reason for liver replacement would be primary hepatic malignancies, including hepatoma. An example of the kind of extensive hepatoma we treated in the early trials is shown in Figure 2. Our enthusiasm was quickly dampened by a repetitive experience which we will illustrate for you with a single case.

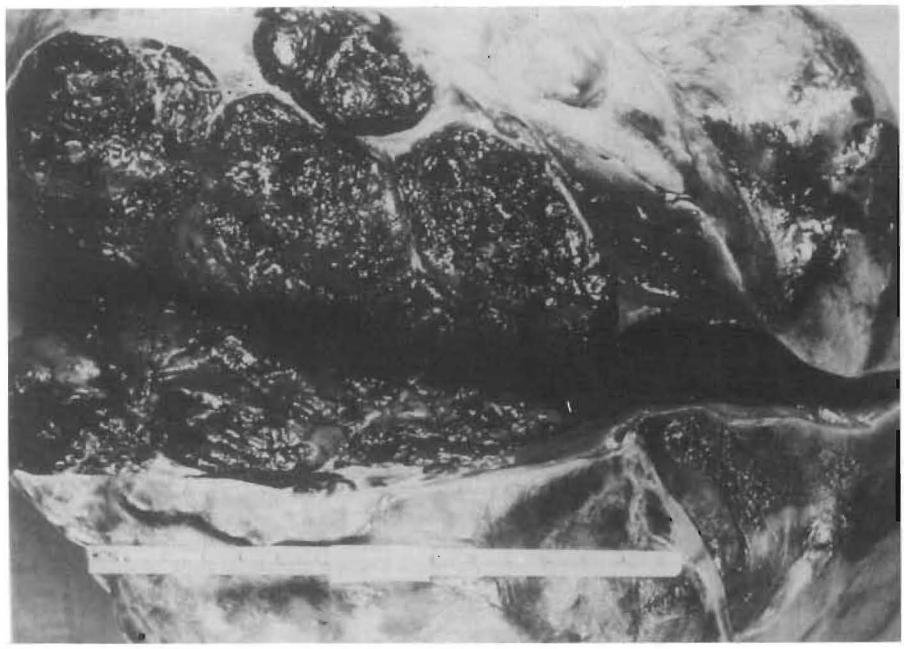

Fig. 2. — The hepatoma and remaining liver excised from a 29 year old woman at the time of orthotopic transplantation. The operative specimen weighed 10 kg (By permission of W. B. Saunders Co., 1969).

In Figure 3 is the chest x-ray of a 15-year-old boy a few weeks after successful orthotopic liver transplantation for a gigantic hepatoma. There is already a small pulmonary metastasis by 29 days. 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 in the homograft at all times after 3 months.

With the destruction of his liver he became secondarily jaundiced (Fig. 5) and finally died of combined hepatic and pulmonary insufficiency. At autopsy, his lungs were a mass of tumor. The same was true of the transplanted liver to an extent that only a remnant of normal hepatic tissue remained. We have had a half-dozen other so-called successful liver transplantations with subsequent widespread metastases and, in fact, three of our patients died beyond one year post-transplantation of this complication.

It is a bit early to conclude once and for all that liver transplantation cannot be used to treat hepatoma, as can also be illustrated by another case. In Figure 6 is the liver of a child with biliary atresia in which was found a small 2 cm hepatoma as an incidental pathologic feature. The child has a perfect result without evidence of tumor recurrence more than 2 years later. Long survival after liver replacement for hepatoma has also been reported by Calne of Cambridge, Daloze of Montreal and Fortner of New York. Nevertheless, we personaly would prefer *not*

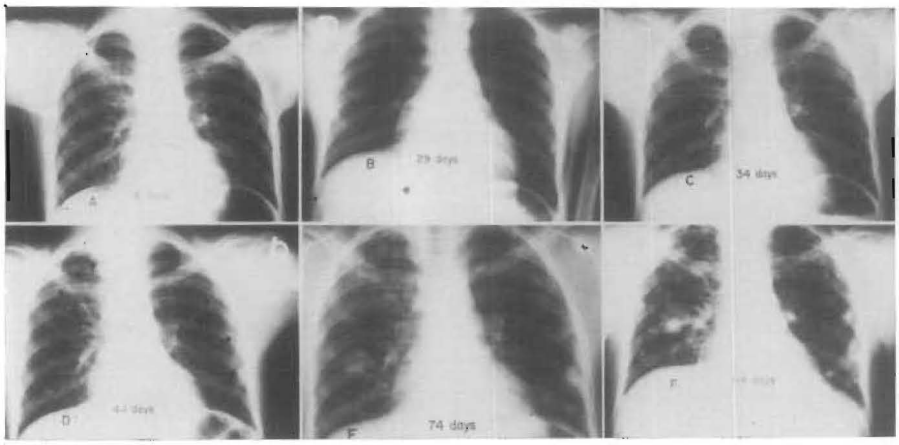

Fig. 3. — The extremely rapid development of pulmonary metastases in a patient whose indication for liver replacement was hepatoma. A. The chest is clear six days after transplantation. B. Twenty-nine days postoperative. Two metastases are visible in the lower left lung field (arrows). C. Five days later the tumor deposits previously seen have grown in size (horizontal arrows) and a third Focus is now present in the right upper iobe (vertical arrow). D. Forty-four days. Only 10 days have elapsed since the last examination. Metastatic growths are scattered throughout the lungs (arrows). E. Seventy-four days postoperative. F. Four months after operation. Transient dyspnea was first noticed a few days later. The patient died of pulmonary insufficiency 143 days after transplantation (By permission of W.B. Saunders Co., 1969).

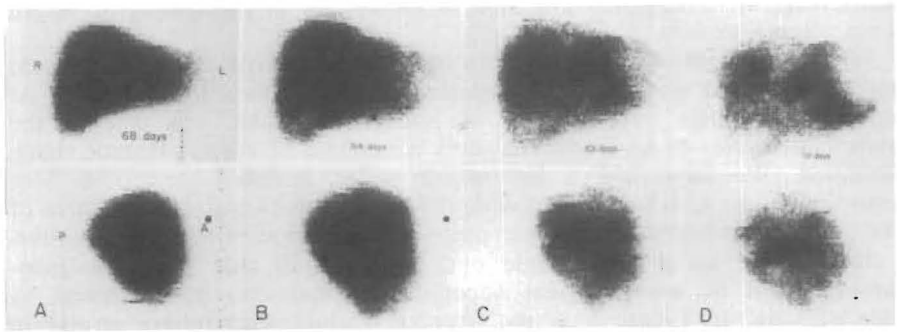

Fig. 4. — Destruction of a hepatic homograft by tumor recurrence, as demonstrated by serial technetium liver scans. A. 68 days — The scan appears normal. B. 94 days — The patient had become jaundiced. Hepatomegaly is evident. C. 101 days — Multiple areas of poor isotope concentration are now visible. D. 111 days — The process has continued its rapid progression. By the time of death one month later, the homograft was almost completely replaced by tumor (By permission of W.B. Saunders Co, 1969).

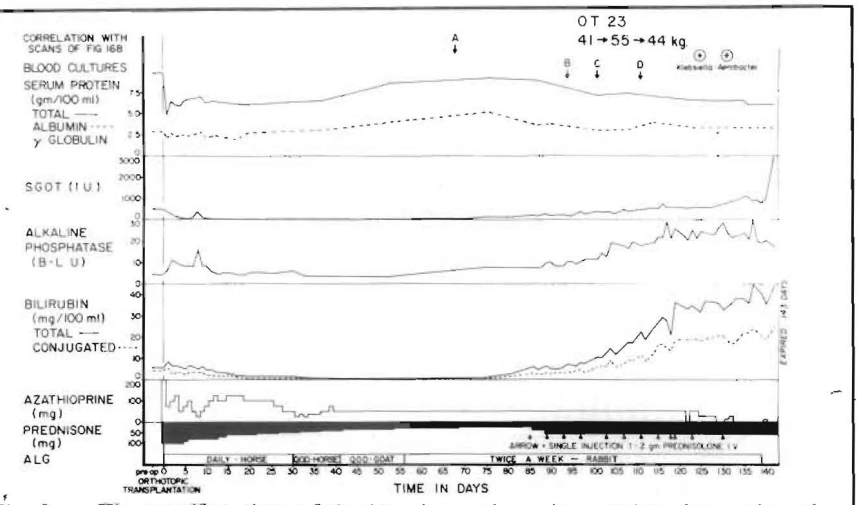

Fig. 5. — The manifestations of the invasion and nearly complete destruction of an orthotopic liver homograft by recurrent hepatoma. The sporadic large doses of intravenous prednisolone were given because of the possibility that the deteriorating liver function was due to delayed rejection. At autopsy almost all the transplanted hepatic tissue was replaced by tumor. The liver scans of this patient shown in Figure 4 are indicated by the lettered arrows (A-D). The normal range for Bessey-Lowry (B-L) alkaline phosphatase units is 1 to 3. The normals for the SGOT and SGPT units at this age are 60 to 100 and 5 to 35, respectively. (By permission of W. B. Saunders Co., 1969.)

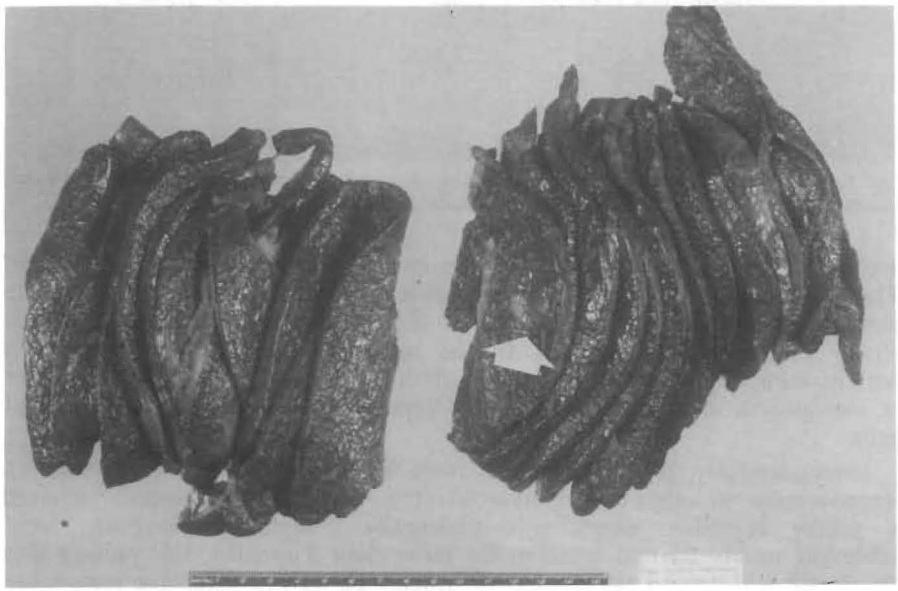

Fig. 6. — The liver removed from a child with biliary atresia at the time of orthotopic hepatic transplantation. Note the 2 cm hepatoma (arrow) which was an incidental finding in the specimen.

to do more hepatomas at this time since the high incidence of metastases (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. It would not be surprising if non-resectable cholangiocarcinomas would be good candidates. Then there are the rare neoplasms of which the gross specimen in Figure 7 is an example with widespread multifocal primaries. This liver

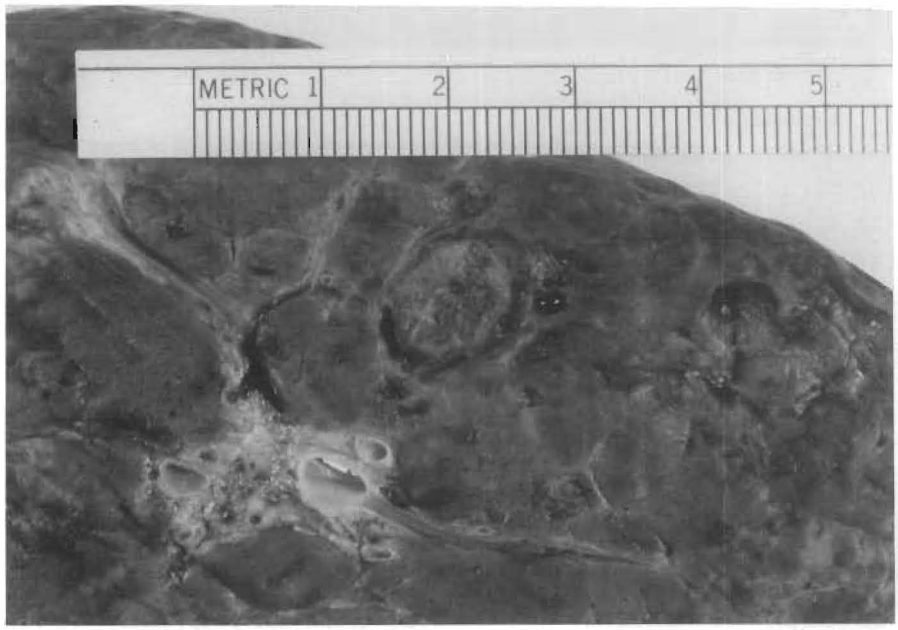

Fig. 7. — Macroscopic appearance of the liver excised at the time of hepatic transplantation of the indication of hemangioendothelial sarcoma.

was taken from a 52-year-old man who had a hemangioendothelial sarcoma. The neoplasm kills with incredible swiftness, usually within a few weeks and by intraabdominal hemorrhage or the development of hepatic insufficienry rather than by spread. In the summer of 1971, we treated this patient with orthotopic liver transplantation. The histopathologic character of the growth showed nearly normal hepatic cells and malignant Kupffer cells.

Postoperatively, the bilirubin fell from 40 to near normal along with an improvement in other liver functions (Fig. 8). Then the patient survived a severe rejection which was eventually completely reversed. After achieving nearly normal function for more than 3 months, this patient also developed widespread pulmonary metastases, as well as extensive recurrence in his liver graft. Thus, we encountered here one more example of the usual futility of treating hepatic malignancy with hepatic transplantation.

We draw your attention to the fact that one of the immunosuppressive agents used for this patient was cyclophosphamide rather than azathioprine (Fig. 8). Cyclophosphamide is, itself, one of the most widely used of the anti-cancer chemotherapeutic drugs. It is also one of the best immunosuppressants. In addition, heterologous ALG and prednisone were used.

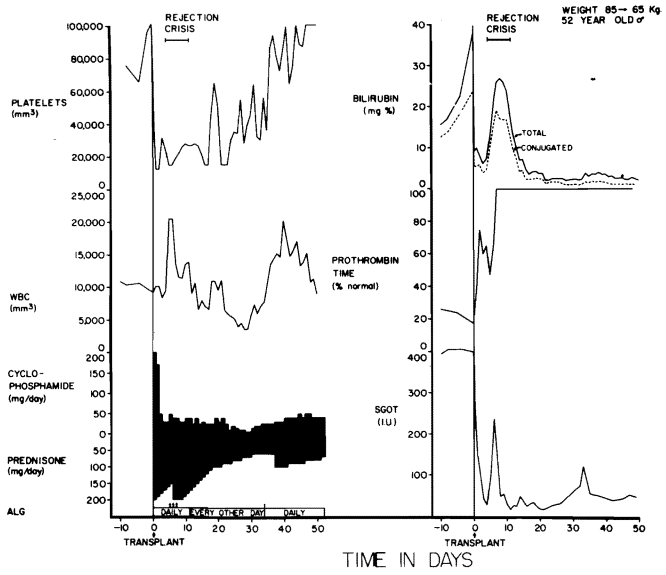

Fig. 8. — The early course of a 52 year old male who had total liver replacement as treatment for a hemangioendothelial sarcoma. This rare liver tumor usually causes death from fulminating hepatic failure in a few weeks or months, but it does not commonly metastasize. After transplantation, there was a severe rejection crisis. The protracted thrombocytopenia postoperatively is often noted after liver transplantation and is probably due to thrombocyte sequestration in the homograft. ALG - horse anti-lymphocyte globulin ; SGOT - serum glutamic oxalacetic transaminase in international units ; and ARROW - 625 milligrams of methyl prednisolone intravenously (By permission of Surg. Gynec. Obstet. 133 : 981, 1971).

Benign Hepatic Disease

Starting in such a negative way about the indications for liver replacement is one way of indicating that the important future of hepatic transplantation is for the treatment of *benign* hepatic disease. There is little point in listing the diseases since the end-stage is much the same. In fact, our general position now is that anyone under 40 who is not a sociopath and who is dying of hepatic insufficiency should theoretically be a candidate for liver

transplantation. The most common diagnoses would, of course, be cirrhosis, chronic aggressive hepatitis, and biliary atresia.

The longest survivor in the world to date after liver transplantation was a boy whose operation was in July, 1968. His early course is shown in Figure 9. There was a very minimal rejection crisis in the second post-operative

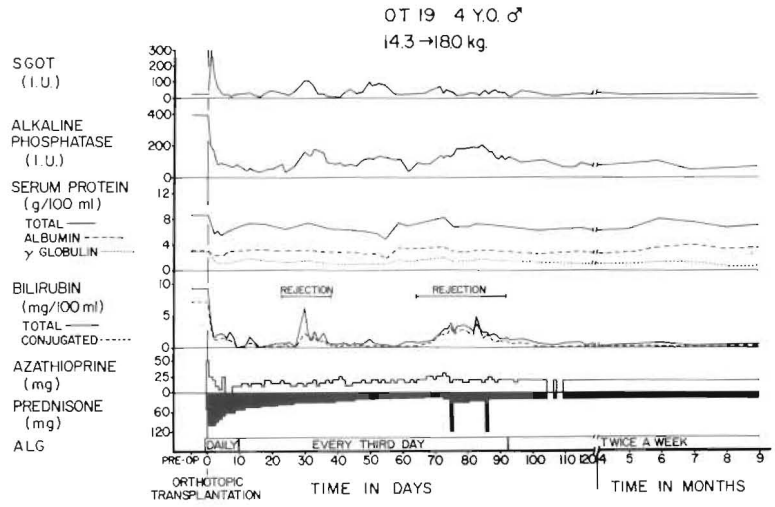

Fig. 9. — The early course of a 4 year old child who survived for 3 1/2 years after orthotopic liver transplantation for the indication of biliary atresia. Note the rejection episodes at 1 month and 2 1/2 months, which were easily controlled. (By permission of W. B. Saunders Co., 1969.)

month. His liver was biopsied at 3 years and found to be almost normal. Then suddenly just before Christmas he developed a violent hepatitis for which the most likely etiologic explanation was the Herpes or chicken pox virus (virology and pathology studies are still in process). He died of acute hepatic insufficiency a few days later after a total survival of 3 1/2 years, of which almost all was spent in good health.

In Figure 10 is the liver of another patient with benign disease. This child was suffering from Wilson's disease which led to cirrhosis and finally profound liver failure. After operation, he had a grave rejection crisis which eventually reversed and with an ultimately good result now after more than 2 1/2 years (Fig. 11). He has returned to his home in Ohio where he now goes to school.

As all of you know, Wilson's disease is an inborn error of metabolism of which the precise pathophysiology has never been worked out. The essential biochemical finding is the deposition of copper in all tissues, including the liver and brain. The characteristic Kayser-Fleischer rings by which the ophtalmologist can make the diagnosis are nothing more than copper

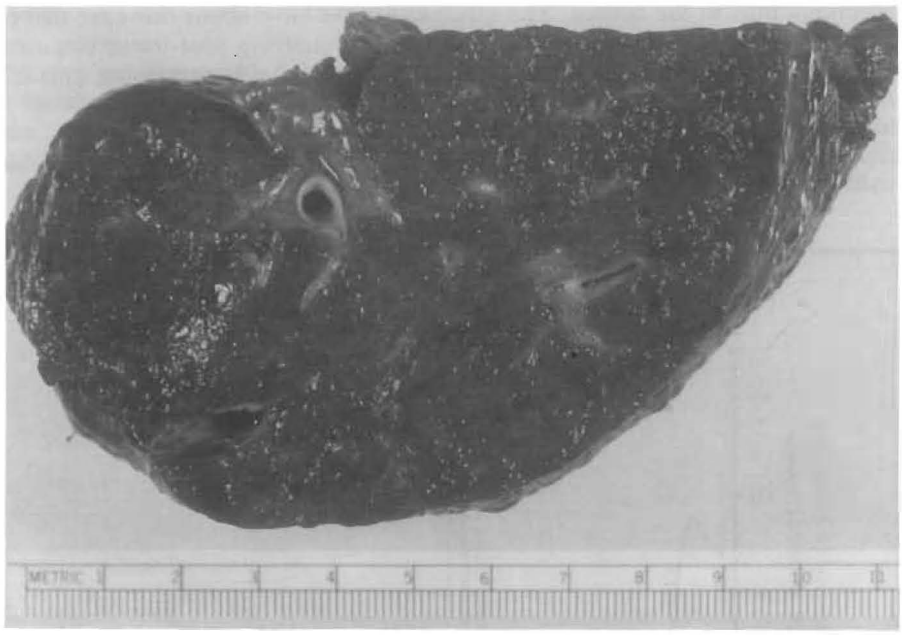

Fig. 10. — The native liver of a child whose hepatic failure was caused by Wilson's disease. The recipient's postoperative course is shown in Figure 11.

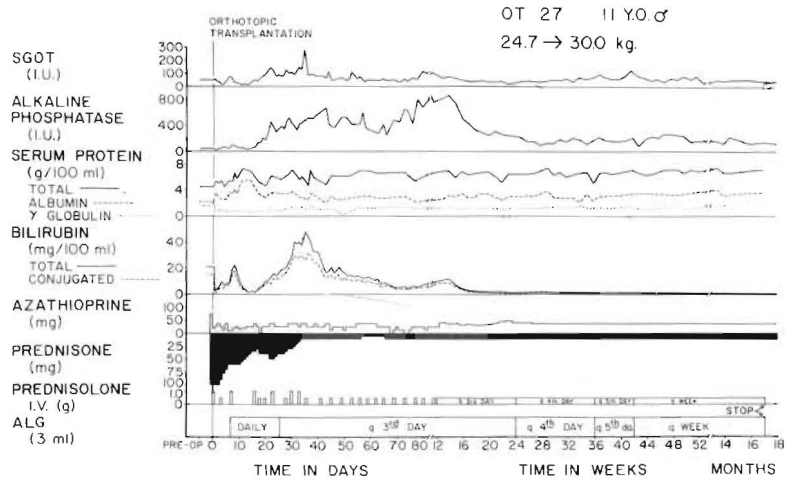

Fig. 11. — Postoperative course of an 11 year old recipient of an orthotopic liver homograft for cirrhosis secondary to Wilson's disease. A severe rejection crisis beginning about 3 weeks post-transplantation eventually reversed and hepatic function has been essentially normal since the sixth postoperative month. The patient remains in good health 2 1/2 years after operation.

accumulations in the cornea. The information we have about this case makes us believe that this copper accumulation is not recurring post-transplantation and that, on the contrary, copper metabolism is probably remaining normal. After operation, there was a massive cupriuresis which lasted for almost 6 months (Fig. 12). At this time, the liver was biopsied and then a biopsy was repeated after 1 1/2 years. On both occasions the liver copper content was entirely normal.

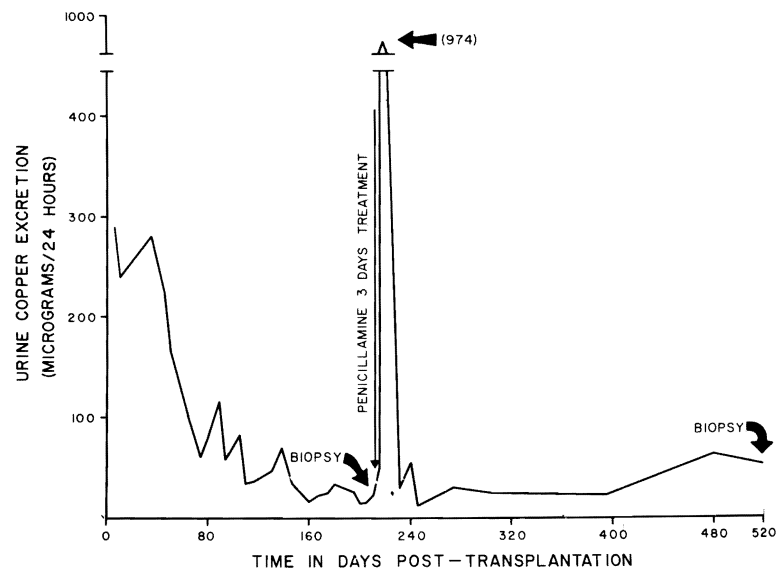

Fig. 12. — Urinary excretion of copper after orthotopic liver transplantation for Wilson's disease. Following operation there was a massive cupriuresis lasting 6 months. A secondary peak of copper excretion occurred in response to a 3-day test course of penicillamine. (By permission of Lancet 1 : 505, 1971).

We have treated another patient with Wilson's disease, this time almost a year ago. In this second patient the main indication for proceeding was extremely severe neurologic involvement that was not controlled by penicillamine therapy. In fact, the recipient was so neurologically crippled that he had some respiratory distress. The early course of the patient is shown in Figure 13. It is a complicated graph but one from which some important points can be illustrated. First, the immunosuppressive treatment was again with cyclophosphamide (or Cytoxan) instead of azathioprine (Imuran) ; in addition to the cyclophosphamide, horse ALG and prednisone were administered. Second, rejection probably never occurred in this patient. There was a marked deterioration of hepatic function in the second post-operative month at which time the boy became jaundiced and had rises

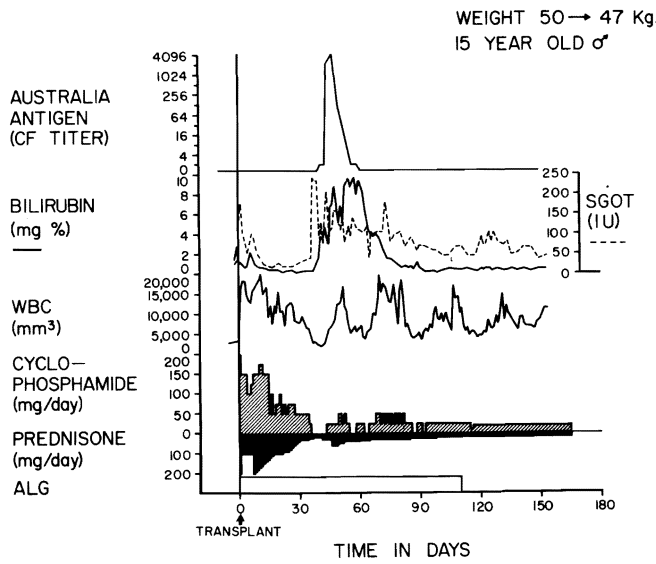

Fig. 13. — Triple drug therapy with cyclophosphamide, prednisone and horse antilymphocyte globulin (ALG) in a patient who had an orthotopic liver transplantation for Wilson's disease. Rejection has never been diagnosed postoperatively. The temporary deterioration in hepatic function in the second postoperative month was accompanied by Australia antigenemia detected by the complement fixation (CF) technique and consequently was thought to be a manifestation of serum hepatitis. (By permission of Surg. Gynec. Obstet. 133 : 981, 1971).

in his transaminases. However, this was probably not rejection for, at the same time, he developed Australia antigenemia with prodigious increases in his complement fixation titers. Immunosuppression was not intensified and he spontaneously recovered. The reason for mentioning this second point is that we now realize how many factors *other than rejection* can cause deterioration of hepatic homograft function. The most important of these non-immunologic complications are serum hepatitis, such as demonstrated in Figure 13, biliary duct obstruction, which we will return to later since it is a dreaded complication, and drug-induced hepatotoxicity.

This concludes our remarks about indications. If we have not made our position clear, it can be summarized with one sentence. We believe the situation is completely analogous to that in renal transplantation in which field benign disease is also the prime indication for treatment.

CLINICAL RESULTS

We will now pass to the second question, namely that of the results obtained. Between the spring of 1963 and July, 1967, 7 attempts at orthotopic liver transplantation were made in Denver. All failed with death

in 21 days or less. Our own experience, including these cases and all subsequent ones until a little more than one year ago, has consisted of 36 cases. Survival of at least one year was obtained in 10 of these 36 recipients, or 28 % (Table 1). The record was not disgraceful since all these patients were doomed to early death, but it can certainly stand improvement.

Even after one year, 7 patients were lost for the reasons and at the times you see in Table 2. The most common cause of late failure was

Table 1. — 36 orthotopic transplantations

One year Survival
10/36 (28 %)

Table 2. — 10 one-year survivors after orthotopic transplantation

ALIVE	3/10	1 1/6 to 3 1/3 years
DIED	7/10	1 to 3 1/2 years
12 months		Cancer
12 months		Serum hepatitis, liver failure
14 months		Cancer
15 months		Cancer
15 months		Rejection, liver failure
30 months		Rejection, liver failure
42 months		Hepatitis, liver failure

carcinomatosis, accounting for 3 deaths after one year. Serum hepatitis caused one late death and chronic homograft rejection was responsible for two others. As already mentioned, the death that occurred at 3 1/2 years seemed due to some kind of hepatitis, possibly caused by the Herpes virus, although this has not been proved.

The whole question of serum hepatitis in transplant patients is just beginning to unfold but there is plenty of reason to know that it is a potentially serious matter. Liver disease and, specifically, hepatitis in *renal* transplant patients is a very common complication, occurring in 10-20 % of all kidney recipients in our center. The incidence of serum hepatitis in our liver patients is even higher and we have already shown you one example of this. In view of these observations, is there any hope of treating lethal serum hepatitis with liver transplantation ? We do not know the answer to the question. However, it is worth telling of an extraordinary patient whose reason for transplantation was chronic aggressive hepatitis, Australia antigen positive. She was in profound hepatic failure.

Transplantation was carried out more than 18 months ago. The Australia antigen became negative for almost 2 months and then returned to positive at the same time as a clinical bout of acute serum hepatitis (Figure 14). She recovered from this but her Australia antigen has remained positive to the present. A repeat biopsy 14 months after transplantation revealed recurrence of the chronic aggressive hepatitis in her transplanted liver.

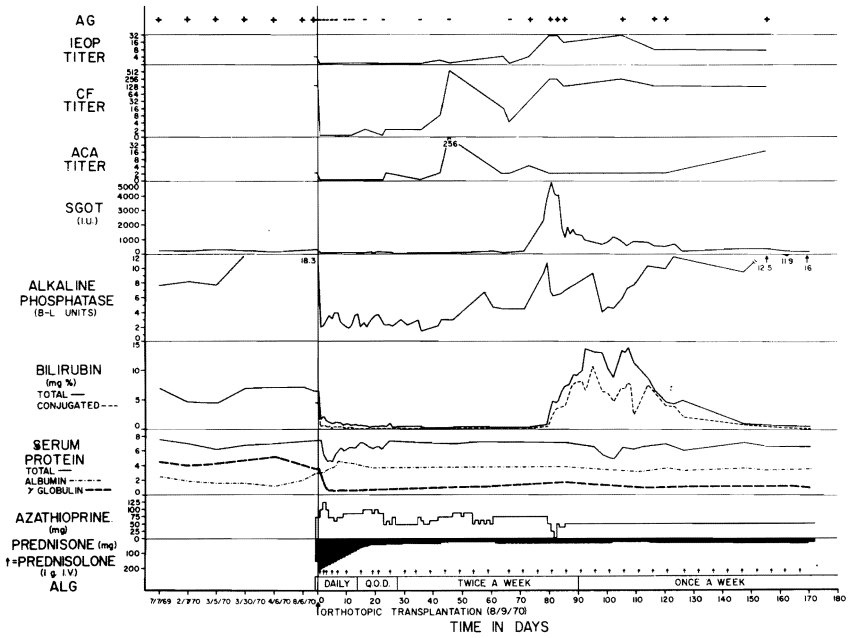

Fig. 14. — Orthotopic hepatic transplantation for liver failure caused by chronic aggressive hepatitis. The Australia antigen, which had been detectable in multiple serum samples for one year before operation, disappeared within hours after removal of her own liver. However, the Au antigen reappeared in her blood stream about 2 months post-transplantation at a time when she developed a clinical episode of hepatitis.

Nevertheless, her health remains satisfactory and, for her, meaningful life has been prolonged. In view of this, the issue of whether more similar patients should be treated is perhaps more of a philosophical than a medical one.

FUTURE PROSPECTS

We will now turn to the third question posed at the outset, namely the prospects of improving the outlook after liver replacement, and assuming that only reasonable candidates with non-malignant disease are accepted. First, we are convinced that one of the real Achilles heels of this procedure is ineffective reconstruction of the biliary duct.

With cholecystoduodenostomy, we have had obstruction at or near the junction of the common and cystic ducts. The nature of the lesion can be appreciated by the kind of operative cholangiogram that is performed with a Foley catheter inserted into the gallbladder (Fig. 15). The kind of

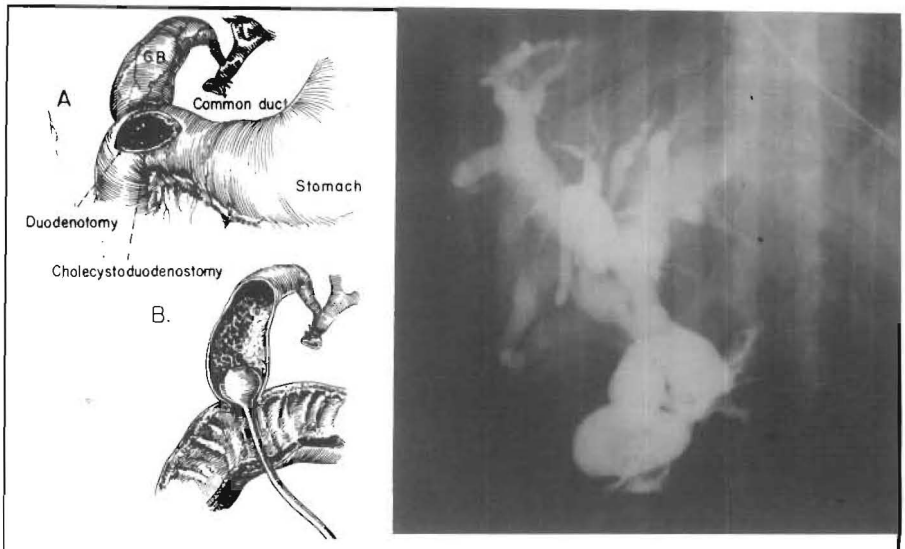

Fig. 15. — Cholangiography of a hepatic homograft in which biliary reconstruction was with cholecystoduodenostomy. LEFT — Technique of dye injection through a duodenotomy and the anastomosis. RIGHT — Obstructed duct system. Despite re-exploration and conversion to choledochoduodenostomy, the recipient died of uncontrolled sepsis 46 days after transplantation.

obstruction of the duct system shown in Figure 15 was corrected in 2 cases at reoperation but too late. All 4 of the patients with this lesion died.

A crucial question in cases like that shown in Figure 15 concerns the reason for obstruction at or near the cystic duct. In four recent cases of this kind in which specimens became available for histopathologic examination, Dr. K.A. PORTER of London has made some intriguing observations. He found that the extrahepatic ducts had ulcerations and edema even though there was little or no evidence of active rejection. The epithelial cells of these ducts were swollen and had intranuclear inclusions resembling those of cytomegalovirus (CMV). Thus, the very real possibility has to be kept open that this variety of biliary duct obstruction has an infectious etiology.

Whatever its cause, it is possible that this kind of biliary obstruction could be avoided if the small caliber cystic duct were not made part of the conduit for bile drainage. In 4 recent cases of liver transplantation, we have performed choledochoduodenostomy by the technique shown in Figure 16 and 17 in which the common duct is passed through a short duodenal tunnel and then everted with a few sutures. Unfortunately, one of these patients died after disruption of the choledochoduodenostomy and the development of biliary peritonitis. As a consequence of this sad experience we have reversed ourselves again and are inclined to perform cholecystoduodenostomy as a primary procedure. However, we would promptly re-explore with the slightest suspicion of

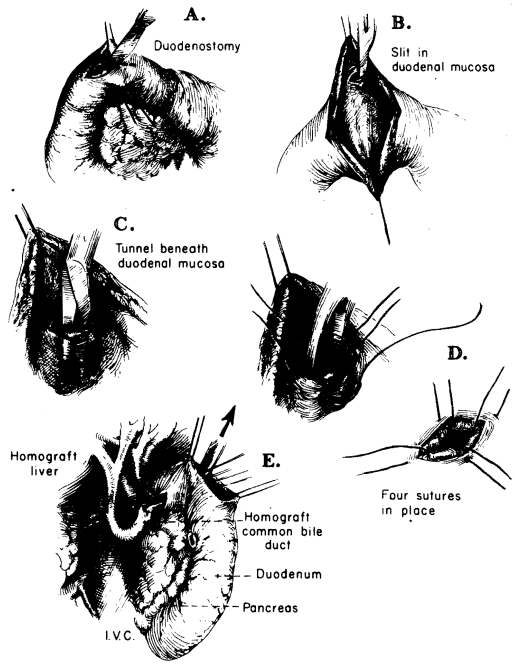

Fig. 16. — Technique of choledochoduodenostomy. After opening the duodenum (A), a submucosal tunnel is created (B, C) through which the homograft common bile duct is passed (E).

mechanical obstruction and then convert to the type of anastomosis shown in Figures 16 and 17 or to some other alternative hookup.

In addition to improving the technical performance of liver transplantation, we believe it is important to try to use immunosuppressive agents that have low hepatotoxicity and with this objective we have switched since early last year to cyclophosphamide instead of azathioprine for all our fresh cases. The usefulness of this major change will require much more evaluation before it can be generally recommended. However, we would like to tell you now that our primary treatment in the next cases will be with cyclophosphamide, prednisone and ALG. After 3 to 8 weeks, we will then switch from cyclophosphamide to maintenance azathioprine. This switch-over technique has already had an extensive and highly satisfactory evaluation with laboratory experiments and after human renal transplantation.

SUMMARY

A brief answer will now be given to each of the three questions posed at the beginning. First, the prime indication for liver replacement is non-neoplasic hepatic disease. Second, the one-year survival in our clinic for all

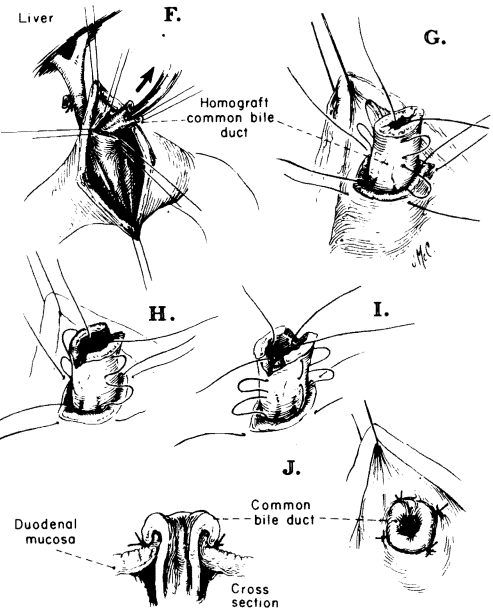

Fig. 17. — Choledochoduodenostomy (continued). The homograft bile duct is secured in place with four fine sutures (G, H, I) in such a way as to create an everting nipple (J).

patients treated up to one year ago was about 30 %. Third, there should be considerable optimism that this survival can be improved by a better technical performance and especially by improved biliary duct drainage. Some recent developments in immunosuppression in which cyclophosphamide has been to replace or supplement azathioprine may also be beneficial.

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