Chapter 26

TRANSPLANTATION OF THE LIVER

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The first attempt at hepatic transplantation in man was made in 1963 [1]. In the ensuing 10 years, close to 70 patients were treated with such an operation at our institution. By now, a significant number of recipients have benefited from the procedure through return to an essentially normal life. Since 1972, better selection of recipients, increased attention to surgical details, and better methods of immunosuppression have improved the results to some extent.

This chapter first describes the indications for hepatic transplantation. Second, the special surgical and immunologic problems of the procedure are outlined. Third, some intriguing metabolic consequences of hepatic replacement are described. Finally, the long-term results are presented.

I. SELECTION OF RECIPIENTS

All patients with end-stage liver disease for which no other form of treatment is available should be considered as possible candidates for hepatic transplantation. However, patients with severe extrahepatic disease or psychiatric abnormalities, including uncontrolled alcoholism, should usually be excluded. On-going infections constitute a potential contraindication because of the necessity to compromise the patients immunologic response after transplantation. Finally, patients over 45 years of age should presently not be considered for transplantation; of eight attempts at treatment in this age group in Denver, all have failed in the first few post-operative months.

Nonresectible, malignant liver tumor was initially believed to be an important indication for liver replacement and our experience at Denver included patients afflicted with hepatoma, cholangiocarcinoma, and hemangio-endothialsarcoma, but none with secondary hepatic tumor. Before proceeding with transplantation in these cases, great care was exercised to exclude the existence of extrahepatic metastases. Nonetheless, tumor spread was subsequently encountered in a prohibitive number of cases.

Noncorrectable, congenital extrahepatic biliary atresia presently constitutes the most definite indication for liver transplantation because of its inexorable course. In the case of intrahepatic biliary atresia, the indication is more relative because prolonged survival is achieved in some instances with conservative treatment.

For children with intrahepatic atresia, as well as for adult patients with liver failure caused by other kinds of nonneoplastic disease, the decision for transplantation must be based on a highly individualized evaluation of the patient's prognosis. When the first attempts were made to treat patients in liver failure caused by nonneoplastic hepatic disease, it was necessary to wait until there was clearly no hope. Consequently, gastrointestinal bleeding,

hepatic coma, or renal insufficiency were usually present. Obviously, such conditions reduced the chances for success. With recent improvements in results, there should be justification to operate before the advent of these terminal complications.

In Denver, biliary atresia has been the most common single indication for hepatic transplantation. Most of the children have been between 1 and 2 years of age, but the youngest has been treated at 3 months of age. More recently, the number of patients with chronic aggressive hepatitis and cirrhosis has increased. The latter group includes patients with Laennec's cirrhosis, primary biliary cirrhosis, and juvenile cirrhosis. In addition, two boys with Wilson's hepaticolenticular degeneration have been treated with hepatic replacement.

II. SURGICAL CONSIDERATIONS

A. The Graft

Hepatic homografts can obviously be obtained from cadaveric donors only. The requirements for a physiologically satisfactory donor include the absence of malignancy or generalized sepsis and a reasonable size similarity to that of the recipient. In the early days of liver transplantation, most patients received grafts that had been damaged by ischemia while residing in the donor. Since the acceptance in 1968 of the brain death criteria, it has been possible to harvest the liver before circulatory arrest or if necessary, the cadaver can be supported by a heart-lung machine. At extirpation, the liver is cooled and cleared of blood by brief perfusion with a chilled electrolyte solution. After removal, the viability at the graft may be preserved for several hours by continuous hypothermic perfusion in vitro [2].

B. The Transplantation

Two different procedures are available [2]. In orthotopic liver transplantation, the diseased, native liver is removed and replaced by a graft with anatomic reconstruction of the vasculature (Fig. 1). In this operation, the removal of the native liver may be a most difficult undertaking because of extensive adhesions around the liver, portal hypertension, and scarring caused by previous surgical interventions. The implantation of the graft entails end-to-end anastomosis of the inferior vena cava above and below the liver and of the portal vein. In two instances existing portacaval shunts

have had to be taken down. In patients with standard hepatic arterial
anatomy, reconstruction is with an end-to-end anastomosis. However, in
several instances it has been necessary to accommodate vascular anomalies
in the graft or recipient (Fig. 1). A biliary outflow tract is usually accom-
plished by cholecystoduodenostomy, following ligation of the graft and
patient common bile duct. Choledochoduodenostomy or end-to-end anasto-
mosis of the graft and recipient common ducts have also been employed.
The last procedure obviously cannot be applied in cases with biliary atresia.
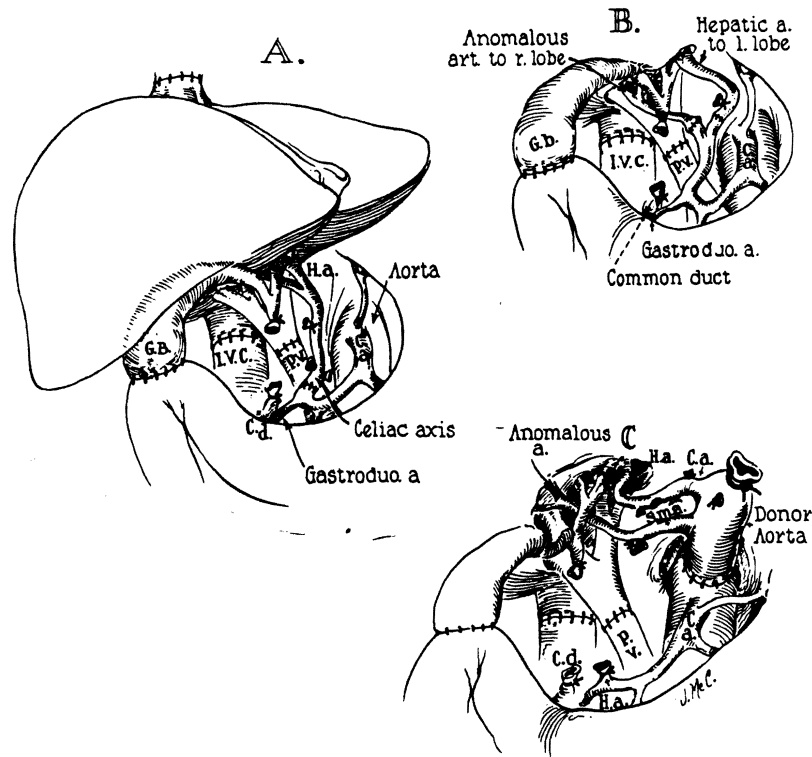

FIG. 1. Orthotopic liver transplantation. (A) Anatomic reconstruction
of the inferior vena cava (I.V.C.), above and below the liver, and of the
portal vein (P.V.) and the hepatic artery (H.A.). Biliary drainage is with
cholecystoduodenostomy after ligation of the graft as well as the patient's
common duct. (B) and (C) Arterial reconstruction used in two patients in
whom the homograft had a double arterial blood supply. (B) Two anasto-
moses; (C) anastomosis of donor to recipient aorta. Several other vari-
ations have been necessary in other patients. [By permission of Ann. Surg.,
168, 392 (1968).

The alternative procedure, which can be used in nonmalignant hepatic disease, is the insertion of a heterotopic hepatic graft with the diseased native liver left in place (Fig. 2). In this operation the inflow into the graft portal vein may be from the patient's systemic venous system (vena cava or iliac vein), or from splanchnic sources following anastomosis of the graft portal vein to the recipient splenic or mesenteric vein. If systemic blood is used for portal inflow, a standard shunt procedure may have to be added in order to relieve existing portal hypertension. Cholecystoenterostomy provides a biliary outflow tract.

C. Postoperative Care

Prior to 1968 several patients received grafts badly damaged by ischemia. In these cases, there was invariably an abnormal bleeding tendency during the operation and the postoperative course was complicated by clotting abnormalities, hypoglycemia, and the development of a third fluid space with hypoproteinemia. There was also severe electrolyte and acid-base disturbances.

In contrast, the early course after the provision of a well-functioning graft is usually not difficult. Elaborate respiratory care with frequent monitoring of arterial blood gases may be important. Repeated measurements of serum potassium and glucose with swift and appropriate adjustments in therapy are also important. Albumin and diuretics are usually administered over the first several postoperative days. Vitamin K is given to support the synthesis of prothrombin. In most patients antibiotics covering a broad spectrum of gram-negative and -positive bacteria are administered for the first postoperative week.

D. Technical Complications

Although portal or caval vascular complications have been uncommon, a 5-10% incidence of graft hepatic arterial thrombosis has occurred. If the occlusion is complete, graft necrosis and patient death ensue. The small size of the vessels, especially in children and in patients with arterial vascular anomalies, is probably the main cause of this complication but the multiple effects of the liver on blood coagulation with the evolution of a hypercoagulable state may be contributing factors.

So far, cholecystoduodenostomy has been the most common choice for biliary tract reconstruction. It has become clear, however, that this kind of anastomosis is accompanied by a 20% or greater frequency of obstruction at the site of the cystic duct, caused either by surgical errors or most
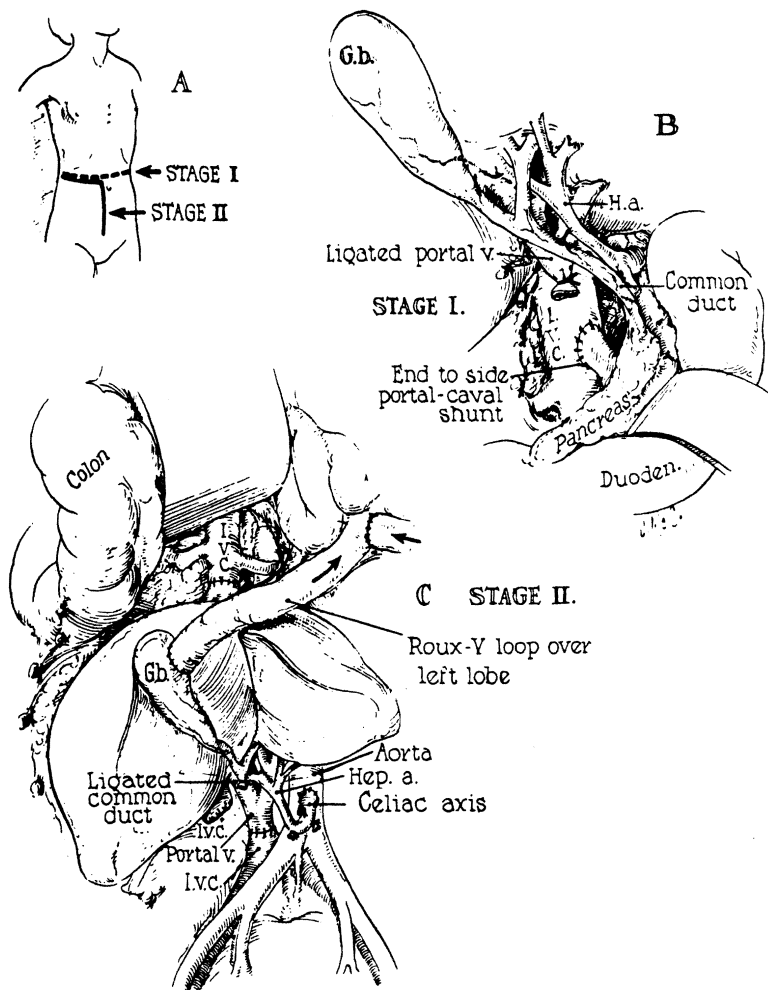
FIG. 2. Heterotopic liver transplantation. (A) The incision; (B) portacaval shunt performed prior to transplantation; (C) the hepatic graft revascularized in the lower abdomen. The portal inflow is from the patient's inferior vena cava; the inferior end of the graft vena cava has been closed. The hepatic artery of the graft is anastomosed to the recipient aorta. Biliary drainage is with cholecystoenterostomy to a Roux-Y loop. In other patients the portal vein has been anastomosed to the splenic or mesenteric vein, thereby providing inflow of splanchnic blood into the graft. Abbreviations as in Fig. 1. [By permission of Arch. Surg., 93, 107 (1966).]

commonly, by swelling or secondary distortion of the duct wall. It has been shown that infestation of duct epithelium with such agents as cytomegalovirus may lead to delayed bile stasis.

Whatever the cause, with obstruction a characteristic syndrome develops with rises in serum bilirubin and alkaline phosphatase and with fever and gram-negative septicemia in the event of cholangitis [3] (Fig. 3). Secondary reconstructions have been carried out with one of the other methods mentioned above, but with a few exceptions the patients have succumbed from intrahepatic abscesses or cholangitis. The use of primary choledochoduodenostomy or choledochocholedochostomy averts this dangerous complication but these methods have been reported to carry a higher risk of bile leakage [2, 4].

Unusual surgical complications include venous infarction of the right adrenal gland secondary to caval resection, paralysis of the right hemidiaphragm caused by inadvertent crushing of the right phrenic nerve with vascular clamps, and intraoperative air embolism.

III. IMMUNOLOGIC CONSIDERATIONS

A. Graft Rejection

Until 1970, an attempt was made to select a donor-recipient combination on the basis of antigenic similarity as measured with histocompatibility (HL-A) testing. With the finding in the last few years that the degree of such similarity did not correlate well with clinical results in recipients of nonrelated homografts, the interest in this kind of "immunologic" selection diminished.

When acute homograft rejection occurs there is fever and an increase in liver size. The most characteristic changes in the standard liver function tests include an increase in serum bilirubin and alkaline phosphatase that parallels concomitant morphologic findings of intrahepatic cholestasis. If the condition progresses, rises in the serum transaminases, prolongation of prothrombin time, and other indications of cellular injury occur (Fig. 4).

Standard biochemical tests thus differentiate poorly between graft rejection and other forms of hepatic pathology, i.e., biliary obstruction, infectious hepatitis, and injury caused by drugs, all of which may occur in homograft recipients. Intravenous or percutaneous transhepatic cholangiograms, technetium and Rose Bengal radioisotope scans, needle biopsy, and the determination in serum of Australia antigen can all aid in the differential diagnosis.
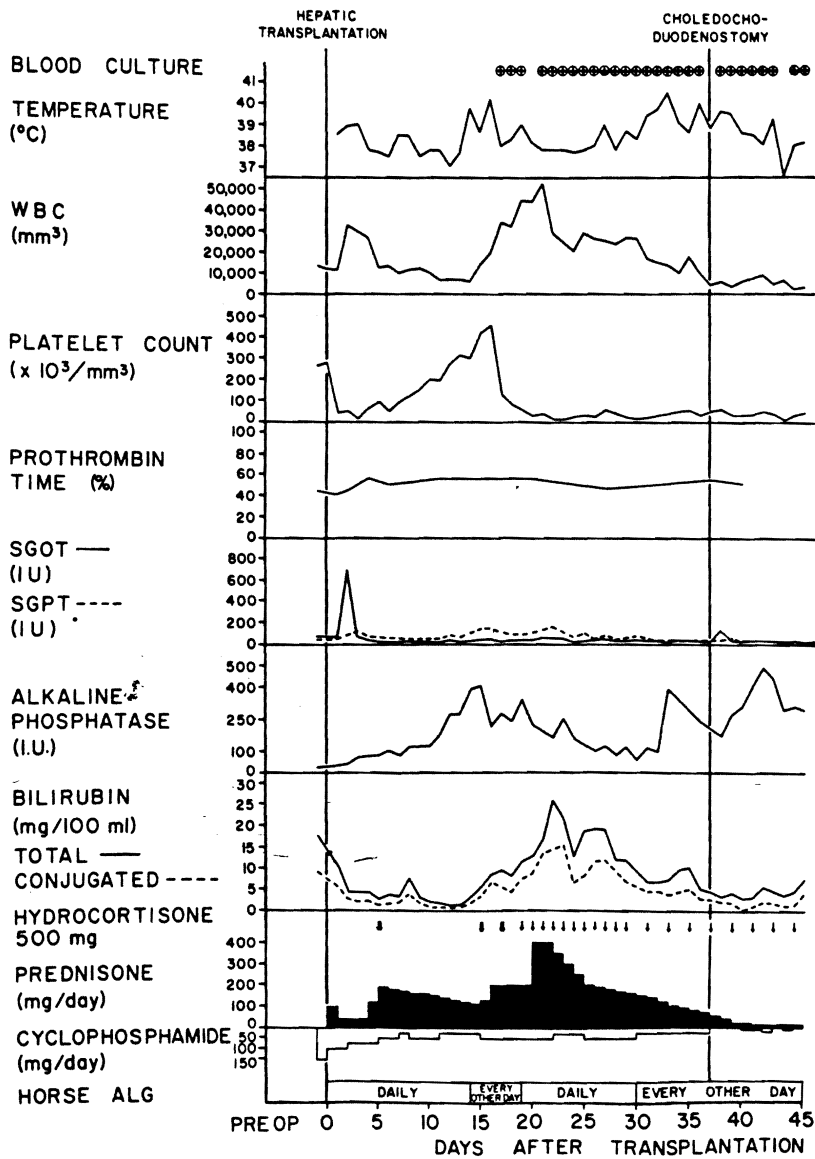
FIG. 3. The course of a 16-year-old recipient of a hepatic homograft. Although liver function was satisfactory initially, hyperbilirubinemia developed 15 days after operation but receded slightly with intensification of immunosuppression. Systemic sepsis prompted reexploration, at which time a cholangiogram showed an obstructed duct system. Biliary diversion was converted to choledochoduodenostomy. However, the child died of uncontrolled sepsis 46 days after transplantation. [By permission of Surgery, 72, 604 (1972).]

Inadequate control of homograft rejection has been a major cause of failure in approximately one third of our patients. In a few patients with graft failure, a second transplantation has been carried out and in one case the recipient of a second graft has lived on for more than a year (Fig. 4).

B. Immunosuppression

The extensive experience with clinical renal transplantation provides the foundation for the immunosuppressive regimens used in human hepatic transplantation. The first patients have been given two immunosuppressive agents, the cytotoxic drug azathioprine and the synthetic adrenal corticosteroid prednisone. During the last several years heterologous antihuman lymphocyte globulin (ALG) has been added to this combination [2] (Fig. 4). More recently, another cytotoxic agent, cyclophosphamide, has been found to be as effective an immunosuppressant as azathioprine in man [5] and, because the former drug may be less hepatotoxic as well as less influenced by variations in liver function, it has been used in the early postoperative period to replace azathioprine [6] (Fig. 5). During the first postoperative weeks, prednisone is given in very high doses but subsequently the doses are gradually reduced (Figs. 4 and 5). If evidence of graft rejection occurs the steroid dose is again increased. In most cases, the required dose of prednisone diminishes considerably with time. The mechanism underlying this "graft accommodation" is poorly understood but it is the prerequisite for long-term success because the side effects of prolonged administration of high doses of prednisone are prohibitive.

The question concerning the effect of the liver on the metabolism of the immunosuppressive drugs has special implications in hepatic transplant recipients. Cyclophosphamide becomes an active, immunosuppressive agent only after an in vivo activation process in which the liver plays an important role, and the same consideration probably applies to azathioprine. Consequently, the drugs may become less activated and thus decreasingly immunosuppressive if the liver function deteriorates. Alternatively, because the degradation and detoxification of azathioprine, cyclophosphamide, and prednisone occur mainly in the liver, it may be suggested that the effect of the drugs becomes enhanced with liver dysfunction. In fact, some evidence has been adduced that renal transplant recipients require reduced immunosuppression when they are afflicted with severe liver dysfunction. However, the practical implications of the described interactions between the immunosuppressive drugs and the liver for the care of the hepatic transplant recipient remain obscure.
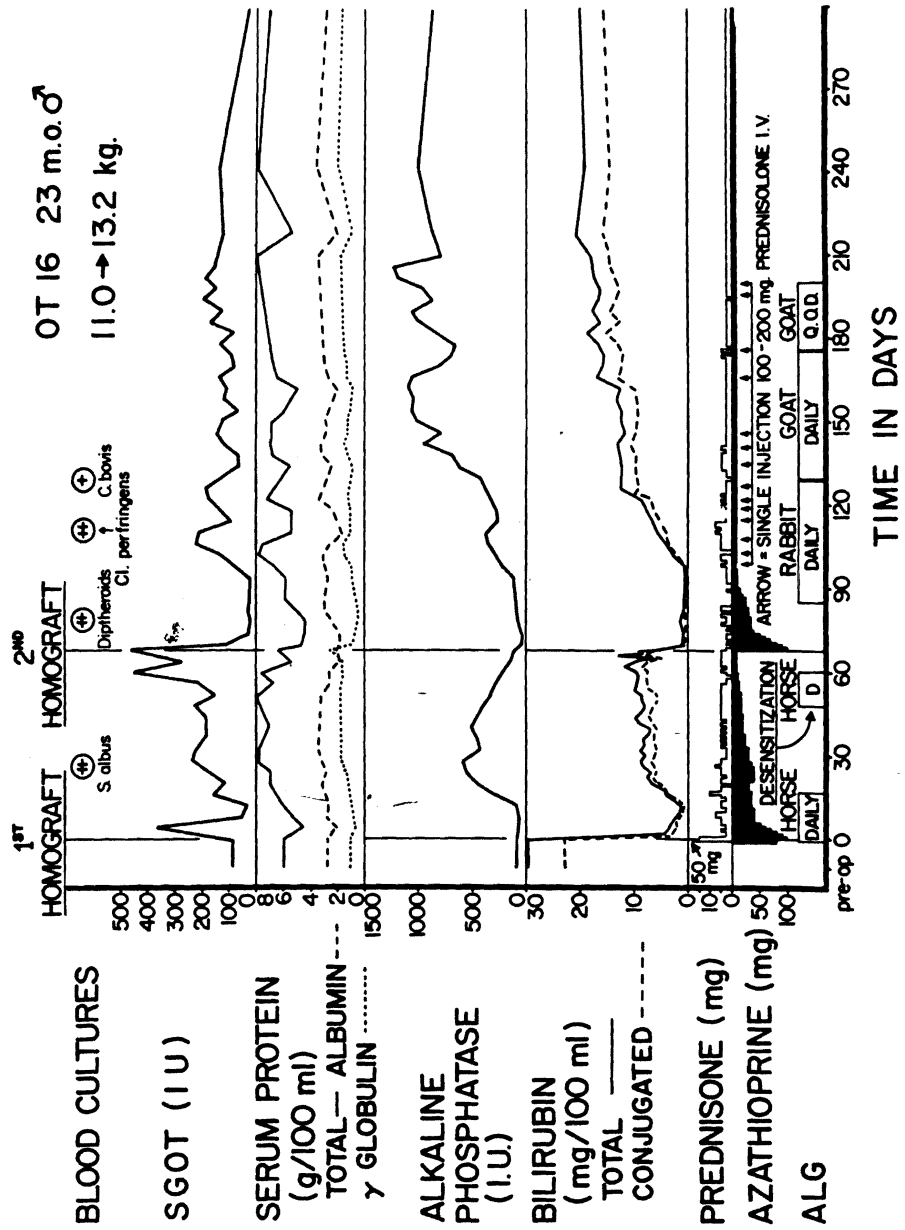
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11.0→13.2 kg.

FIG. 4. Course of a 2-year-old child with biliary atresia. The first hepatic graft was rejected in 2 months. Note the hyperbilirubinemia and the marked elevation of alkaline phosphatase accompanying a moderate increase in serum transaminases. After the second hepatic transplantation, graft function was excellent at first. Later there was evidence of acute rejection but this time the process could be reversed. The patient lived another 12 months. Immunosuppression was with azathioprine, prednisone, and horse and rabbit antihuman lymphocyte globulin. (From Experience in Hepatic Transplantation, 1969, by permission of W. B. Saunders Co., Philadelphia.)
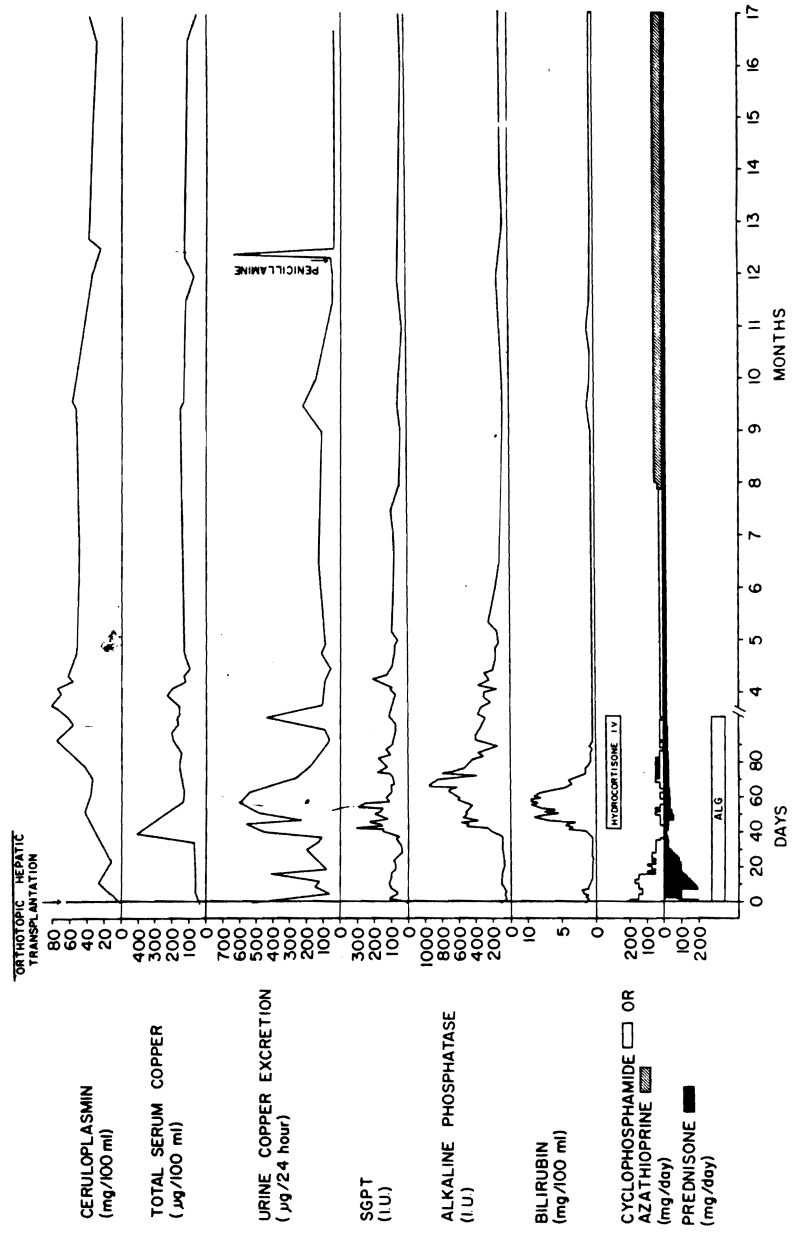
MONTHS

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FIG. 5. Course of a 14-year-old boy with Wilson's disease treated with orthotopic hepatic transplantation. Postoperative immunosuppression was initially with a triple drug regimen consisting of cyclophosphamide, prednisone, and antilymphocyte globulin (ALG). After 9 months azathioprine was given instead of cyclophosphamide. The temporary deterioration in graft function in the second month was thought to be caused by serum hepatitis and not rejection. Note the rapid Normalization in serum ceruloplasmin and copper following the provision of a new, normal liver. Urinary copper excretion is elevated during the early period of graft dysfunction but has since then been essentially normal. The patient has normal hepatic function more than 2 years after transplantation. [By permission of Transplant. Proc. (1973).]

C. The Compromised Host

The dose of immunosuppression required to prevent rejection may induce various degrees of immunologic invalidism. As a consequence, a large number of patients have had a postoperative course complicated by severe pulmonary or systemic infections. Often, the infectious agent has belonged to the opportunistic organisms that become pathogenic only in an immunologically compromised host. Examples are Candida, Aspergillus, Nocardia, and Cryptococcus among the fungi; cytomegalovirus, herpes simplex, and varicella-zoster among the viruses; and a nonclassified microorganism, Pneumocystitis carinii (Fig. 6). Infections with all these organisms have been encountered in hepatic transplant recipients and in many patients such infections have contributed to early or late postoperative death.

In addition to these infections, which plague all patients on immuno-suppression, the liver recipients have had a high incidence of septicemia with gram-negative bacteria of the types existing in the endogenous intestinal flora. Evidence indicates that the hepatic graft, during biliary obstruction or when afflicted by rejection, readily becomes infected with such bacteria, which then enter the systemic circulation. In some patients large septic infarcts have developed, probably as a consequence of uncontrolled rejection (Fig. 7). Frequent blood cultures are important in caring for these recipients and growth of gram-negative bacteria in the bloodstream is strong evidence of graft injury or obstruction.

IV. SPECIAL METABOLIC CONSIDERATIONS

A. Plasma Proteins

In early experimental and clinical studies it was not unexpectedly reported that most of the electrophoretically measurable protein fractions declined rapidly after the implantation of a poorly functioning hepatic homo-graft [2]. In contrast, these fractions were well maintained after provision of a properly functioning graft. A similar relationship between the quality of graft function and protein levels was found also for the liver based clotting factors. The changes in these latter factors were very rapid and reflected changes in consumption as well as in synthesis [2].

More recently, the complement system was assayed in recipients of hepatic homografts [7]. In five patients with terminal liver failure, successful replacement of the diseased livers restored markedly depressed total complement activity as well as the C^4 and C^3 component activities. At the

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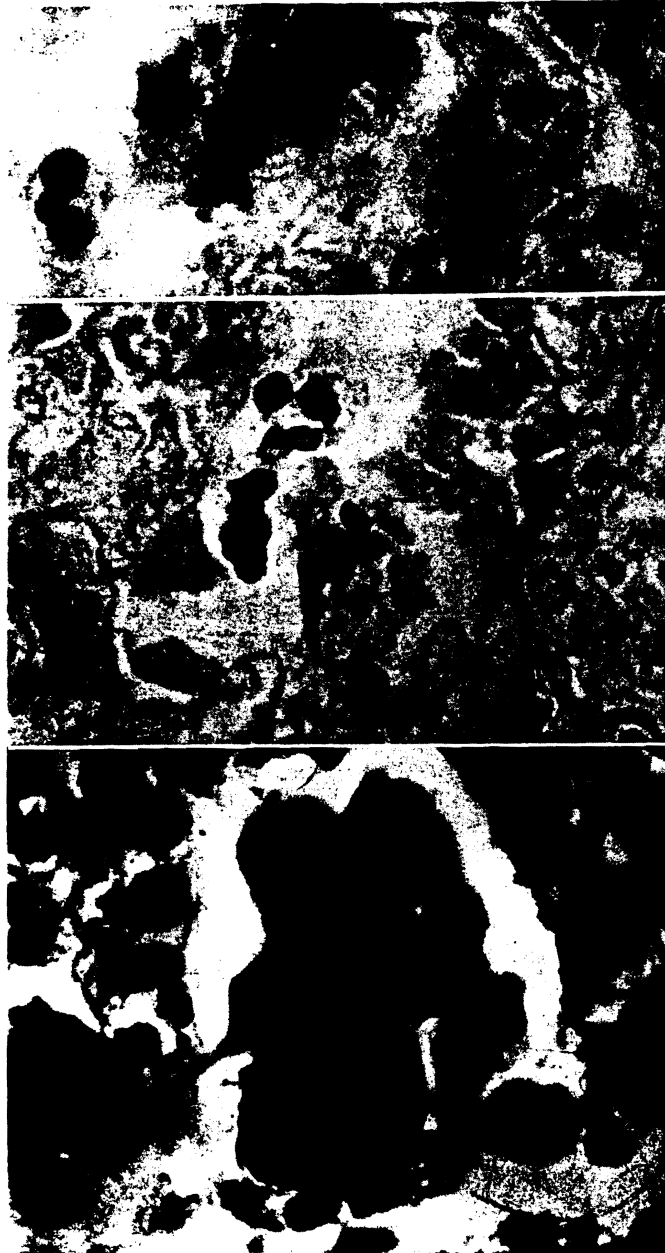
FIG. 6. Multiple infectious agents in the lungs of a $1\frac{1}{2}$-year-old child treated for biliary atresia. The patient died $3\frac{1}{2}$ months after transplantation from pneumonitis. (Left) Cytomegalovirus (hemotoxylin and eosin, x200). (Middle) Pneumocystis carinii (methenamine silver, x200). (Right) Gram-negative bacteria (hemotoxylin and eosin, x200). (From Experience in Hepatic Transplantation, 1969, by permission of W. B. Saunders Co., Philadelphia.)
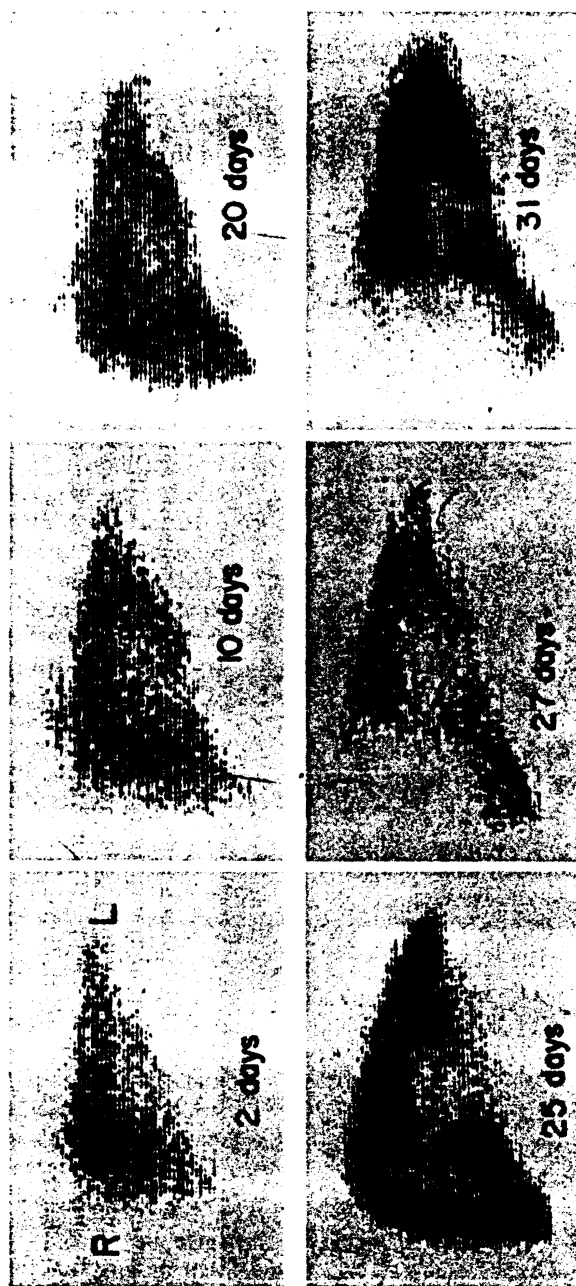
FIG. 7. Postoperative technetium scans in a $1\frac{1}{2}$-year-old child treated with orthotopic hepatic transplantation for biliary atresia. At 2 days the small homograft is normal; at 10 days, an increase in size is evident, although the general configuration of the organ is still normal. At 20 days, no further change is noted. At 25 days, the examination was conducted as an emergency when the child developed gram-negative septicemia and very high increases in the transaminases. Areas of decreased isotope uptake are obvious in the right lobe and the central part of the liver. At 27 days, a striking extension of the process can be seen less than 48 hr later. A debridement procedure was carried out the same evening. At 31 days, 4 days after debridement, the radiographic appearance was improved. The child died 186 days after transplantation. (From Experience in Hepatic Transplantation, 1969, by permission of W. B. Saunders Co., Philadelphia.)

same time the C_5 component increased from low to high normal. In contrast, the C_2 and C_9 components were normal throughout, whereas C_1 showed variable changes (Fig. 8).

Two of the recipients developed postoperative liver function abnormalities that were thought to be caused by homograft rejection. Concomitantly there were marked decreases in total complement activity and in the C_4 and C_3 components (Fig. 8). One of these patients later developed biliary obstruction that required surgical correction. At this time there were no changes in the complement system. Two other patients had temporary liver dysfunction at a time when steep rises in Australia antigen titers indicated the occurrence of serum hepatitis. In one of these patients, a transient decrease in complement activities was recorded but in the other the complement remained unaffected.

It is concluded from these data that complement assays may aid in the otherwise equivocal diagnosis of hepatic homograft rejection. In addition, the data are consistent with the hypothesis that the liver is a main or possibly even the sole source of the C_4, C_3, and C_5 components of the complement system.

B. Inborn Errors of Metabolism

In several liver transplant recipients, the genetically determined phenotypes of the α-globulins, haptoglobin, and group-specific component converted to those of the donors [2]. This early finding indicated that the hepatic homograft retained its metabolic specificity in a new host and that the liver-based inborn errors of metabolism would be correctable by the provision of a new, normal liver.

There have not yet been any successful liver transplantations for a proved inborn error of hepatic metabolism. However, two Denver patients underwent liver replacement for Wilson's disease, a disorder that has been speculated to be caused by a hepatic defect. The first patient, who was transplanted when in terminal liver failure, had a marked cupruresis following transplantation, and biopsy specimens of the graft collected over 3 years have shown no accumulation of copper as had occurred in the native liver.

The second patient had all the classical stigmata of Wilson's disease, with a very low level of the copper-containing serum protein ceruloplasmin, a low total serum copper, a high urinary copper excretion, and a high liver copper; postnecrotic cirrhosis and Kayser-Fleischer rings were found as well. In spite of treatment with chelating agents, the patient became severely crippled by neurologic symptoms. When hepatic transplantation was carried out it was hoped that the provision of a normal liver would improve the copper metabolism with consequent amelioration of the extrahepatic manifestations of the disease [8].

HEPATIC
TRANSPLANTATION

CH50 (units/ml)
IA50 (reciprocal of titer)
C1 C4 C2 C3 C9 (units/ml)
Clq (mg/ml)
C4 (mg/ml)
C3 (mg/ml)
C5 (mg/ml)
SGOT (I.U.)
SGPT (I.U.)
BILIRUBIN (mg/100 ml)
TOTAL PROTEIN
ALBUMIN
γ GLOBULIN
AZATHIOPRINE (mg/day)
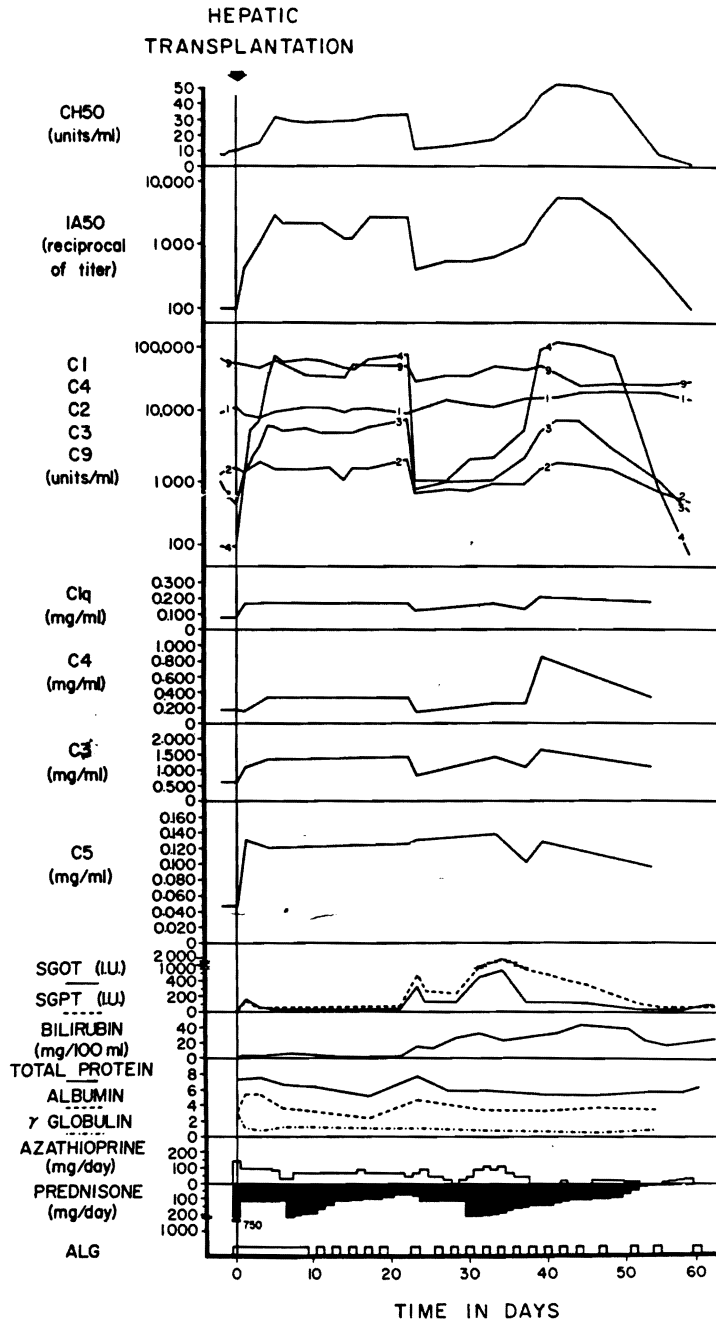PREDNISONE (mg/day)
ALG

TIME IN DAYS

FIG. 8. Changes in the complement system in a patient who developed
liver dysfunction 3 weeks after operation presumably because of rejection.

Several findings indicated that the handling of copper was indeed affected. The serum ceruloplasmin and copper normalized shortly after transplantation and biopsy specimens of the graft showed only a slightly elevated copper concentration (Fig. 5). Moreover, the neurologic symptoms abated and the Kayser-Fleischer rings became less prominent, indicating that the extrahepatic manifestations were being favorably affected by the hepatic replacement. These findings were consistent with the hypothesis that the metabolic defect in Wilson's disease was liver based. The future course could provide grounds for a definite conclusion concerning the role of the liver in the pathogenesis of the disease.

V. LATE RESULTS

In Denver, 62 patients have been treated with orthotopic liver transplantation up until the end of 1972. Fifteen have survived the first postoperative year and three have lived past 3 years. Eleven patients are presently alive, the two longest survivors having essentially normal hepatic function 3 years, 10 months and 3 years, 4 months after the operation, respectively (Table 1).

Following transplantation for benign liver disease, three of seven patients afflicted with chronic aggressive hepatitis survived for at least 1 year. Promising results have been recorded also in the treatment of Wilson's disease; two patients are alive more than 2 and 3 years after surgery. Among the children with biliary atresia the 1-year survival rate is six of 27; two of the patients that survived beyond 3 years were in this group (Table 1).

The worst results in the Denver series have been in patients suffering from Laennec's or primary biliary cirrhosis, with only two of 13 patients surviving beyond 1 year. The reason for this is probably an unfavorable case selection and should not discourage further efforts to operate on such patients (Table 1).

Of a total of six patients with the primary diagnosis of malignant hepatic tumor (five hepatomas, one sarcoma) who lived more than 2 months after transplantation, all eventually died with tumor recurrence. Two of the patients lived beyond 1 year posttransplantation. In these two cases, and

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Legend for Fig. 8 cont.
Note the concomitant marked drop in total complement and several of the components. Subsequently, biliary tract obstruction was diagnosed without the occurrence of changes in complement. The patient succumbed 16 days later; shortly before death complement levels again decreased. [By permission of Clin. Exp. Immunol., 12, 21 (1972).]

FIG. 9. Hepatic metastases in the liver transplant of a 15-year-old patient whose original disease was hepatoma. After 143 days, the homograft (sectioned views on left and right of photograph) was replaced by tumor except for small residual areas. There were also metastases to the lung (center bottom), brain, and retroperitoneal space.

TABLE 1

Denver Series of Orthotopic Hepatic Transplantation

Indications	Total number	Survivors (years)		
		1	2	3
Biliary atresia[a]	27	6[b]	3	2
Cirrhosis	13	2		
Chronic aggressive hepatitis	7	3		
Wilson's disease	2	2	2	1
Carcinoma	12	2		
Sarcoma	1	-		
Total	62	15		
Presently alive				

[a]One patient had a small hepatoma.

[b]One patient received two grafts.

in two of the others, the metastases had also invaded the graft (Fig. 9). The only patient at risk in whom metastases did not develop was a child treated more than 3 years ago for biliary atresia. In this case a small hepatoma was an incidental finding. Survival for several years after liver replacement without recurrence of malignancy was also reported by Daloze in Montreal and Calne in Cambridge, England.

The rapidity and extent of occurrence of posttransplantation metastases in the patients treated for hepatic malignancies may be related to the immunosuppressive treatment. Loss of the "immunologic surveillance" by which mutant cells can be eliminated or restricted in their growth potential has been postulated in the immunologically compromised patients [9].

There has been no example of extended survival among a total of four patients treated with heterotopic hepatic transplantation at our center. All recipients died in the first postoperative months from complications directly related to the grafting or from progressive hepatic insufficiency not relieved by the transplantation. Inherent disadvantages of the method probably account for the poor results. These include technical difficulties with the nonanatomical anastomoses, and abdominal overcrowding caused by the addition of an extra organ. In addition, residual function in a host liver may enable it, by a process loosely termed "interliver competition," to depreciate the chances of good function and survival of the transplant. These disadvantages apparently offset the possible advantage offered by retaining the residual function of the native liver.

Considerably better results than in the total series have been achieved in cases treated with orthotopic transplantation during 1972. Seven out of 11 patients (64%) are presently alive with a followup time ranging from 6 to 18 months. These results indicate that the prospects for success are now approaching those for cadaveric renal transplantation.

Several reasons for the improvements are obvious. First, the operation has been performed at an earlier stage, i.e., before the patient is agonal, as has so often been the case in the past. Second, extensive collaboration within the medical community regarding utilization of organs from patients with brain death have increased the chances of treating more patients at the right time. Third, careful preoperative evaluation of vascular and biliary anatomy primarily with radiographic techniques has prevented some of the technical complications. Fourth, patients with hepatic malignancy have been excluded from consideration for the time being. Fifth, aggressive reexploration and secondary reconstruction of biliary continuity has been practiced in the last year, with successful conversion of cholecystoduodenostomy in two cases. Finally, some improvements in the means for controlling of the immune response have been achieved.

The improved results warrant a considerably larger number of cases to be treated with hepatic transplantation in the future. The vast need for this kind of radical treatment in hepatic disease can be appreciated from the other chapter of this book.

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