

## Chapter 30

# Transplantation of the Liver

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**H**EPATIC TRANSPLANTATION, even in experimental animals, is a product of recent times. The first attempts to transfer a whole liver from one dog to another were made by Welch<sup>78</sup> only 14 years ago. In his experiments, the liver was revascularized in the right paravertebral gutter of the recipient without disturbing the host organ (auxiliary transplantation).

Liver replacement (orthotopic transplantation) was described by Cannon<sup>10</sup> in 1956, although the procedure led to the immediate death of all of his animals. A short time later, programs to investigate orthotopic transplantation in dogs were independently begun at the Peter Bent Brigham Hospital under the direction of Francis D. Moore<sup>42,43</sup> and in our own laboratories at Northwestern University.<sup>60,61</sup> Since then, a very complete picture has emerged about the technical requirements for these operations, the features of rejection which can be expected with or without immunosuppressive therapy, and the organ-specific complications which make the transplantation of hepatic homografts an unusually difficult undertaking.

Literature about experimental liver transplantation has grown exponentially in the last few years and has been reviewed exhaustively in a recent text.<sup>64</sup> In this chapter, the same material will not be recapitulated. Instead, an attempt will be made to develop a clinical point of view about liver transplantation based upon the still small, but highly significant, human experience. In trying to meet this objective, laboratory research will be alluded to only as it directly relates to problems that have been encountered in man.

### CANDIDACY FOR OPERATION

The potential usefulness of liver transplantation can be appreciated by the fact that more than 5,000 in Great Britain<sup>75</sup> and 15,000 persons in the United States<sup>13</sup> die of liver disease each year, excluding infants with biliary atresia. Admittedly, only a fraction of such potential patients could be treated with liver transplantation, since it is highly desirable that recipients be relatively young (preferably under 45 years), free of disease in other organs, and psychologically equipped to withstand the rigors of postoperative therapy. The last condition might well preclude the majority of those with alcoholic cirrhosis. The potential pool is constantly further narrowed by the fact that a

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person who is a legitimate candidate for liver transplantation usually cannot wait long for definitive treatment to be instituted. A host of complications, such as gastrointestinal ulceration, bleeding diathesis, renal failure and coma may cause death before the only operation can be attempted which might hold any hope of survival.

### Primary Hepatic Malignancy

With liver-cell or duct-cell carcinoma that cannot be excised with conventional technics of subtotal liver resection, removal of the diseased organ is obligatory if the treatment is to be transplantation. It is important to carry out a systematic search for extrahepatic spread with chest x-rays, bone surveys and bone marrow examinations. In spite of these precautions, it is usually not possible to make a final decision for or against organ replacement until a cadaveric liver has become available and exploration carried out. In several cases, the effort has been abandoned at the last minute when tumor was found outside the liver.

### Liver Metastases

At the present time, it seems doubtful that orthotopic hepatic transplantation will be a useful way of treating metastases, even when these are apparently confined to the liver. The reasons for this view or even for a pessimistic attitude about the value of such treatment for primary hepatic malignancies will be considered later. There have been only 2 examples of liver transplantation for secondary hepatic neoplasms. The diagnosis was known in Demirleau's case,<sup>10</sup> but in Moore's the preoperative impression of hepatoma had to be revised when a small primary carcinoma of the sigmoid colon was found at autopsy, 11 days after transplantation.<sup>41</sup>

### Non-neoplastic Diseases

The central issues are if and when to proceed, whether or not to use an auxiliary or orthotopic homograft, and what the life expectancy might be without this heroic form of treatment.

*Congenital biliary atresia.* The decision is not difficult if the diagnosis is extrahepatic atresia, a disease in which survival is uncommon for more than two and essentially unheard of for more than four or five years.<sup>26</sup> Moreover, there are factors favoring the orthotopic in preference to the auxiliary operation beyond the fact that the latter procedure has special physiologic disadvantages as will be discussed later. The mechanical handicap to respiration imposed by the hepatomegaly and splenomegaly in these infants is eliminated by removal of both organs in the course of orthotopic homotransplantation. If an auxiliary transplant is attempted, there is little room in the already overcrowded abdomen for another large organ as was well illustrated by Absolon's case.<sup>1</sup>

If the diagnosis is intrahepatic atresia, a distinction that can usually be made with biopsy, a doubly cautious attitude is necessary in recommending transplantation. In a few children with intrahepatic atresia, survival for 10 years or longer has been recorded.<sup>25,30,71</sup>

*Postnecrotic and alcoholic cirrhosis.* There have been few recorded attempts to treat cirrhosis with liver transplantation, probably for two reasons. Often, cadaveric organs cannot be obtained when they are needed. Consequently, a number of prospective recipients have died in our institutions and elsewhere while awaiting hepatic homografts. Secondly, there has been a reluctance on the part of all concerned to consider this procedure at any other time than just before death, since the benefit that might come from intervention was entirely unproven and had to be balanced against the chance, however remote, that spontaneous improvement might occur. Now that the possibility of obtaining extended survival has been established, it may become possible to relax the indications for operation, particularly in cases of postnecrotic cirrhosis, where the maximum value of abstinence from alcohol has already been realized.

The question of which kind of operation to offer such patients has not been answered, but will probably be contingent upon the circumstances of organ supply. For example, if the liver of an infant or child became available for an adult, it might be best to place it as an auxiliary organ. On the other hand, an adult liver would be placed orthotopically, if it were thought that such a procedure could be tolerated.

*Other chronic diseases.* Chronic hepatic failure due to less common diseases should also be amenable to treatment by liver transplantation. Examples could include primary biliary cirrhosis, Wilson's hepatolenticular degeneration, irreparable biliary tract injury and hemochromatosis. To our knowledge, liver transplantation has not been attempted for any of these indications.

Other intriguing possibilities stem from the recent disclosures that liver homografts retain their metabolic specificity after transfer to a new host. This was first shown by the studies of serum haptoglobins (Hp) and group specific component (Gc) of the  $\alpha_2$  globulin fraction in patients before and after orthotopic liver transplantation.<sup>24,37,63</sup> In some of these cases, the donors had different Hp and Gc types than the recipients. After operation, the protein phenotypes completely and permanently became those previously present in the donors (Fig. 1).

A practical implication of these demonstrations is that a number of liver-based metabolic disorders<sup>45,51</sup> might become treatable with either orthotopic or auxiliary transplantation. The concept has been conclusively tested by Kuster et al.<sup>29</sup> Using mongrel canine donors, they were able to cure the gout naturally present in Dalmatian recipients. Conversely, the transplantation of Dalmatian livers conferred the defect in uric acid metabolism upon mongrel recipients.

*Acute liver failure.* The role, if any, of transplantation in the treatment of fulminating viral or toxic hepatitis will probably be determined by clinical trial. Whether homografts placed in an auxiliary location might permit healing and regeneration of the gravely damaged host liver is open to some question. For one thing, the infecting virus in cases of hepatitis might contribute to the acute destruction of the homograft and, in addition, perhaps be made more virulent by the immunosuppression necessary to prevent homograft rejection. Even with acute yellow atrophy due to drugs or other toxic agents, it may be

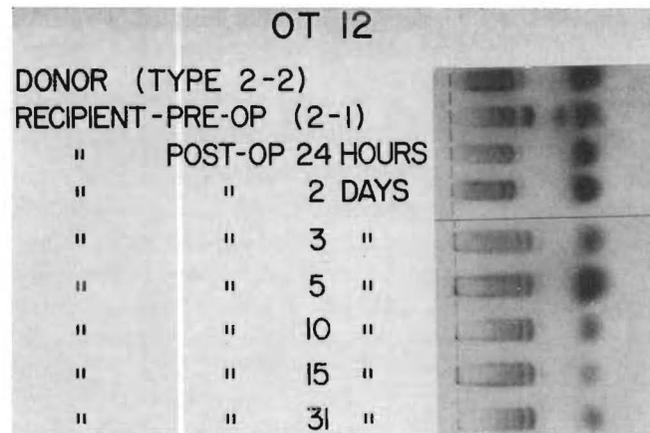


FIG. 1—Effect of orthotopic liver transplantation on serum haptoglobin (Hp). The patient had Smithies type 2-1; her donor was Hp type 2-2. After transplantation only the donor phenotype was detectable in the recipient sera. The determinations were by electrophoresis in a vertical starch gel.<sup>24</sup>

found (see below) that metabolite competition by an auxiliary homograft could inhibit to a variable degree the recovery of the injured host liver.

### HOMOGRAFT PROCUREMENT AND STORAGE

The only source of organs for hepatic transplantation is the recently deceased cadaver. Because of the exceptional sensitivity of liver tissue to anoxia, the circumstances under which donation can be accepted are extremely limited. To begin with, it is almost mandatory that the imminence of death be known for at least several hours in advance. In addition, it is important that good circulation be maintained until just before the end of life, a condition which usually is found only in the victim of a massive and acute central nervous system injury.

As soon as word is received that a potential cadaveric donor may be available, a number of examinations are carried out, including liver function tests. The ABO blood type is also an essential piece of information, since the donor either must be the same blood group as the recipient or have a blood type which permits the kind of pairing shown in Table 1.<sup>63</sup>

In addition to red cell typing, study of lymphocyte antigens is immediately

TABLE 1—*Direction of Acceptable Tissue Transfer when the Donor and Recipient have Different ABO Red Cell Types\**

O to non-O	Safe
Rh- to Rh+	Safe
Rh+ to Rh-	Relatively Safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous

\* O is universal donor; AB is universal recipient.

begun in order to establish the histocompatibility profile of the donor and to see how this matches with that present in any possible recipient. A full description of the techniques, virtues and deficiencies of histocompatibility analysis is beyond the scope of this presentation. However, there is growing evidence that such methods of prospective selection can be expected to reduce the difficulties with rejection that subsequently must be dealt with.<sup>15,72,76</sup>

Other factors also are important in considering the advisability of using the liver from any given cadaveric donor. The role of age in determining the quality of the organ is important, but relatively unpredictable. Morgan and Feldman,<sup>44</sup> Cohen et al.<sup>11</sup> and Peters<sup>48</sup> have all provided evidence that perfectly adequate livers may often be present in the seventh or eighth decade of life. However, it has been our recent policy not to take the chance that degenerative changes might be present and only livers from donors of less than 45 years have been accepted.

### **The Events of Death and Immediate Preservation**

The liver can be subjected to severe ischemia under normothermic conditions with the expectation of prompt recovery, but only if the insult is of very short duration. Part or all of this slender margin of safety may be used up during the terminal hours or days of donor life if there is a protracted pre-mortem interval of ineffective circulation. After death further tissue injury is inevitable; this can be minimized in various ways, including the institution of postmortem cardiac massage.

However, the most important step is to cool the liver at once. This can be done simply (Fig. 2) by intraportal infusion of a chilled (2°C.) electrolyte solution. Alternatively, the entire cadaver or its lower half can be cooled by the use of postmortem cardiopulmonary bypass.<sup>32,69</sup> With this technic, a heat exchanger is introduced into the circuit for temperature control (Fig. 3). The advantage of this approach is that the homograft is simultaneously refrigerated and provided with an artificial circulation.

### **Donor Hepatectomy**

The excision of the homograft is never begun until the homograft is cold; it can then be completed with 15 or 20 minutes if absolutely necessary. However, about an hour is required if the major hilar contents are to be carefully dissected, if all potential bleeding sites are to be ligated, and if long vascular cuffs are to be developed for later anastomosis. The use of cadaveric perfusion, as described above, allows time for the more deliberate approach.

The technical steps in removing the liver are straightforward and will not be described in detail. Several points, however, deserve special emphasis. It is important to try to develop as long a suprahepatic vena cava cuff as possible.

During the hilar dissection, anomalies of the arterial blood supply must be looked for since they occur in about 25 per cent of cases. The most common deviation from normal is to have a right hepatic branch arise from the superior mesenteric artery and to have the left branch originate from the celiac axis (Fig. 4C).

In children it is often desirable to remove a segment of aorta in continuity

*2° C Balanced Electrolyte Solution  
with 50 mgm procaine, 100 mgm  
heparin and 25 gm low molecular  
weight dextran per liter.*

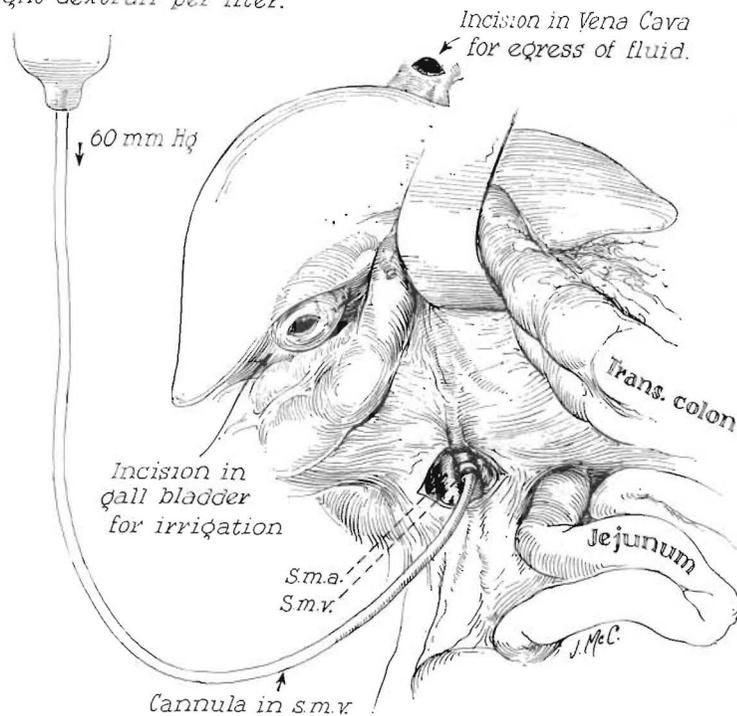


FIG. 2—Method of rapid core cooling of the human cadaveric liver by infusion of a chilled (2° C.) electrolyte solution via the splanchnic venous circulation. Immediately after entering the abdomen, a cannula is placed into the superior mesenteric vein, readily accessible at the base of the transverse mesocolon. This vessel is far enough away from the portal triad so that the portal vein, which will ultimately be used for anastomosis, is not in danger of injury during the initial hasty dissection. Egress of the perfusate is provided for by a venotomy in the supra- or infrahepatic inferior vena cava. Bile is washed from the gallbladder through a cholecystotomy. (By permission of *Ann. Surg.* 168:392, 1968.)

with the hepatic arterial supply (Fig. 5). One reason is that the option of performing an aorto-aortic anastomosis in the recipient is, thereby, left open. Another advantage is that the aorta can be used as a perfusion receptor if the extended preservation to be described below is to be carried out.

### Extended Preservation

Until now there has been only one experimental technic for preserving excised canine livers which has permitted the use of the organs as orthotopic homografts after much longer than 2 hours. The method was reported in 1967<sup>4,5</sup> and subsequently applied clinically. It employed a combination of hypothermia, hyperbaric oxygenation, and perfusion with diluted blood. The preservation chamber is shown schematically in Fig. 6. The details of flow,

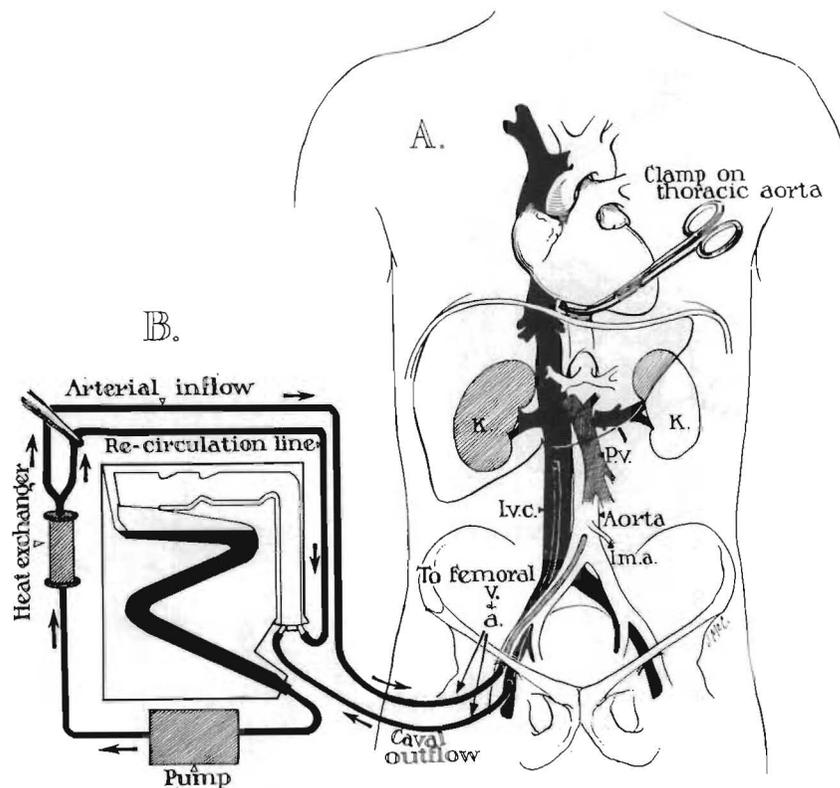


FIG. 3—Technic of extracorporeal perfusion with cardiopulmonary bypass. Catheters are inserted via the femoral vessels into the aorta and inferior vena cava as soon as possible after death. The extracorporeal circuit is primed with a glucose or electrolyte solution to which procaine and heparin are added. The cadaver is, thus, anticoagulated with the first surge of the pump. Temperature control is provided by the heat exchanger. To limit perfusion to the lower part of the body, the thoracic aorta may be cross clamped as shown. (By permission of W. B. Saunders, 1964.)

temperature control, compression and decompression, and acid base control were specified in previous publications.<sup>4,5</sup>

In dogs, it was found<sup>4,5</sup> that canine livers could invariably support life when placed as orthotopic homografts from 8–10 hours after donor sacrifice. Even after 24 hours recipient survival could often, though not always, be obtained. Similarly, life sustaining human livers have been preserved after death for as long as 7½ hours.<sup>6,57</sup>

### The Consequences of Hepatic Injury

In almost all the first unsuccessful attempts at human liver transplantation<sup>53,68,69</sup> poor initial function of the homografts, which had been seriously damaged by anoxia, played an important or decisive role in the early fatal outcome. The tissue injury was at least partly a reflection of poor donor selection, inasmuch as the agonal period of donor life in these cases was almost always very protracted and characterized by a poor circulation.

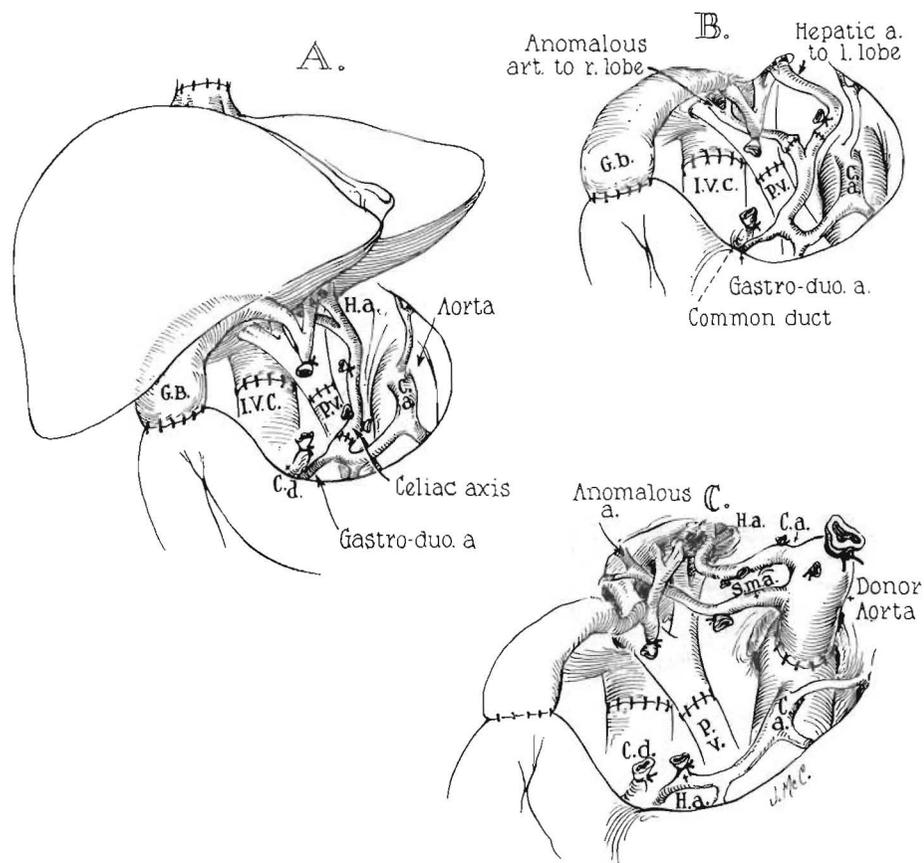


FIG. 4—Variations in hepatic arterial reconstruction in recipients of orthotopic homografts.

(A) If no hepatic arterial anomalies are encountered in either the donor or recipient, the homograft common hepatic artery or celiac axis is usually anastomosed to the recipient proper or common hepatic artery.

(B) The most common anatomic deviation is the presence of an anomalous right hepatic artery originating from the superior mesenteric artery. In one such case in which this anomaly was encountered in the donor, the left and right hepatic arteries of the homograft were individually anastomosed to the left and right branches of the recipient proper hepatic artery.

(C) Alternatively, the homograft aorta may be anastomosed directly to the recipient aorta. Methods of reconstruction when similar anomalies are present in the recipient are shown in Fig. 13. Biliary drainage is established with cholecystoduodenostomy. (By permission of *Ann. Surg.* 168:392, 1968.)

In one of these early recipients a hemorrhagic diathesis ensued almost immediately, leading to death in 4 hours. There was massive fibrinolysis<sup>69,77</sup> which was not affected by treatment with epsilon amino caproic acid (EACA), fresh blood and fibrinogen; at autopsy the liver was almost entirely necrotic. Several other recipients survived operation and a similar though less severe intraoperative bleeding diathesis, but died from 6–23 days after orthotopic

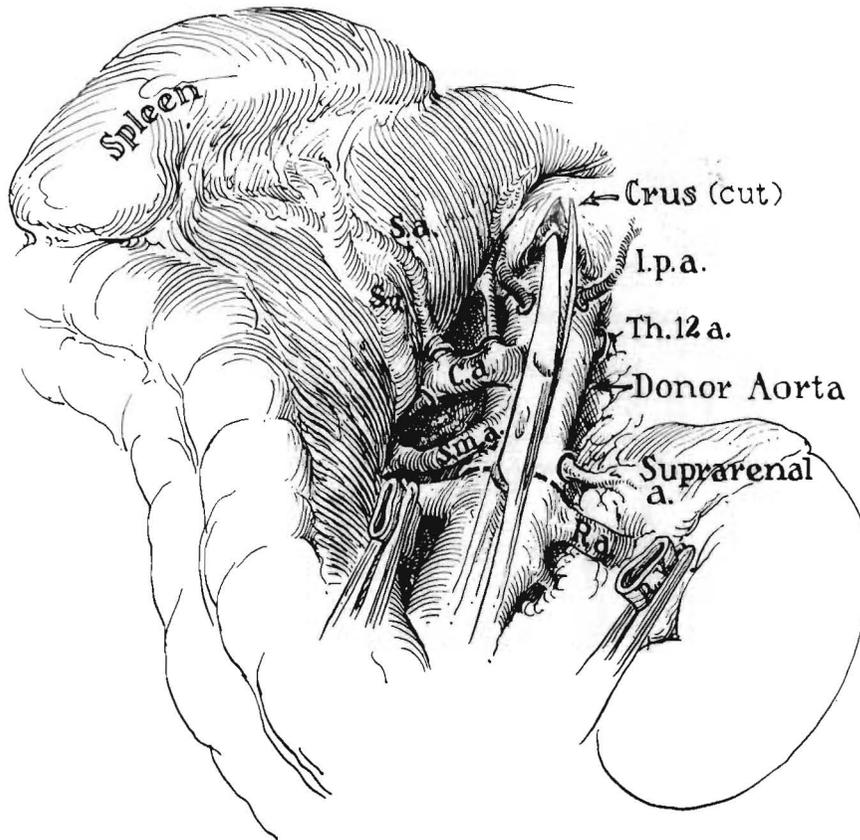


FIG. 5—Mobilization of the aorta during donor hepatectomy. Rapid identification and ligation of the branches is facilitated by applying variable traction to the distal aorta. During the initial dissection, all the aortic branches except the celiac axis and superior mesenteric artery are ligated and divided; the latter vessel is cut only after it has been shown not to give rise to an anomalous hepatic arterial branch. (By permission of *Ann. Surg.* 168:392, 1968.)

transplantation of multiple complications including hepatic insufficiency. In these patients, there were obvious defects in protein metabolism leading eventually to severely depressed levels of all protein fractions and clotting factors formed by the liver. Coincidentally, a large, third, fluid space was seen with ascites or even anasarca. Within a few days after operation jaundice became evident.

At autopsy, the homografts in these unsuccessful early cases all had histologic signs of previous severe ischemic damage. Invariably, there was necrosis, in some instances massive in extent. Most of the livers had little evidence of homograft rejection. Other serious complications such as gastrointestinal ulceration and hemorrhage, pulmonary embolization or uncontrollable infection were the immediate cause of death. Nevertheless, acute hepatic insufficiency had played a prominent role in every instance.

The livers used for all patients since the summer of 1967 have been of a

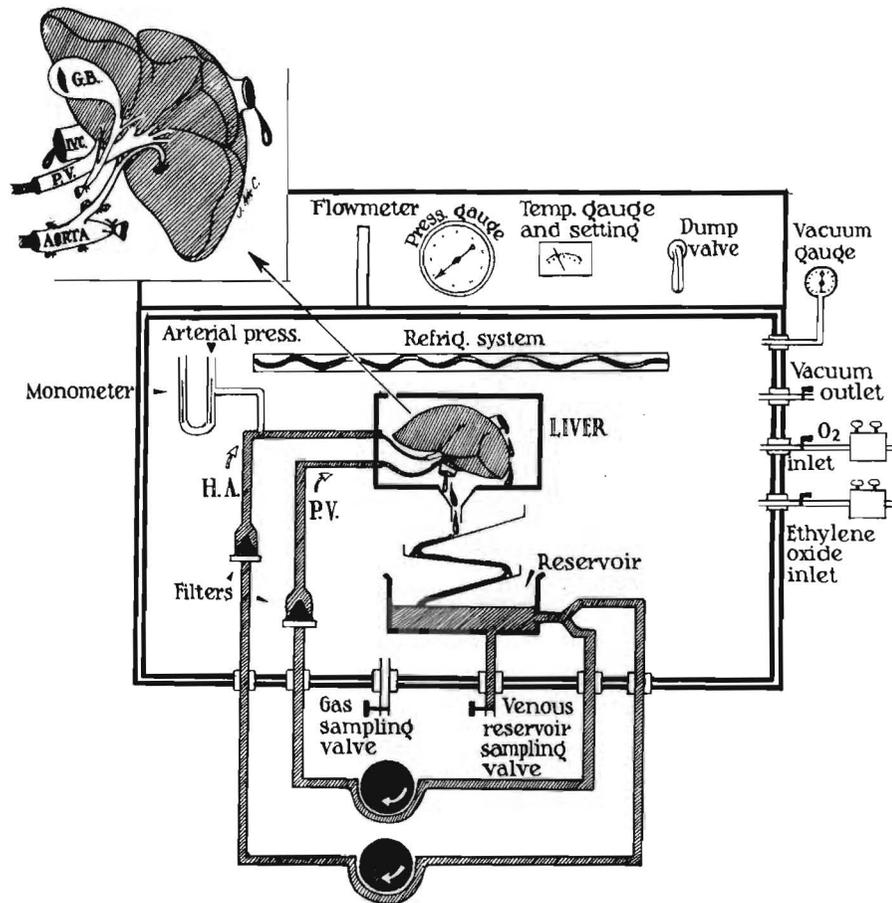


FIG. 6—Preservation unit. The perfusion pumps are located outside the hyperbaric chamber; the organ receptacle, the oxygenator and the venous reservoir are inside. The various chamber inlets permit sampling of the perfusate, gas sterilization, and oxygen delivery and removal. The temperature is electronically controlled. (By permission of Surg. Gynec. Obstet. 126:263, 1968.)

much higher quality, mainly because of more discriminating donor selection. In these last cases almost all the donors had short terminal illnesses and effective circulation until shortly before death.<sup>54,56,57</sup> In addition, many of the homografts were preserved in the efficient conservation apparatus alluded to above. The organs have provided adequate or excellent function in 11 of 14 cases. The only exceptions were in 3 patients who developed acute occlusion of the common hepatic artery or portal vein.

## ORTHOTOPIC TRANSPLANTATION

### Recipient Technic

In concept, the procedure is an extremely simple one involving only the reconstruction of vascular channels entering and leaving the liver, as well as provision for bile drainage. The ways in which these requirements have been

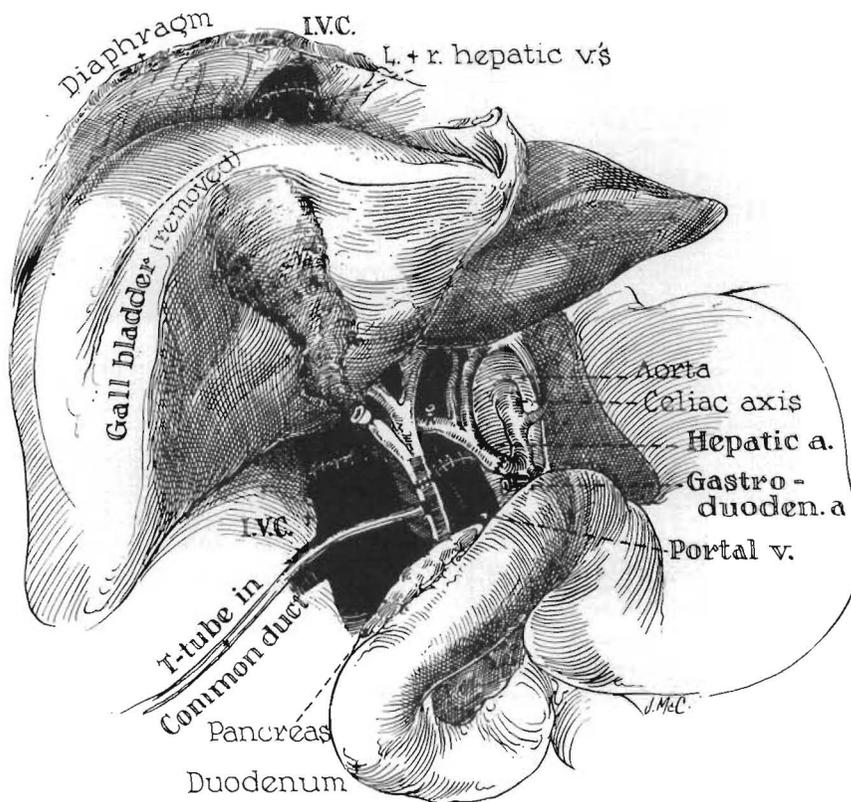


FIG. 7—Technic of reestablishing biliary drainage with choledochocholedochostomy. A T tube is placed through a stab wound in the recipient portion of the reconstructed common duct. Disruption of the anastomosis was the cause of death in one of the early cases. In all subsequent recipients, the common bile duct has been ligated and cholecystoduodenostomy performed (Figs. 4 and 13).

met are shown in Figs. 4 and 13. A more physiologic means of reestablishing homograft biliary drainage than cholecystoduodenostomy would be with choledochocholedochostomy (Fig. 7). Disruption of the anastomosis caused the death of one of the recipients. Since then the common duct has been ligated and the gallbladder anastomosed to the duodenum in all cases (Fig. 4).

There are factors which can render the operation difficult. Most patients who have a need for a liver homograft have more or less severe portal hypertension which can make recipient hepatectomy a dangerous and bloody task and one which is further complicated by the huge size of some of the livers. Shown in Fig. 8 is the specimen removed from a 29-year-old woman. The liver and tumor weighed 20 pounds.

A special technical point concerns the need, during the anhepatic phase, to occlude both the inferior vena cava and portal vein (Fig. 9). In dogs, the acute obstruction of the 2 venous beds for more than a few minutes is incompatible with life. To circumvent this difficulty, prosthetic bypasses have been used in laboratory research for temporary decompression (Fig. 10). The same



FIG. 8—The liver removed at the time of orthotopic homotransplantation from a 29-year-old woman whose indication for transplantation was hepatoma. At operation a massive, multinodular tumor was found to have virtually replaced both hepatic lobes. There was no discernible tumor spread beyond the liver.

kinds of devices were employed in the first clinical cases and may have contributed to the pulmonary embolization which occurred in 3 of the first 4 patients in our institutions who survived operation.<sup>68,69,77</sup>

Subsequently, it has been learned that the human can tolerate cross clamping of both the portal vein and inferior vena cava for the time necessary to transplant the liver.<sup>56,57</sup> In patients with severe portal hypertension there have been almost no consequent cardiodynamic alterations and, even in recipients who had few venous collaterals, only minimal hypotension was seen.

After completion of all the anastomoses, it is probably important to reattach the suspensory ligaments of the homograft to the companion structures in the recipient. When extended survival was finally obtained clinically, delayed thrombosis of the right hepatic artery developed in 5 of 6 consecutive infants and led to partial gangrene of the right lobe. Autopsy studies performed in an attempt to clarify the etiology suggested (Fig. 11) that the right lobe of livers that were not so reattached tended to rotate downward and medially and to partially kink the right hepatic artery.<sup>57</sup>

### Immediate Mortality

*Early experience.* From March 1963 to May 1967, 7 patients were treated with orthotopic homotransplantation.<sup>53,68,69</sup> In 5, the indication was primary hepatic malignancy and in the other 2 it was extrahepatic biliary atresia. One patient was 11 months old, a second was 3 years, and the other 5 were 29–67 years. There was one immediate death and survival in the remainder of

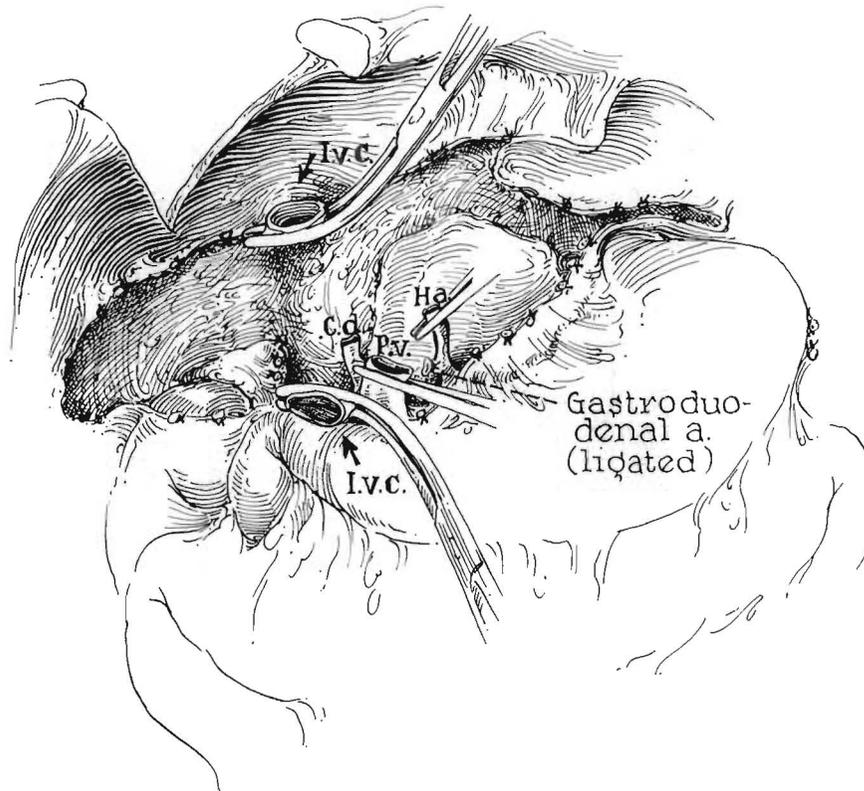


FIG. 9—The operative field after human recipient hepatectomy. Note that both the inferior vena cava and portal vein are cross clamped during the anhepatic phase. The consequent acute obstruction of both venous beds is well tolerated in man without bypass decompression, as is required in the dog. (By permission of Surg. Gynec. Obstet. 117:659, 1963.)

6½, 7, 7½, 10, 22, and 23 days. As mentioned earlier the use of badly or hopelessly damaged organs in these cases probably precluded long-term success. Moreover, it made evaluation of the effectiveness of immunosuppressive therapy an impossible task. These cases, which will not be considered further in this chapter, led to the decision<sup>52,53</sup> that further clinical trials would not be attempted until better techniques of both immunosuppression and organ preservation could be applied, and then not unless an effort could be made at prospective histocompatibility typing. These objectives were met in the next 14 cases.

*Later experiences.* Fourteen more patients were treated with orthotopic liver transplantation from July 1967 until August 2, 1968. In this group there were 3 deaths in the immediate postoperative period. One patient, aged 11 months, developed thrombosis of her homograft hepatic artery within a few hours after completion of the procedure. Almost immediately, she became somnolent and had a sharp fall in blood pressure. Diagnostic changes in her serum transaminase activities did not develop until almost a day later (Fig. 12),

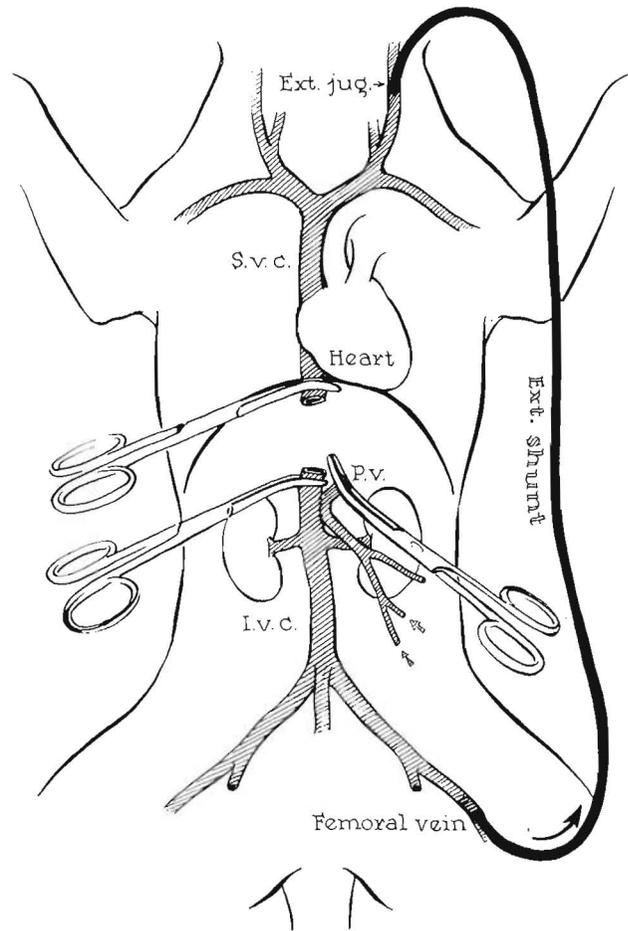


FIG. 10—Method of decompression of the inferior vena caval and splanchnic venous systems during removal of the canine liver and replacement with a homograft. A preliminary portacaval shunt has been constructed. This temporary anastomosis, connecting the 2 venous systems, allows their decompression with a single external bypass. (By permission of *Surg. Gynec. Obstet.* 111:733, 1960.)

by which time it was thought that the opportunity for reintervention had been lost. She died 3 days later after developing hemolysis which was so extreme that it was impossible to find a single normal red cell on smears of her peripheral blood.

Two other infant recipients died within one day of operation as a result of vascular occlusion. In both, there was a double hepatic arterial supply to the recipient liver, the right branch originating from the superior mesenteric artery (Fig. 13A), leading to a decision to anastomose the homograft celiac axis to the recipient aorta. Both the donor livers had been obtained from children who were considerably larger than the recipients and the inferiorly protruding caudate lobes of the homografts compressed the arterial blood supply (Fig. 13A). The complication was not appreciated in the first child who died

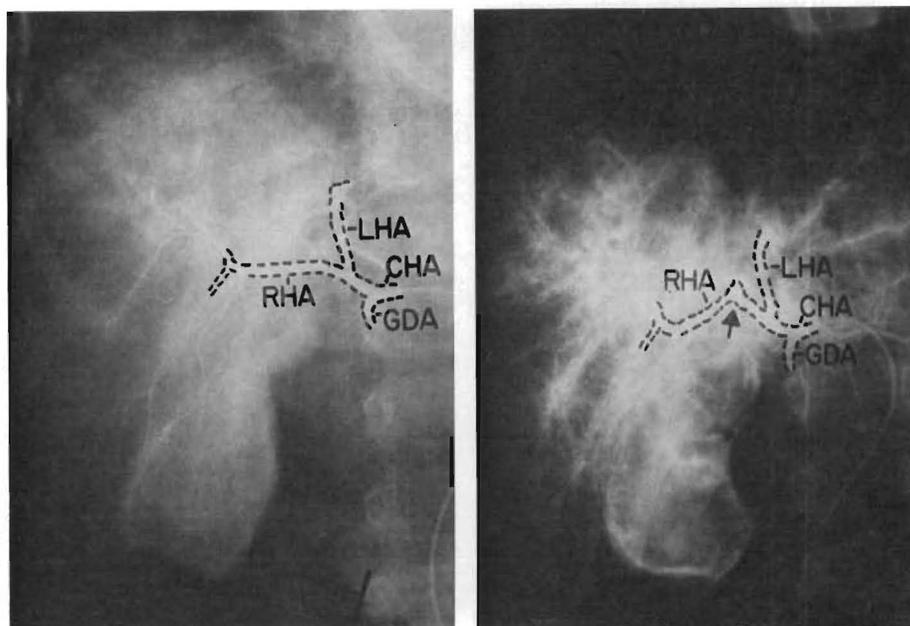


FIG. 11—Angiographic studies performed in a 5-year-old child immediately after her death from a head injury. Dye was injected into the common hepatic artery (CHA) proximal to the gastroduodenal artery (GDA).

(*Left*) Initial injection. Note the smooth course of the right hepatic artery (RHA).

(*Right*) The restraining ligaments of the liver have been incised, a cholecystoduodenostomy performed, and the head of the x-ray table elevated to 60°. The right lobe of the liver has rotated down and medially. The course of the left hepatic artery (LHA) is undisturbed. However, the right hepatic artery (RHA) is now severely kinked where it passes beneath the common duct. (By permission of *Ann. Surg.* 168: 392, 1968.)

12 hours later of acute hepatic insufficiency. It was recognized in the second patient and the hepatic artery was detached (Fig. 13B) and anastomosed to the vessel that originated from the superior mesenteric artery. The portal vein thrombosed a day later with death following in a few hours.

The other 11 patients all survived for at least 35 days and will be considered as a group later in the chapter, since valuable postoperative observations were made in each case. In these patients it was possible to assess the effectiveness of immunosuppressive therapy and to study the process of liver homograft rejection for the first time in humans.

### Rejection in Unmodified Recipients

With renal homotransplantation, the first clinical trials were in patients who were not altered by therapy inasmuch as techniques of immunosuppression were not then available. There will never be an occasion with liver homografts to obtain exactly analogous information. Instead, reliance must be placed on extrapolation to man of the events of hepatic rejection in unmodified animal recipients. All the studies of this kind have been carried out in dogs and pigs.

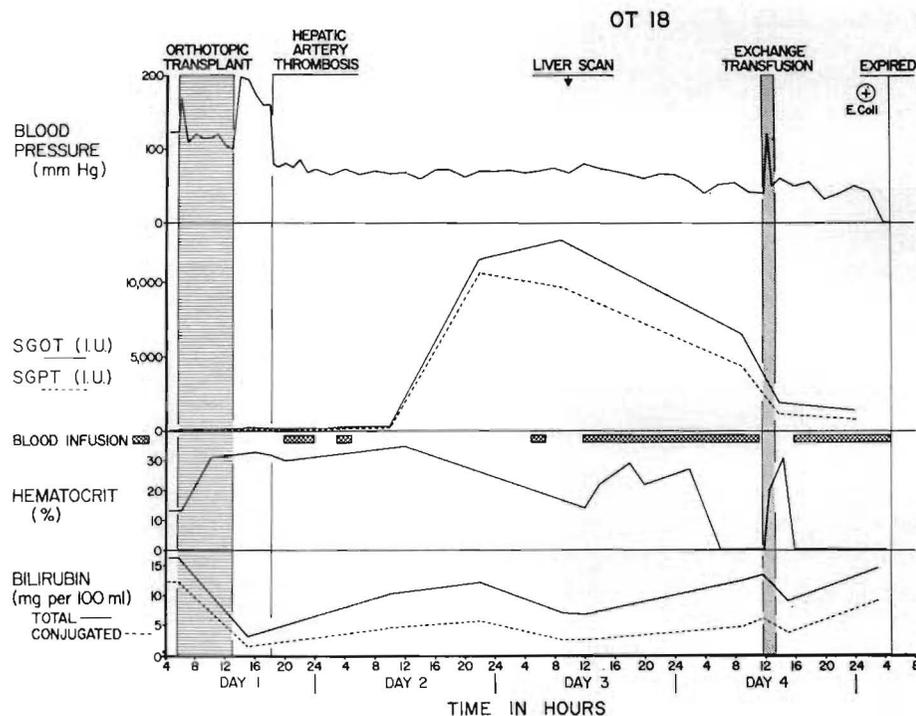


FIG. 12—Course of a patient whose reconstructed hepatic artery thrombosed a few hours postoperatively. The recipient was a 12-month-old, 5.7 Kg. child with extrahepatic biliary atresia. The donor was 21 months old and weighed 10.5 Kg. Following transplantation, she was returned to the intensive care unit awake and with a blood pressure of 150 mm. Hg. Five hours later the blood pressure suddenly fell to 80 mm. Hg. and she became somnolent. Thrombosis of the hepatic artery was suspected but the serum transaminases remained only slightly elevated for the next 24 hours; the SGOT and SGPT then rose abruptly. A liver scan performed at this time showed almost no isotope uptake by the liver. Hemolysis became so overwhelming that the hematocrit fell to zero during the last day of life; concomitantly, there was rapidly deepening jaundice. At autopsy, the hepatic artery was thrombosed, the portal vein was patent and the liver showed massive but incomplete necrosis. (By permission of Grune & Stratton, 1969.)

*Dogs.* If a technically perfect operation is performed, most canine recipients of orthotopic homografts recover promptly from anesthesia and are able to resume a diet within the next 24 hours. For the ensuing few days, they may be scarcely distinguishable for normal animals.

However, a well ordered and almost invariable sequence of events subsequently unfolds.<sup>61</sup> Within 4 or 5 days, manifold evidence of rejection becomes evident (Fig. 14). The dogs stop eating. The serum transaminase activities increase, usually to high levels, in rough temporal relation to parallel changes in that of alkaline phosphatase. Jaundice develops rapidly at the same time. The character of the jaundice is of interest; a variable, but substantial, fraction of the serum bilirubin is in the direct reacting form (Fig. 15). With the development of icterus, conjugated bilirubin appears in the urine, usually

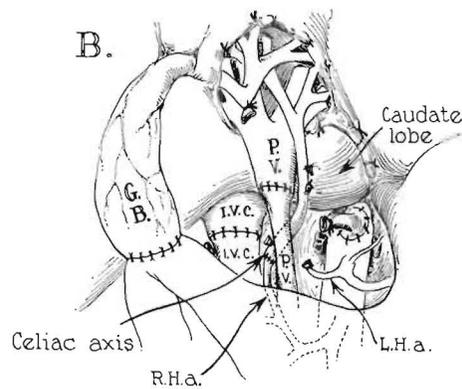
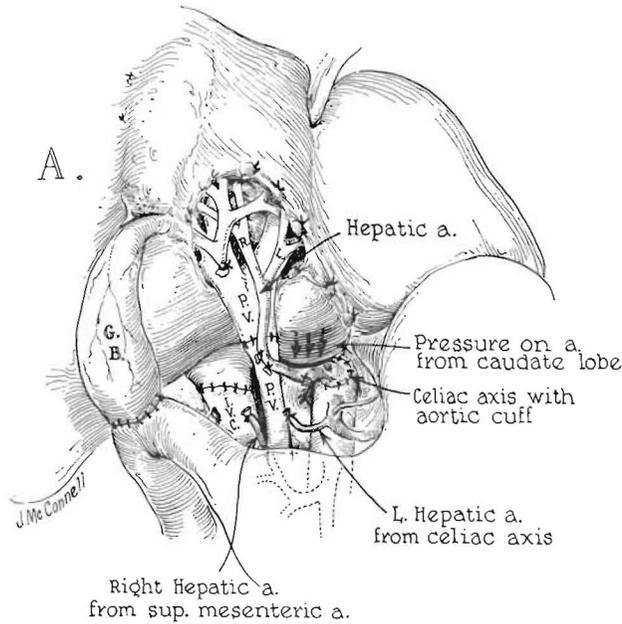


FIG. 13—Anomalous hepatic arterial supply encountered in 2 pediatric recipients of orthotopic homografts. In each, the larger right hepatic artery originated from the superior mesenteric artery, the small left branch from the celiac axis.

(A) Attempted arterial reconstruction. The homograft celiac axis was anastomosed directly to the recipient aorta. Note the compression of the homograft arterial supply by the caudate lobe of the oversized homograft. This was not detected in one case and resulted in death 12 hours later.

(B) In the second patient, it was recognized that the above reconstruction would not be satisfactory; the homograft celiac axis was then anastomosed to the anomalous vessel originating from the superior mesenteric artery. However, the child died of portal vein thrombosis to which the size disparity of the portal vessels probably contributed. (By permission of Grune & Stratton, 1969.)

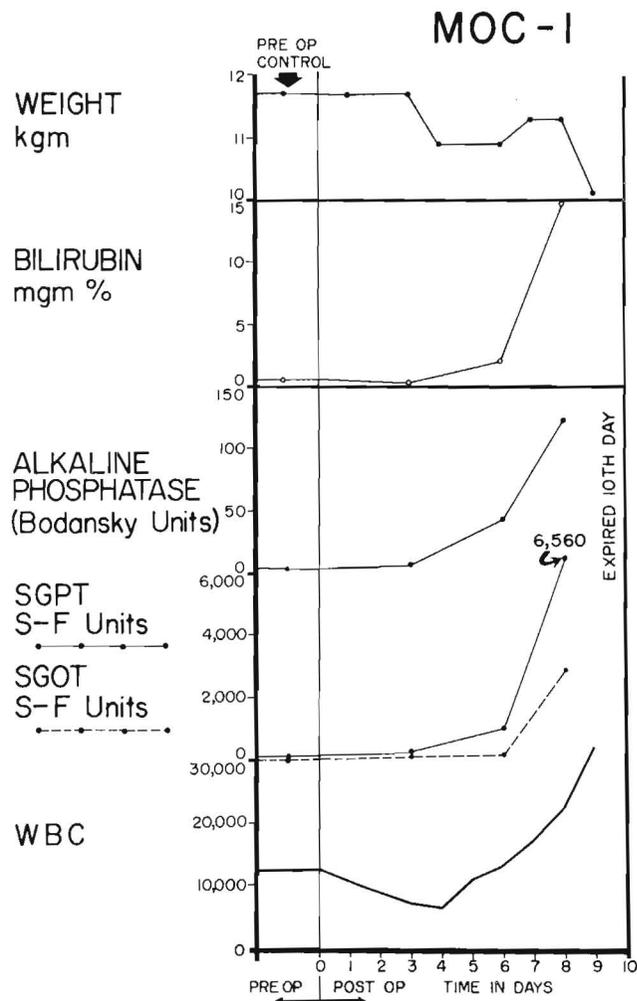


FIG. 14—The biochemical changes usually seen after orthotopic liver transplantation in the untreated canine recipient. A brief period of good function follows operation, but deterioration of the biochemical pattern is unrelenting once it has begun. (By permission of Year Book Medical Publishers, 1966.)

before the disappearance of urine urobilinogen. Finally, the stools become clay colored. Thus, the syndrome of rejection has features of parenchymal cell injury and necrosis, plus an element suggestive of biliary obstruction.

After the onset of jaundice, survival is uncommon for more than a few days despite the fact that complex hepatic functions of protein synthesis and carbohydrate metabolism may be retained surprisingly well<sup>27,28,61</sup> until just before death. In one of our control series,<sup>67</sup> 22 of 23 dogs who received livers from nonrelated mongrel donors survived for at least 2 days after operation and 19 (83 per cent) lived for at least 6 days. All the animals were dead by the tenth day. The mean survival was  $7.1 \pm 2.2$  SD days. The longest survival ever recorded in an untreated mongrel recipient was 31 days.<sup>28</sup>

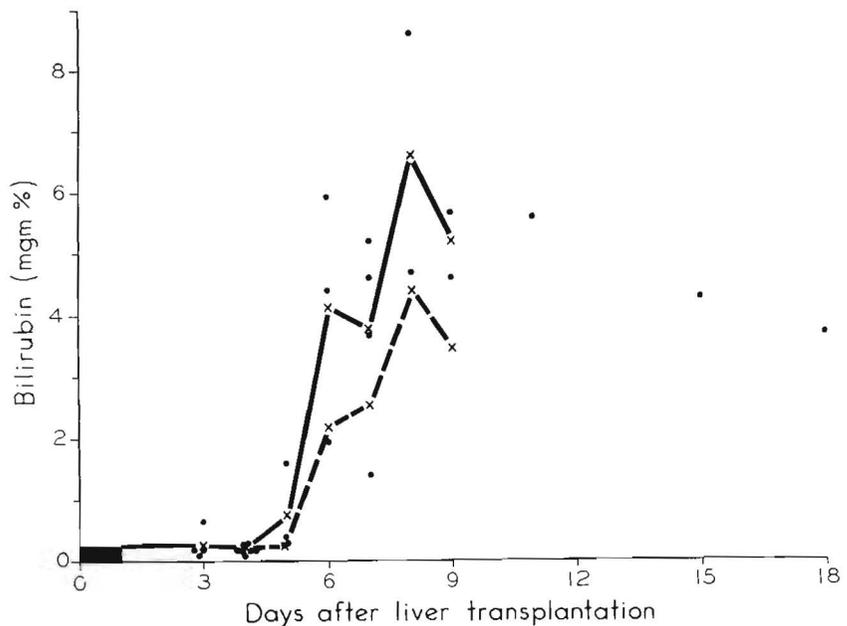


FIG. 15—Character and onset of jaundice in untreated orthotopically transplanted dogs. The dots represent total bilirubin determinations for individual animals; the solid line connects the mean for each day. The broken line represents the mean of the corresponding direct-reacting bilirubin determinations. Note the absence of chemical jaundice until the sixth day and its substantial conjugated component. (By permission of Surg. Gynec. Obstet. 112:135, 1961.)

The effect of rejection upon hepatic blood flow was studied by Groth.<sup>19</sup> At the same time that there was biochemical evidence of homograft deterioration, sharp and progressive reductions were recorded in both hepatic arterial and portal venous blood flows (Fig. 16). Groth's companion pathologic studies suggested that the immunologically mediated ischemia was due to damage to the sinusoidal bed and small veins of the homografts.

*Pigs.* The foregoing background in dogs was later supplemented by analogous studies in untreated pigs, first by Garnier, of Paris,<sup>12,17</sup> and later by Peacock and Terblanche et al.,<sup>46,47</sup> by Calne,<sup>8,9</sup> and in our own laboratories. In all these investigations, beginning with those of Garnier, the mild and indolent nature of the rejection was noted (Fig. 17). In Peacock's series, for example, one of the recipient pigs had survived without any immunosuppressive therapy for more than one year<sup>46</sup> and Terblanche<sup>73</sup> has informed us that the animal was ultimately sacrificed more than 2 years after operation. Both Jaffe<sup>22</sup> and Calne<sup>9</sup> and their associates provided evidence that the pig was capable of rejecting other kinds of homografts.

The explanations favored by Jaffe, Symes, and Terblanche<sup>22</sup> for the relative blandness of hepatic homograft rejection in pigs included the possibilities that the liver was not strongly immunogenic, that its large mass might have played a role by means of antigen overload, or that the organ was uniquely capable

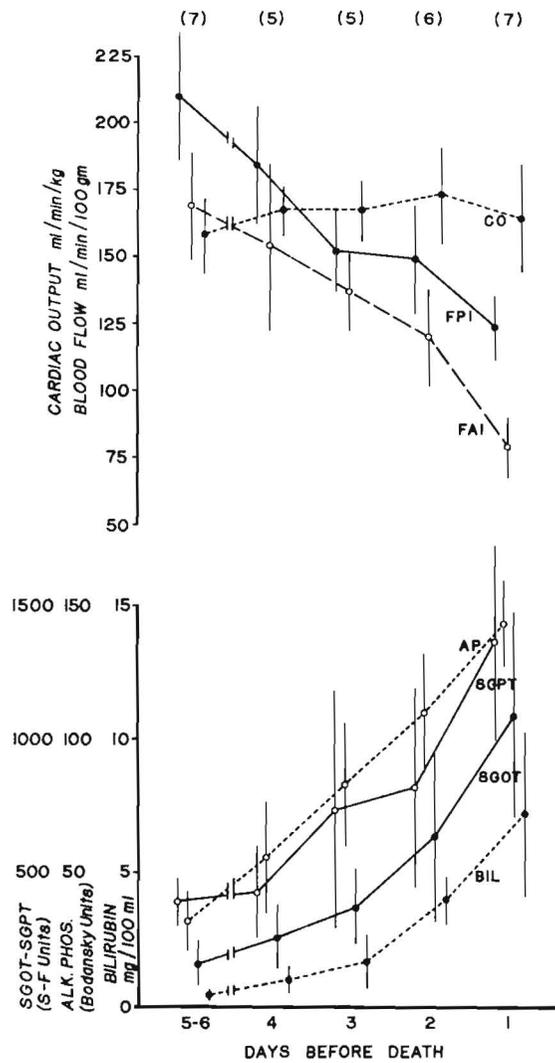


FIG. 16—Liver blood flow as determined by the xenon isotope ( $Xe^{133}$ ) washout technic. The flows obtained on portal venous (FPI) and hepatic arterial (FAI) injection, cardiac output (CO) and liver function tests were measured in 7 unmodified canine recipients. The mean values  $\pm$  SE are shown, as well as the number of observations (in parentheses) for each day. Note that both the hepatic arterial and portal blood flows decrease concomitant with deterioration of hepatic function. (By permission of Surgery 63:658, 1968.)

of withstanding the resulting host immunologic attack. Calne has proposed another hypotheses—that the liver homograft has an inherent immunosuppressive effect.<sup>8</sup> In support of this contention, he cited experience with combined liver and renal homografts. The porcine kidneys, which were rejected in the usual way when transplanted alone, now functioned for periods as long as several months.

While Calne's speculations are intriguing, the specificity of the last finding is open to some question, since it has been shown that other combinations of organs can lead to a less vigorous host reaction than that evoked by the constituent parts. The units tested have included multiple gastrointestinal viscera<sup>59</sup> and the kidney plus spleen.<sup>31</sup>

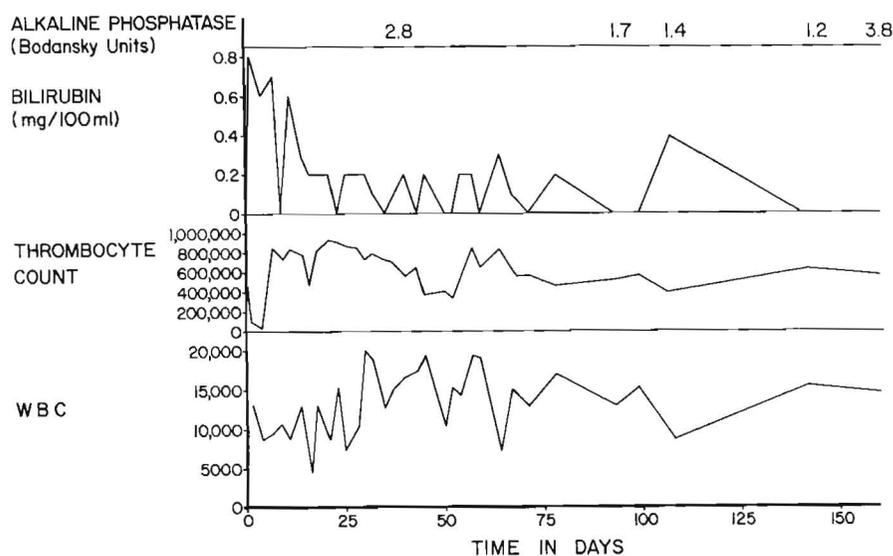


FIG. 17—Course of a pig which received an orthotopic hepatic homograft from a nonrelated donor. Although no immunosuppressive therapy was ever given, there has been neither clinical nor biochemical evidence of rejection at any time post-transplantation. The animal is still alive with normal liver function more than 8 months later. Note the sharp decline in the platelet count immediately after surgery; thrombocytopenia has also been seen in canine and human recipients of orthotopic homografts.

### The Effect of Immunosuppression

There have only been 2 agents, azathioprine and antilymphocyte serum (ALS) or its globulin derivative (ALG), which have been definitely proven to prolong survival in animals beyond that which can be achieved in nontreated controls. Azathioprine was first successfully used in early 1964. A series of 84 transplantations were performed between nonrelated mongrel dogs.<sup>67</sup> Forty-three and 23 recipients from the total of 84 lived for 25 and 50 days, respectively. Two of the animals are still in good health more than 4 years postoperatively (Fig. 18).

As the survival statistics imply, azathioprine therapy when used alone provided good and permanent control of homograft rejection only in the minority (about 20 per cent) of experiments. In another third, rejection was not even significantly mitigated. The remaining animals had prolongation of survival despite the development of liver function abnormalities; however, they usually died, eventually, of hepatic insufficiency (Fig. 19).

The same kind of spectrum was evident in the canine trials of heterologous ALS and ALG. A review of the experimental history of this kind of immunosuppressive therapy is beyond the scope of the present discussion. The substances are prepared by immunizing horses against the species to be eventually treated (Fig. 20). When the raw serum or a crude globulin extracted from it is injected by any of the common routes, a highly significant effect upon homo-



FIG. 18—Two recipients of orthotopic hepatic homografts from nonrelated canine donors. The dog on the right is now 4 years post-transplantation; the one on the left is 4½ years. Immunosuppressive therapy with azathioprine was stopped 4 months after operation in both. Neither animal has shown signs of rejection, subsequently, despite discontinuance of treatment.

graft rejection can be easily demonstrated. This can be achieved whether or not doses large enough to cause depression of the lymphocyte count are used.

In the first trials of ALS and ALG for canine liver transplantation<sup>21,62,66</sup> there were 18 experiments. Ten, 9, 7, and 6 of the recipients survived for at least 15, 20, 30, and 50 days; 4 of the animals are still living at 4 months and the longest survival was for more than a year (Fig. 21). Similar results were later reported by Pichlmayr and Mikaeloff<sup>39,49</sup> and by Birtch et al.<sup>3</sup>

In the foregoing studies, with both azathioprine and antilymphocyte globulin, the consistency with which really long-term survival was obtained was unacceptable in terms of potential clinical application. There were at least two obvious reasons. First, complete control of rejection was usually not achieved. Second, it was difficult to prevent or treat infectious disease complications in a standard kennel environment. Whatever the explanation, it is probable

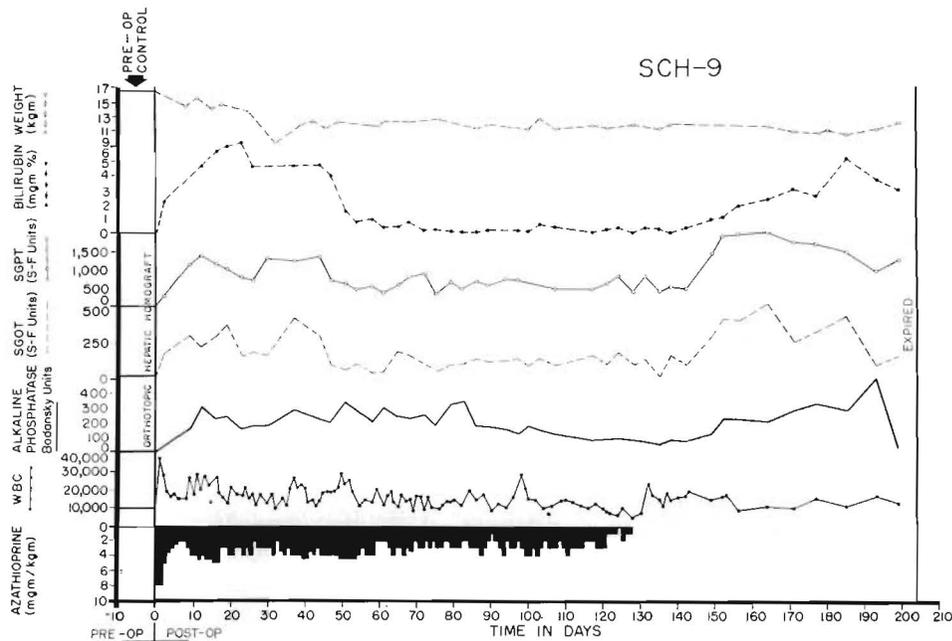


FIG. 19—Course of a dog showing incomplete reversal of a rejection episode following orthotopic liver transplantation. Note the severe jaundice which subsequently disappeared. Immunosuppression was with azathioprine; the animal also received  $S^{35}$ -methionine, L-methionine and choline. No alterations in immunosuppression were made at the time of rejection. Azathioprine therapy was stopped 127 days after operation. Slow deterioration of hepatic function then developed and the dog died 203 days post-transplantation. The immediate cause of death was perforation and bleeding of a peptic ulcer at the esophago-gastric junction. (By permission of Surgery 58:131, 1965.)

that the animal data would have indefinitely discouraged a clinical trial if it were not for the example of renal transplantation.

With the latter procedure, it had been possible to develop, in patients, moderately reliable regimens of immunosuppression using combinations of agents. Initially, extensive experience was gained with the joint administration of azathioprine and prednisone. It was with these 2 drugs that most of the first recipients of liver homografts were treated. As mentioned earlier, these patients not only obtained poor function from their badly preserved hepatic homografts but also had overwhelming postoperative infections.

Beginning in June 1966, horse ALG was added as an adjuvant agent to azathioprine and prednisone with the plan of restricting its use to the first 4 postoperative months. The best information about the benefit of this change has come from cases of renal homotransplantation.<sup>55,58,66,70</sup> With the advent of ALG therapy, it was found that mortality, after renal transplantation, was reduced in comparison to our past experience, that the homograft function was more consistently maintained, and that these results were possible with reduced doses of both azathioprine and prednisone. While there were a num-

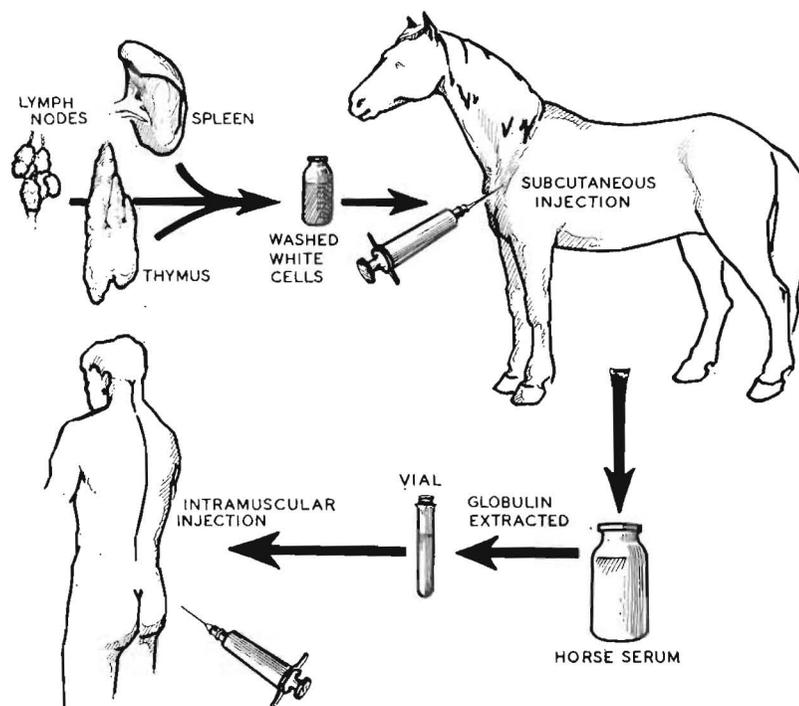


FIG. 20—Schematic representation of the preparation of antilymphocyte globulin (ALG). Horses are injected with lymphoid tissue of the species to be treated; the most convenient source of lymphocytes is the cadaver spleen. After repeated immunizations, the horses are bled and the serum separated. Undesirable anti-red cell, anti-plasma protein, and anti-thrombocyte antibodies are removed by appropriate absorptions. The desired globulin fraction may be extracted by several methods. At present, precipitation with ammonium sulphate is the most practical and reliable technic. Antilymphocyte serum has also been raised in other species, including the rabbit, goat and cow. (By permission of W. B. Saunders, 1968.)

ber of toxic side reactions including anaphylaxis with the administration of the foreign protein,<sup>23</sup> we have not had an ALG related mortality in more than 100 cases.

As a consequence of the encouraging experiences with the kidney, all recent recipients of liver homografts have had treatment, not only with azathioprine and predisone, but also with horse or rabbit ALG. A typical protocol is shown in Fig. 22.

*Acute rejection in modified human recipients.* There have been 11 patients in our experience in which the value of the triple agent immunosuppressive therapy could be assessed. During the early postoperative period, overt rejection was prevented in only a single case. In all the others, some degree of liver function abnormality, including jaundice, developed within the first few weeks (Fig. 23).

However, the process was a relatively self-limited one and in each instance partially or completely reversed without intensification of treatment. The way

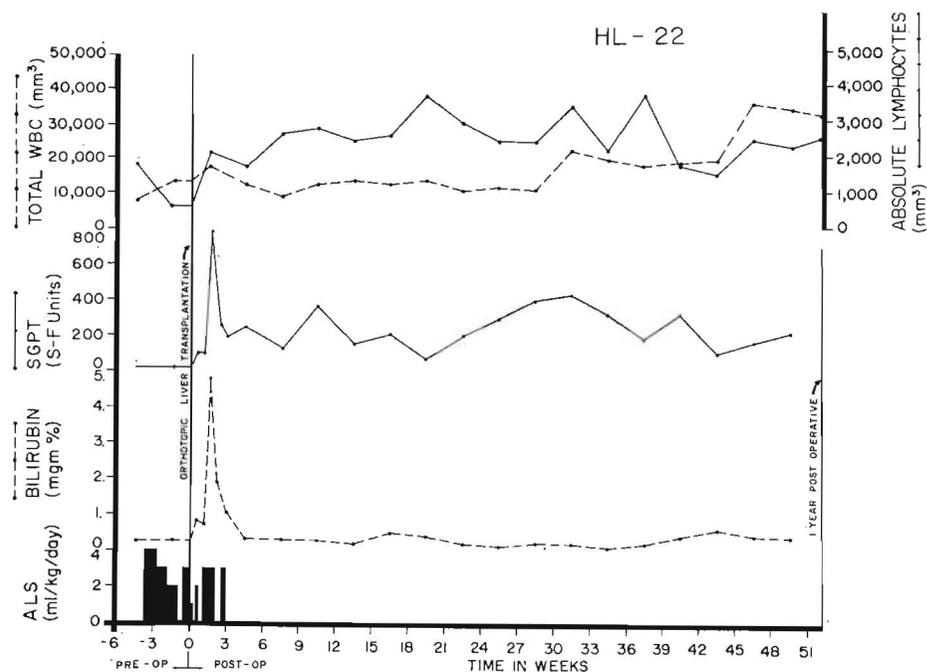


FIG. 21—The first postoperative year of a dog which was treated with intraperitoneal antilymphocyte serum (ALS) for 26 days before and 20 days after orthotopic liver transplantation. No other immunosuppression was given. Note the profound lymphocytosis late in the postoperative period. The animal finally developed ascites and died of chronic liver failure 490 days after operation. (By permission of Butterworths, London 1967.)

in which rejection presented appeared to have a bearing on the ultimate prognosis.

When this developed explosively (Fig. 23) there was suddenly developing icterus, associated with very high rises in the serum activities of transaminases and alkaline phosphatase. In such cases, the biochemical changes then receded almost as abruptly with little or no residual impairment.

In contrast, the much more indolent rejection seen early in several cases has presented a more difficult problem. In these patients, icterus developed insidiously, usually without the severe and disquieting enzyme changes. However, reversal did not follow quickly and, in fact, in neither of the 2 recipients in whom this syndrome was observed did the bilirubin ever completely return to normal. Furthermore, as will be mentioned below, hyperbilirubinemia became even more severe later when the heterologous ALG was stopped.

Five of the 11 patients are still alive 2½, 5, 6, 7, and 8½ months after operation. One of the other patients died of pneumonitis 35 days postoperatively at a time when she had normal liver function. The causes of failure in the other 5 cases will be returned to below.

*Late rejection in patients.* The above observations have made it clear that lethal homograft rejection can be consistently prevented and that less severe

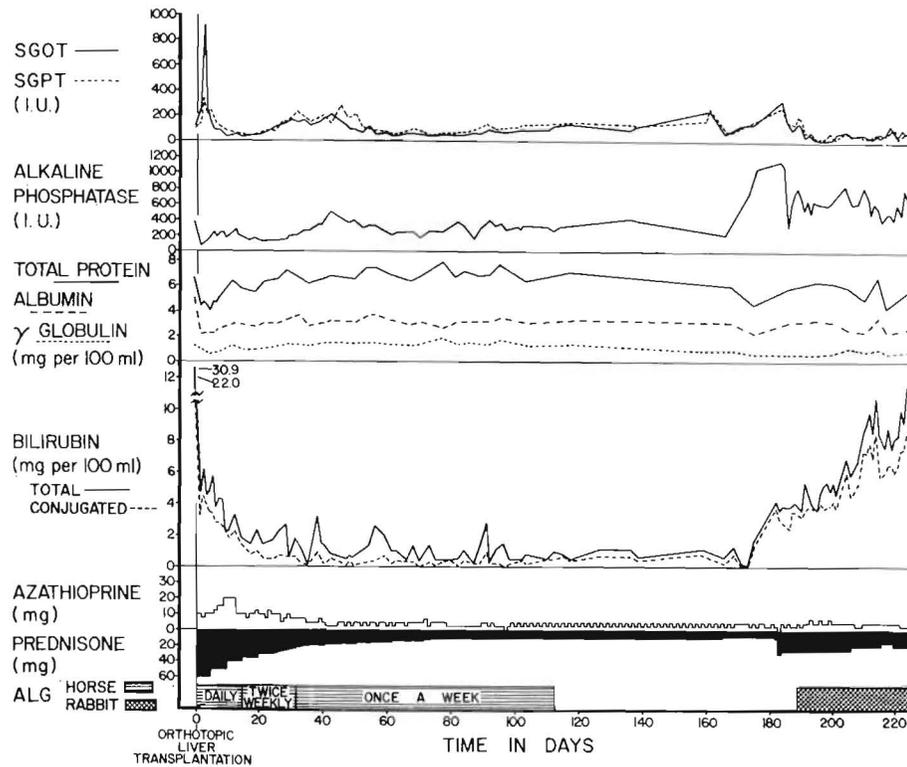


FIG. 22.—Postoperative course of a 2-year-old child with biliary atresia. Azathioprine and prednisone were given on the day of orthotopic transplantation and continued thereafter in variable doses. Horse antilymphocyte globulin (ALG) was given daily for 2 weeks. The dosage schedule was then attenuated and finally terminated after 16 weeks. Nine weeks later jaundice reappeared accompanied by increases in the serum transaminases and alkaline phosphatase, and depression of the serum protein. Increasing the prednisone doses failed to control the rejection. Institution of a course of rabbit ALG resulted in a partial reversal of the enzyme and protein abnormalities; the serum bilirubin has remained elevated, however. (By permission of Grune & Stratton, 1969.)

forms are, at least partially, reversible in the early postoperative period. The picture has been less encouraging in terms of the chronic function of the transplants. As described earlier, the treatment protocol involved immediate triple drug therapy but with discontinuance of ALG after an arbitrary period, which was selected as 4 months; in some of the cases the duration of globulin administration was made shorter than this because of serologic or clinical evidence of sensitization to the horse protein.

In 6 of the 11 patients who lived for 35 days or more, ALG was stopped. In 5 of the cases, jaundice recurred within 1–8 weeks, necessitating drastic revisions in therapy. An example is shown in Figure 22. The recipient, a 2-year-old child with biliary atresia, had no overt rejection for the first 6 postoperative months, but then became jaundiced within a few weeks of cessation of globulin therapy. The late rejection was treated with increased prednisone

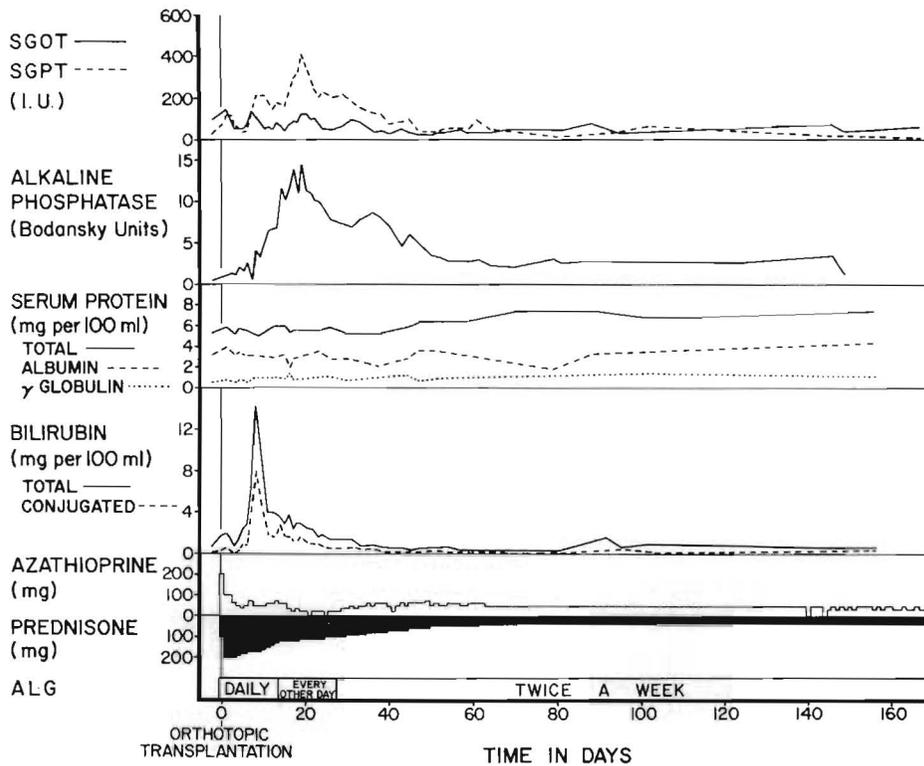


FIG. 23—The course of a 42-year-old man whose indication for orthotopic transplantation was hepatoma. Rejection was diagnosed after one week but rapidly and completely resolved without intensification of therapy. ALG therapy has never been discontinued. Late rejection has not been seen in this patient nor in another patient who also is still receiving ALG.

doses and rabbit ALG which was used because a potentially sensitizing course of horse ALG had already been given. The abnormalities in serum enzymes, which had accompanied the delayed rejection crises, were promptly restored toward normal but the icterus has remained the same for many weeks.

It has now become evident that many, if not most, recipients of liver homografts are dependent on ALG treatment for continuing good function of their transplants. We have had only 2 recipients among the 11 under discussion who have not had one or more bouts of late rejection. In both, treatment with horse ALG has never been discontinued (Fig. 23). There seems to be no reason in future cases to restrict the interval of globulin therapy to any rigid segment of time. Rather, it will probably be advisable to continue injections until they can no longer be tolerated.

Unfortunately, the time it takes to become dangerously sensitized to the foreign protein is highly variable and in some cases it may be rather short. Among the recipients of kidney homografts, more than a third have had to have ALG discontinued before the end of 4 months. In an occasional patient, treatment had to be stopped within less than 4 weeks, either because of intense

local reactions of the injectate or because of the occurrence of anaphylactic reactions. Consequently, other alternative schedules of ALG administration are badly needed. In a recent publication the first experience was cited with a "blitzkrieg" approach<sup>35</sup> in which an attempt was made to induce an early and prolonged tolerance of the kind that has been described in rodents.<sup>36,40</sup>

An alternative solution might be to switch to another species as a source for the heterologous serum in the event of sensitization. In our laboratories, ALS is currently being raised in 4 different species in order to provide a wider choice. Although horse globulin has been used routinely, rabbit ALG has been given to 2 of our liver recipients as a second line measure (Fig. 22 and 25).

It is still too early to speculate on the ultimate seriousness of late rejection. Surprisingly, there has been, usually, little immediate clinical deterioration. One reason probably is that most hepatic functions have not been seriously deranged. The usual syndrome is quite indistinguishable from that of chronic extrahepatic biliary obstruction: an elevated serum bilirubin containing a large direct reacting fraction with a parallel increase in alkaline phosphatase activity. The serum transaminase activities, liver based clotting factors, and serum proteins have remained nearly normal (Fig. 22). In one patient, the findings were so suggestive of duct obstruction that re-exploration was carried out 3½ months after transplantation. Operative cholangiography revealed a patent anastomosis and a well-preserved intrahepatic duct system (Fig. 24). The most prominent feature of the biopsy of the homograft at that time was intrahepatic cholestasis. A moderate infiltration of small lymphocytes was noted around the small bile ducts; this possibly represented a degree of chronic cholangitis. No appreciable vascular lesions were seen and there was no centrilobular cellular infiltration. Thus, there was little histologic evidence of rejection.

So far, none of the 11 patients who have lived for at least one postoperative month has died as a consequence of late homograft rejection. Four of the 5 delayed deaths were due to occlusion of the right hepatic artery, to be mentioned later. The fifth patient died of pneumonitis after 35 days and the sixth patient succumbed to carcinomatosis 400 days after transplantation.

### Retransplantation

The orthotopic transplantation of either of the unpaired vital organs, the liver and the heart, presents a special kind of problem. In both instances, immediate life-sustaining function of the transplant must be obtained, which cannot, thereafter, be permitted to completely cease, even for brief periods. The clinical setting is, thus, different from that encountered with the kidney. Complete failure of a renal homograft does not cause sudden death. Moreover, the availability of dialysis technics permits removal of a rejected organ and maintenance of the patient in relatively good health for as long as necessary before a new kidney can be found. This ordered chain of events cannot be followed with either the liver or the heart for obvious reasons. Nevertheless, one patient in our institutions has recovered satisfactorily from 2 consecutive orthotopic liver transplantations.

The recipient was 23 months old at the time of his first operation for biliary atresia. He received the liver of a 3½-year-old donor with whom he had an

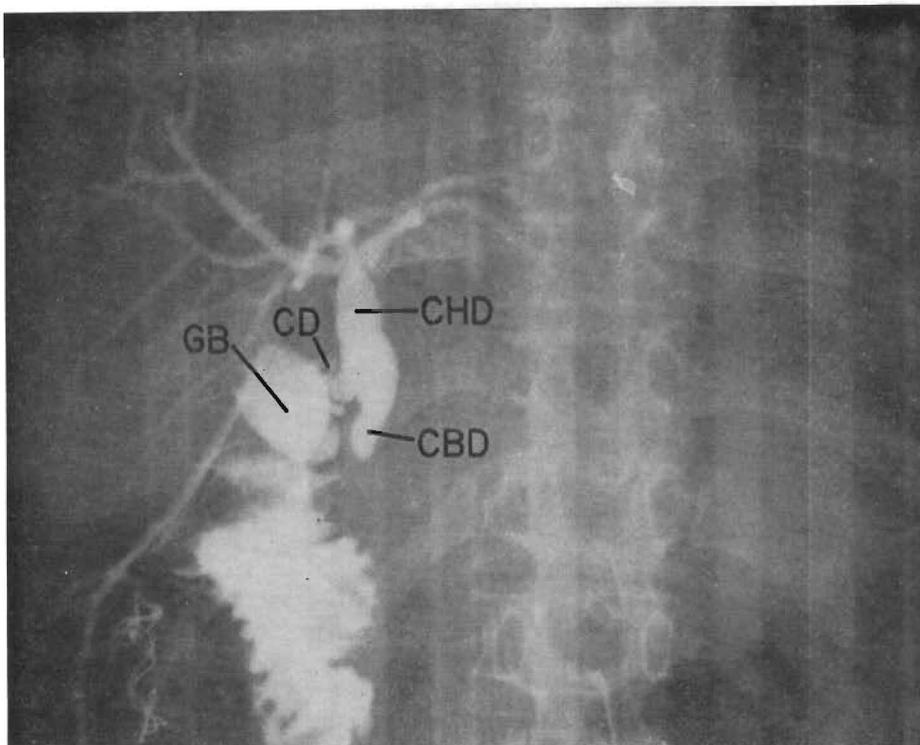


FIG. 24—Operative cholangiogram 3½ months post-transplantation. The duodenum was opened and a catheter inserted through the cholecystoduodenostomy into the gallbladder. X-rays taken after injection of contrast medium revealed a patent anastomosis and a well preserved intrahepatic duct system. The patient is now an outpatient, 7 months post-transplantation. Her bilirubin is 7 mg. per cent. The original diagnosis was hepatoma, from which she has no demonstrable metastases. GB=gallbladder; CD=cystic duct; CHD=common hepatic duct; CBD=common bile duct (ligated).

almost perfect histocompatibility match. Unfortunately, it became necessary to stop horse ALG 17 days later because of intense local reactions at the injection sites. Rejection appeared almost immediately and could not be reversed (Fig. 25). The child became febrile, had a persistent tachycardia, developed anasarca and appeared to be moribund.

Nine weeks after the first transplantation, the rejecting homograft was removed and replaced with the liver of a 7-year-old donor; the histocompatibility match was much less favorable than originally. Life-sustaining function has now been maintained for more than 2½ months. However, the slowly developing and incompletely reversible kind of indolent rejection mentioned earlier has occurred (Fig. 25); the child remains in good condition, nevertheless. Rabbit ALG was used during the second post-transplantation period.

The technical difficulties of removing the enormously enlarged (880 Gr.) homograft were not as great as had been feared. Upon opening the abdomen, the liver surface was mottled and generally discolored (Fig. 26). A plane was

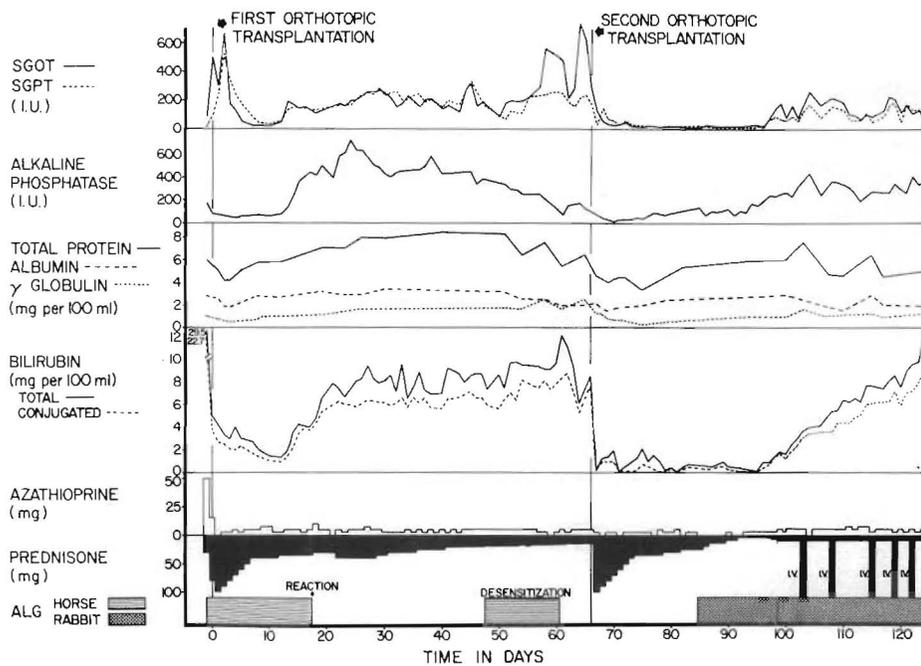


FIG. 25—An example of orthotopic retransplantation of the liver. Uncontrolled rejection of the first homograft occurred shortly after horse ALG had been stopped because of severe reactions at the injection sites. Desensitization to horse protein was attempted. The patient became febrile and developed anasarca. Following retransplantation 9 weeks after the first operation, the enzyme abnormalities promptly reversed and the icterus cleared, only to reappear a month later despite treatment with rabbit ALG.

developed inside the thin fibrous tissue which formed a pseudocapsule around the organ. The recipient vessels were identified and their full previous lengths retained.

The blood supply to the extirpated organ was completely intact, although several small thrombi could be identified grossly in the peripheral radicles of the intrahepatic portal tracts. Histologically, there was dense infiltration of the homograft with mononuclear cells of which many were pyroninophilic. However, the most striking abnormality was thickening of the intima of small branches of hepatic artery leading to narrowing or obstruction of these small vessels (Fig. 27). The thickened intima consisted of many large cells with abundant cytoplasm containing fine droplets of fat. Increased fibrosis, intrahepatic cholestasis, and centrilobular necrosis were also present.

### Regional Hepatic Gangrene

In describing the technic of orthotopic liver transplantation, it was mentioned that right hepatic arterial thrombosis was proved in 4 of the first 4 infant patients who achieved extended survival; the same complication probably occurred in a fifth recipient who survived for more than a year. The etiology of the lobar arterial thrombosis appears to be a complex one, which

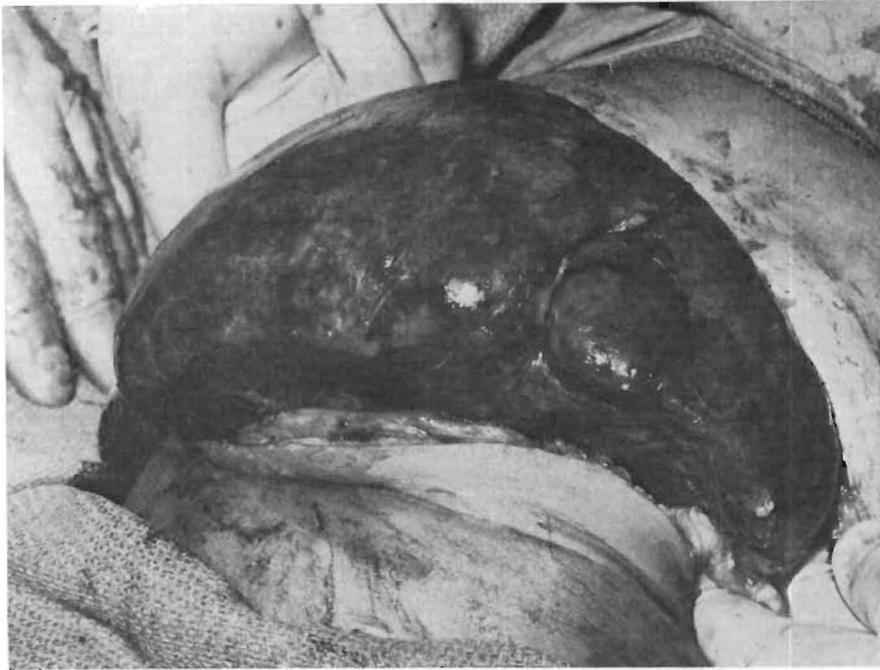


FIG. 26—A rejecting human homograft 9 weeks after orthotopic transplantation. The abdomen has just been opened in preparation for removal of the liver and retransplantation. All vascular anastomoses and the cholecystoduodenostomy were found to be patent. The surface of the enormously enlarged organ was mottled and discolored. After sectioning, many superficially located infarcts were seen. The homograft weighed 880 Gm.

has at least a partially mechanical genesis<sup>57</sup> added to an important element of uncontrolled rejection.

Whatever its cause, the events which follow constitute a special syndrome not seen after transplantation of other organs. The uniqueness of the complication is undoubtedly explained by the interposition of the liver between the intestine and the heart and by the fact that it is also connected to the intestine through the biliary tract anastomosis. The result has been massive bacterial invasion of the dearterialized liver tissue by intestinal microorganisms.

The course of one of these patients is shown in Fig. 28. After a benign early convalescence, the child suddenly became acutely febrile and developed gram negative septicemia. A liver scan showed a large filling defect in the right liver lobe. Debridement of the necrotic tissue was carried out in all 5 cases. In 2, death followed within a few hours or days; 2 other children survived only to die 4 and 6 months later, respectively, with chronic liver failure and widespread upper abdominal sepsis.

The fifth victim of this kind of vascular catastrophe survived for more than a year and finally died of metastases of the original hepatoma. A postmortem angiogram showed that the left hepatic branch also had become occluded, probably at a later time (Fig. 29). The only demonstrable arterial supply to

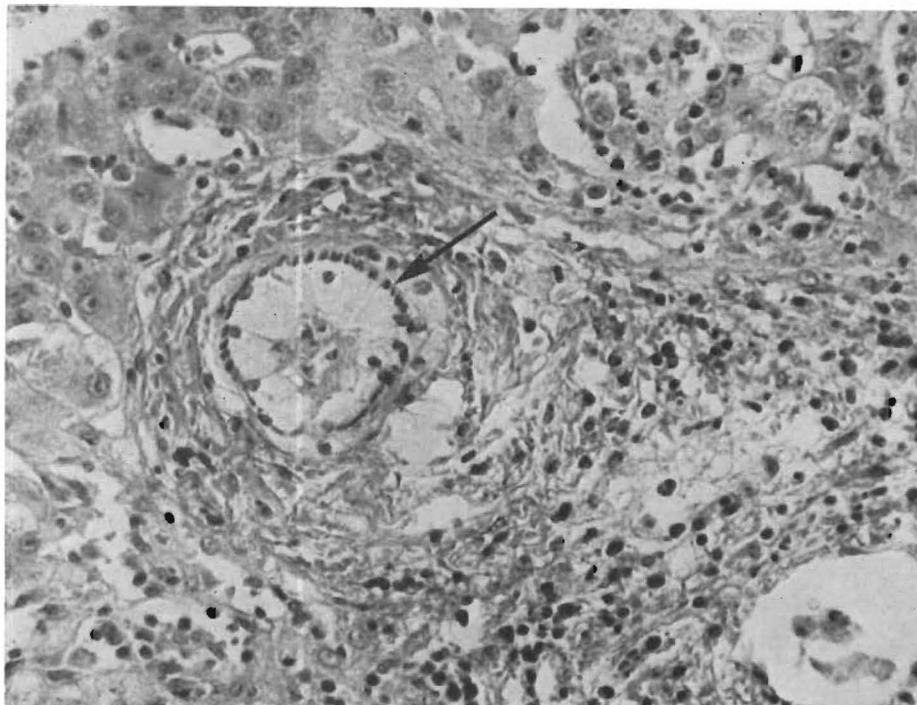


FIG. 27—Biopsy taken just before removal of the homograft shown in Fig. 26. A portal tract is shown. There are large numbers of infiltrating mononuclear cells. A branch of the hepatic artery can be seen to be greatly narrowed by large intimal cells with foamy cytoplasm. The internal elastic lamina of the vessel is marked with an arrow. Elastic stain ( $\times 300$ ). (The photomicrograph was supplied by Dr. K. A. Porter of London, England.)

the homograft was a twig from the right phrenic artery. It is of interest that a patient of Birtch and Moore also lived for many weeks after complete hepatic dearterialization, apparently with little disturbance of liver function.<sup>2</sup>

### Recurrence of Liver Malignancy

In 5 of the 7 attempts at orthotopic transplantation made at our institution before the summer of 1967, the indication for operation was primary hepatic malignancy. The early death of these patients made observations impossible about the effect of the procedure upon the natural history of this disease. The more recent experience is still too limited to permit a decisive conclusion about the question. However, the appearance of metastases in 2 of the 4 more recently treated patients is a discouraging notation. One of the recipients died of infection 35 days post-transplantation and did not have detectable residual tumor at autopsy. Another is alive without recurrent disease after 7 months. A third developed evidence of pulmonary metastases within a few months (Fig. 30) and the fourth died of widespread metastatic carcinomatosis (Fig. 31) 400 days after operation.

Thus, total hepatectomy certainly extends local resectability but does not

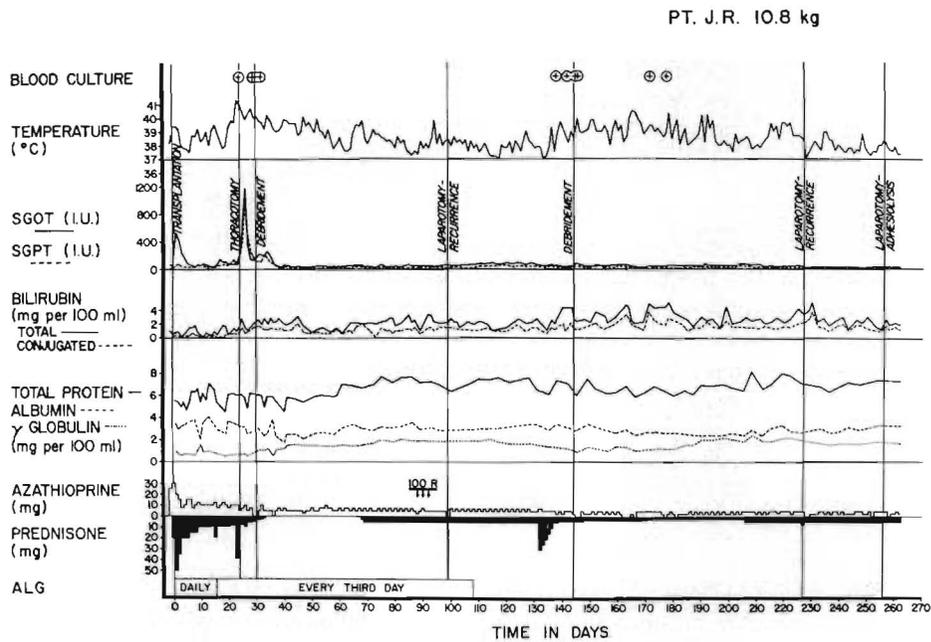


FIG. 28—The first 9 post-transplantation months of an 18-month-old child with hepatoma who survived 400 days after orthotopic transplantation. Note the high rises in the serum transaminases which occurred at the time of the initial liver infarction. The later septicemia developed when the patient became leukopenic during treatment with vincristine for tumor metastases. The thoracotomy was for removal of an unexpanded right upper lung lobe. The first 2 laparotomies were for excision of tumor recurrences. Liver function remained stable until several weeks before death. At autopsy the cholecystoduodenostomy was found to be compressed by tumor and the entire hepatic artery was occluded. (By permission *Ann. Surg.* 168:392, 1968.)

ensure against tumor spread. Indeed, there is reason to be fearful that the immunosuppressive therapy necessary to prevent rejection of the homograft may itself be a factor which could accelerate the dissemination of residual neoplasm. According to Burnet's hypothesis,<sup>7</sup> the consequent immunologic crippling should result in at least a partial loss of the normal surveillance mechanism by which mutant cells are identified as "non-self" and eliminated or, presumably, otherwise restricted in their growth potential. That this view may have some validity is attested by the ease with which carcinoma has been accidentally transplanted from renal donors dying of malignancy but whose kidneys were not grossly involved<sup>18, 35, 80</sup> and by Penn's report<sup>47</sup> of an increased incidence of malignant neoplasia arising de novo in recipients of renal homografts that had been obtained from normal donors. An observation even more relevant to the problem under discussion was recently made by Williams et al.<sup>79</sup> who performed renal homotransplantation in a child 6 months after excision of a Wilm's tumor. Sixteen months after transplantation, at a time when cure of this kind of neoplasm would usually have been assured under normal conditions, metastases became apparent, leading to death within a few weeks.

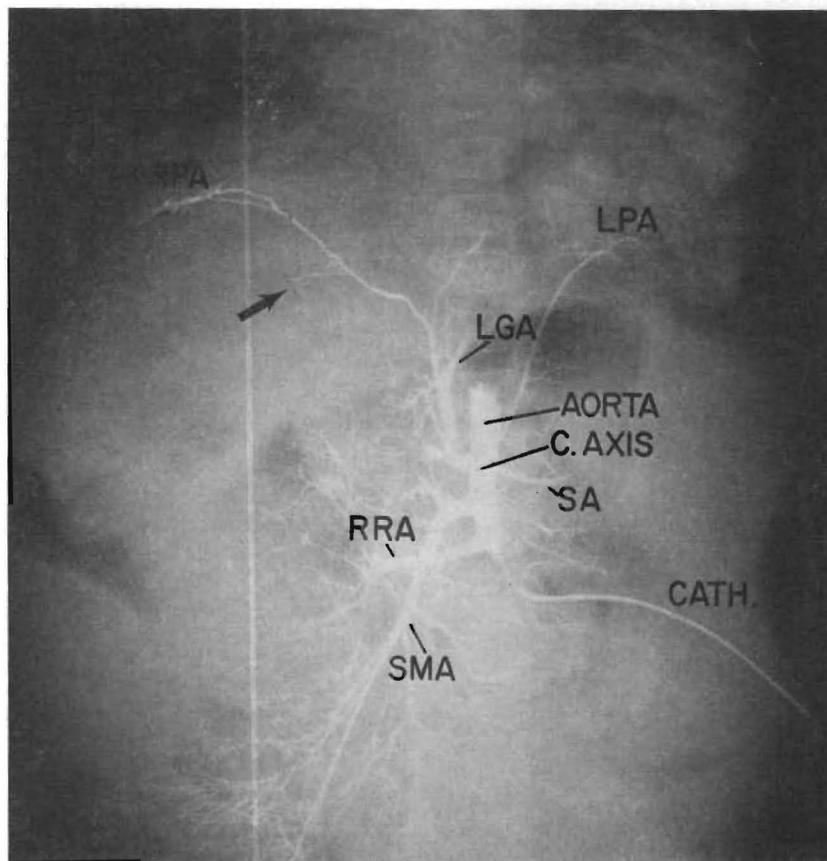


FIG. 29—Postmortem angiogram of a patient who lived 400 days after orthotopic transplantation for hepatoma. The common and proper hepatic arteries are occluded. A small branch (arrow) of the right phrenic artery (RPA) is the only demonstrable arterial supply to the homograft. Thrombosis of the right hepatic artery occurred about 3½ weeks after transplantation; the left probably closed some time later. The superior mesenteric artery (SMA) and the left gastric artery (LGA) are displaced by metastatic tumor. C. axis=celiac axis; LGA=left gastric artery; LPA=left phrenic artery; RPA=right phrenic artery; RRA=right renal artery; SA=splenic artery; SMA=superior mesenteric artery.

### AUXILIARY TRANSPLANTATION

It is highly probable that far more auxiliary than orthotopic transplantations have been attempted. All these efforts to provide a second liver have led to early death of the recipients; unfortunately, only a few such cases have been reported.<sup>1,20,38,50,64,65</sup>

The special appeal of this kind of compromise operation is that the residual function of the patient's own diseased liver is retained. Whether or not this is sufficient reason to select a method of therapy which has yielded inferior results in experimental animals is open to serious question. The longest survival ever reported in which the life-sustaining potential of an auxiliary canine graft was proved has only been 126 days.<sup>34</sup>

### Special Metabolic Considerations

As was mentioned earlier, the first experiments in whole organ liver homografts were carried out in dogs by Welch,<sup>78</sup> placing the extra organ in the right paravertebral gutter and revascularizing it from the lower abdominal vessels (Fig. 32). The organs elaborated bile for a few days and were then rejected, as would be expected in unmodified recipients.

When the same technics were used ten years later in immunosuppressed recipients a curious and disquieting observation was made. Auxiliary livers, inserted by a modification of Welch's technic, underwent rapid shrinkage which was usually evident within 2 weeks and which was very advanced after one month (Fig. 33). The loss in size was due primarily to dissolution of hepatocytes.

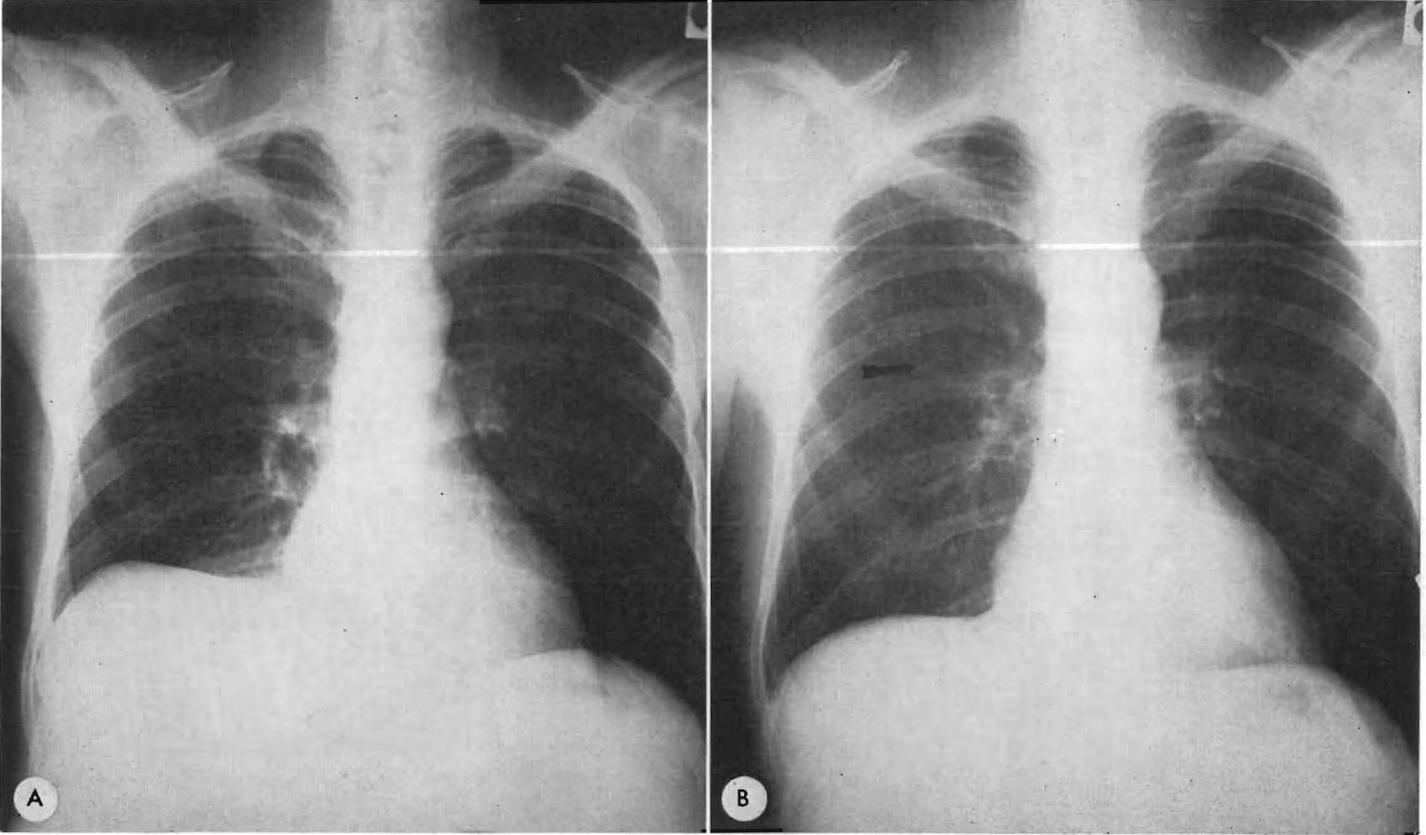
The explanation for this finding was worked out in principle by Marchioro<sup>33,34</sup> and elaborated upon by a number of subsequent authors. Taken together, these studies have shown that there is a competition between coexisting livers which can be unbalanced in favor of one organ or the other in a variety of ways. For example, a distinct advantage is given to a liver if it receives a portal inflow from the splanchnic venous bed, especially if the other liver is deprived of this nutritional source. As would be expected, the competitive capability of the liver can be inhibited in other ways including ligation of the biliary drainage system or by reducing the total blood flow, as with an Eck fistula.

In clinical transplantation, it would be anticipated that the competition between the two organs would be heavily biased in favor of the homograft according to the extent of the disease present in the host liver. The competitive potential of the patient's organ would be expected to be very poor with end-stage cirrhosis, but might not be by any means so retarded with congenital biliary atresia, in which satisfactory parenchymal function is often retained for a surprisingly long time.

The quantitative privilege which must be extended to the homograft is probably variable from case to case, depending upon the magnitude of rejection which is encountered. This was particularly well demonstrated in the experiments of Halgrimson<sup>20</sup> and Daloze<sup>14</sup> who showed that if the host and homograft livers were given equivalent physiologic advantages, the recipient liver flourished, whereas the organ under immunologic attack promptly underwent atrophy. Thus, it would be predicted that both a close donor-recipient histocompatibility match and highly efficient immunosuppression would carry especially important therapeutic implications in the application of auxiliary transplantation.

### Clinical Auxiliary Transplantation

Our own experience is confined to 4 patients, 3 with Laennec's cirrhosis and the other with biliary atresia. In the case of biliary atresia, the recipient and donor were 16 and 7 months old, respectively. The homograft was placed in the left upper quadrant after performing splenectomy and revascularized as shown in Figure 34. There was not enough room in the abdomen for the



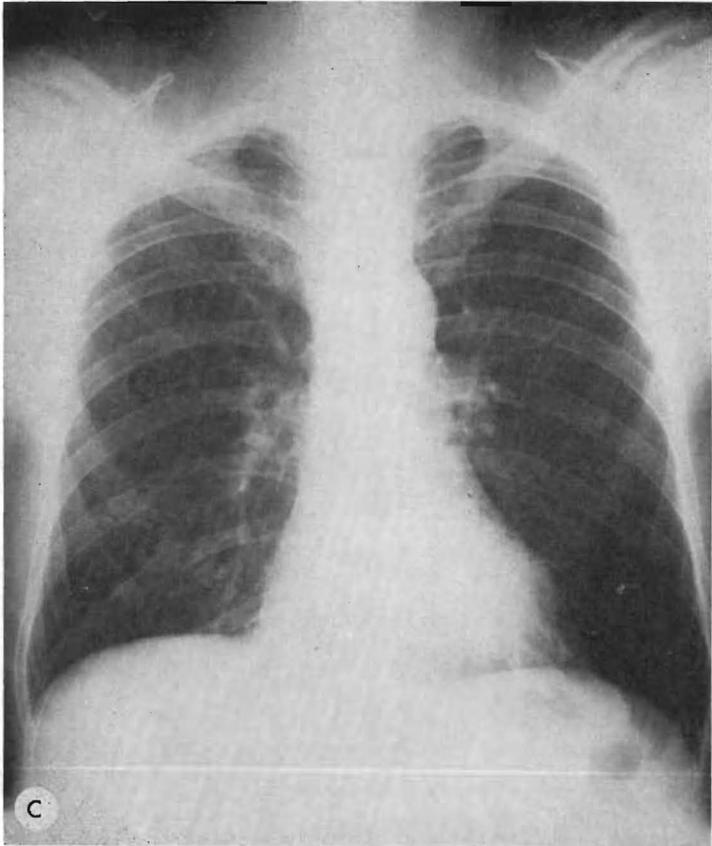


FIG. 30—Chest x-rays of a 42-year-old recipient whose indication for hepatic transplantation was hepatoma.

(A) One and a half weeks after transplantation. There was no evidence of pulmonary metastases.

(B) A suspicious lesion (arrow) was first detectable radiographically 80 days after operation.

(C) Two months after recurrent tumor was first suspected, other metastases became evident in both lungs. He is asymptomatic 6 months after transplantation.

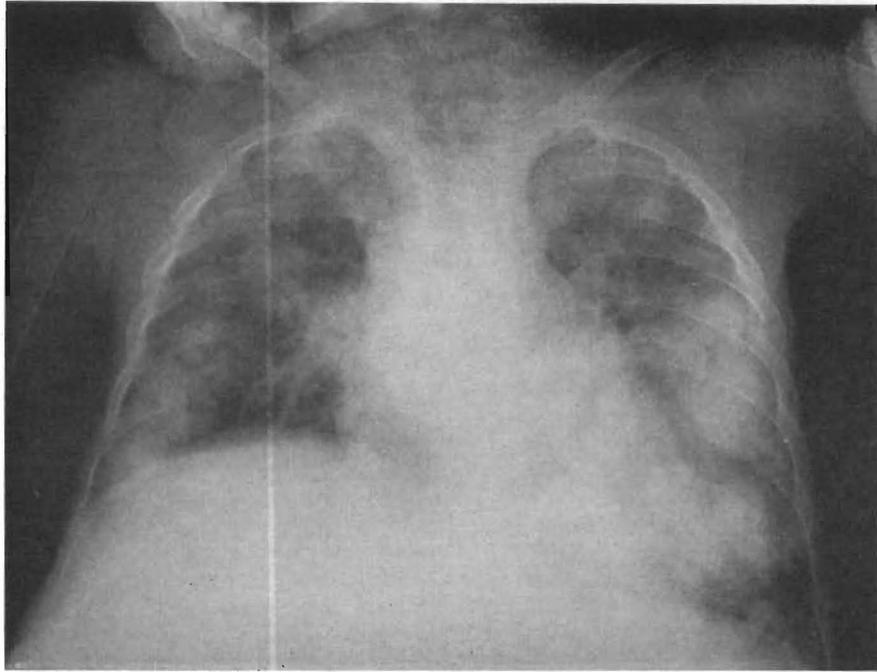


FIG. 31—Pulmonary metastases in an 18-month-old recipient one year after orthotopic liver transplantation for hepatoma. Evidence of spread was first noted 3 months after transplantation. The patient died 400 days postoperatively.

auxiliary organ. When the incision was reapproximated, the arterial supply was kinked off, leading to thrombosis. The organ was removed and the recipient died a few hours later.

Functioning homografts were obtained in the other 3 patients who were 50, 47 and 48 years old. The homografts in the first 2 recipients were taken from 79 and 12-year-old donors and revascularized in the right paravertebral gutter by modifications of the technic shown in Fig. 35. The recipients who had been jaundiced and in semicoma prior to operation were, temporarily, considerably improved (Fig. 36). However, rejection followed within a few days. Ultimately both patients developed leukopenia and died from widespread sepsis. It is unfortunate that heterologous ALG was not available at the time these patients were treated, since good initial homograft function was obtained in both, but could not be sustained for more than a few days, even with doses of immunosuppressive drugs which proved to be highly toxic.

More recently, a 48-year-old patient with cirrhosis was given the liver of a newborn 3.1 Kg. anencephalic. The tiny homograft was used to replace the spleen. The patient had hepatorenal syndrome before operation and required emergency dialysis before being taken to the operating room. His course after transplantation is summarized in Fig. 37. There was little or no evidence of new hepatic function, possibly because of the small size and immaturity of the organ. The recipient died 25 days later of hepatic and renal insufficiency and

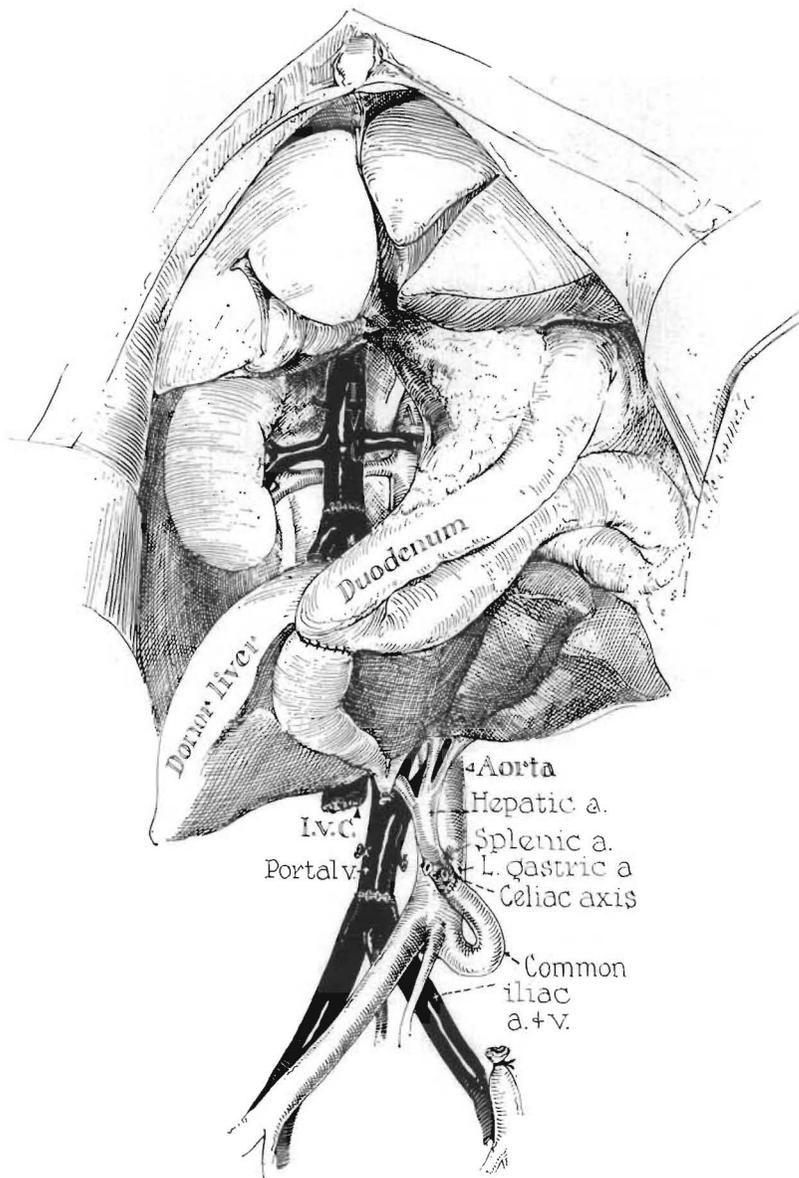


FIG. 32—Auxiliary liver homotransplantation in dogs, using a modification of Welch's method. The reconstituted portal blood supply is from the inferior vena cava; the hepatic artery is anastomosed to the iliac artery. Cholecystoduodenostomy is performed. (By permission of *Ann. Surg.* 160:411, 1964.)

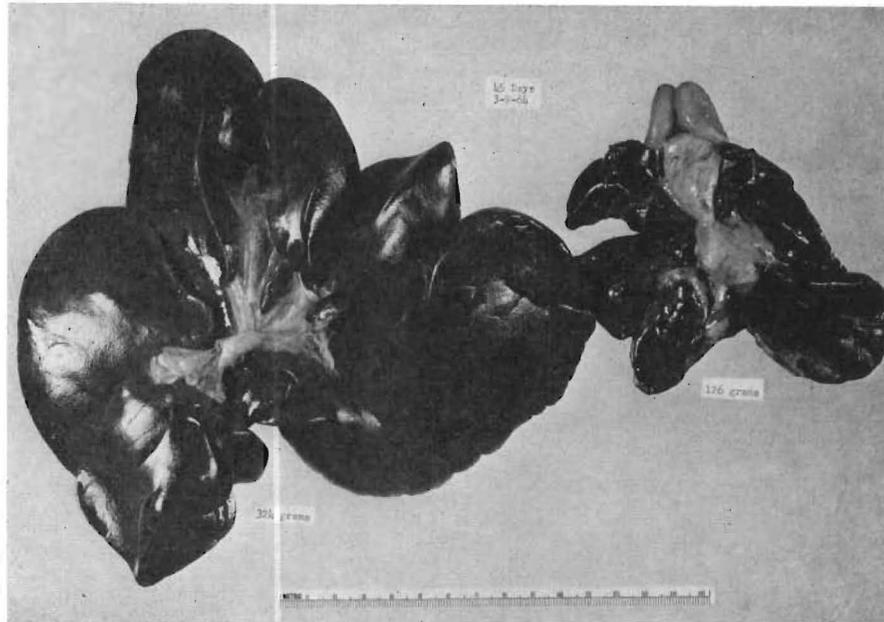


FIG. 33—The auxiliary homograft (right) and the canine recipient's own liver 45 days after auxiliary transplantation. The auxiliary liver was placed in the right paravertebral gutter using a modification of Welch's method, as shown in Fig. 32. Thus, only systemic venous blood passed to the transplant portal vein. Note the well preserved but dimensionally reduced general structure of the homograft. The gallbladder did not shrink proportionately. (By permission of *Ann. Surg.* 160:411, 1964.)

of pneumonitis. At autopsy all the reconstructed vascular channels entering and leaving the liver were patent.

It is of interest that, in the 3 adult cases, there was no evidence of atrophy in any of the 3 homografts that were in residence for 22, 25 and 34 days. Although the organs had some histologic evidence of congestion, there were few signs of active immunologic rejection. Similar findings were present in the patient of Absolon who lived almost 2 weeks. In the other reported cases of auxiliary liver transplantation, death occurred too soon to permit valuable histologic observations about rejection.<sup>1,38,50</sup>

### PRESENT STATUS

Although all the first attempts at orthotopic liver transplantation in humans resulted in early recipient death, the experience compiled since the summer of 1967 has established that this procedure can prolong life in patients dying of hepatic disease. To date, the longest survival has been a few days more than 13 months. Nevertheless, the operation has proved to be a hazardous one, not only because of technical difficulties in its performance, but also because of a number of complications that have been seen at a later time. The latter included regional hepatic gangrene due to thrombosis of a lobar arterial supply and late rejection after discontinuance of heterologous ALG therapy.

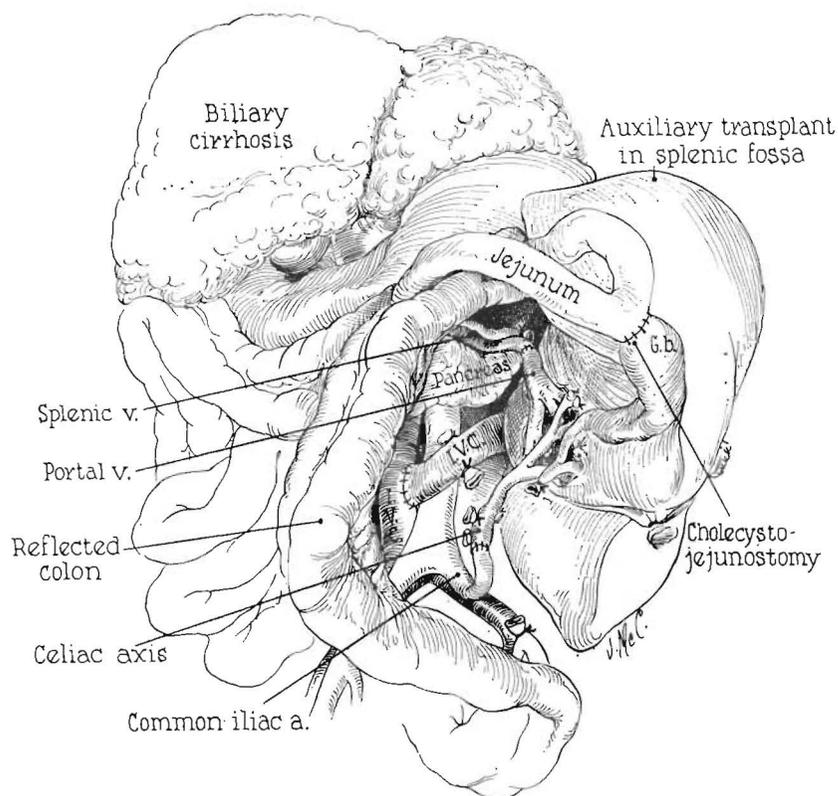


FIG. 34—Technic used for auxiliary transplantation in a 16-month-old female with biliary atresia. The donor was a 7-month-old child. The homograft portal vein and hepatic artery are anastomosed to the splenic vein and common iliac artery, respectively. Note the angulation near the origin of the left common iliac artery. Kinking of this segment at the time of closure of the abdomen resulted in thrombosis, which necessitated removal of the homograft. (By permission of Arch. Surg. (Chicago) 93:107, 1966.)

Results with auxiliary liver transplantation in animals have been inferior to those with the orthotopic operation, at least partly because the homograft must not only face immunologic rejection, but must also, apparently, compete for metabolic substrate with the host's own liver. Although the competition between the two livers would not be expected to be such a severe problem in patients dying with hepatic failure, survival in human recipients of auxiliary homografts has not yet exceeded 34 days.

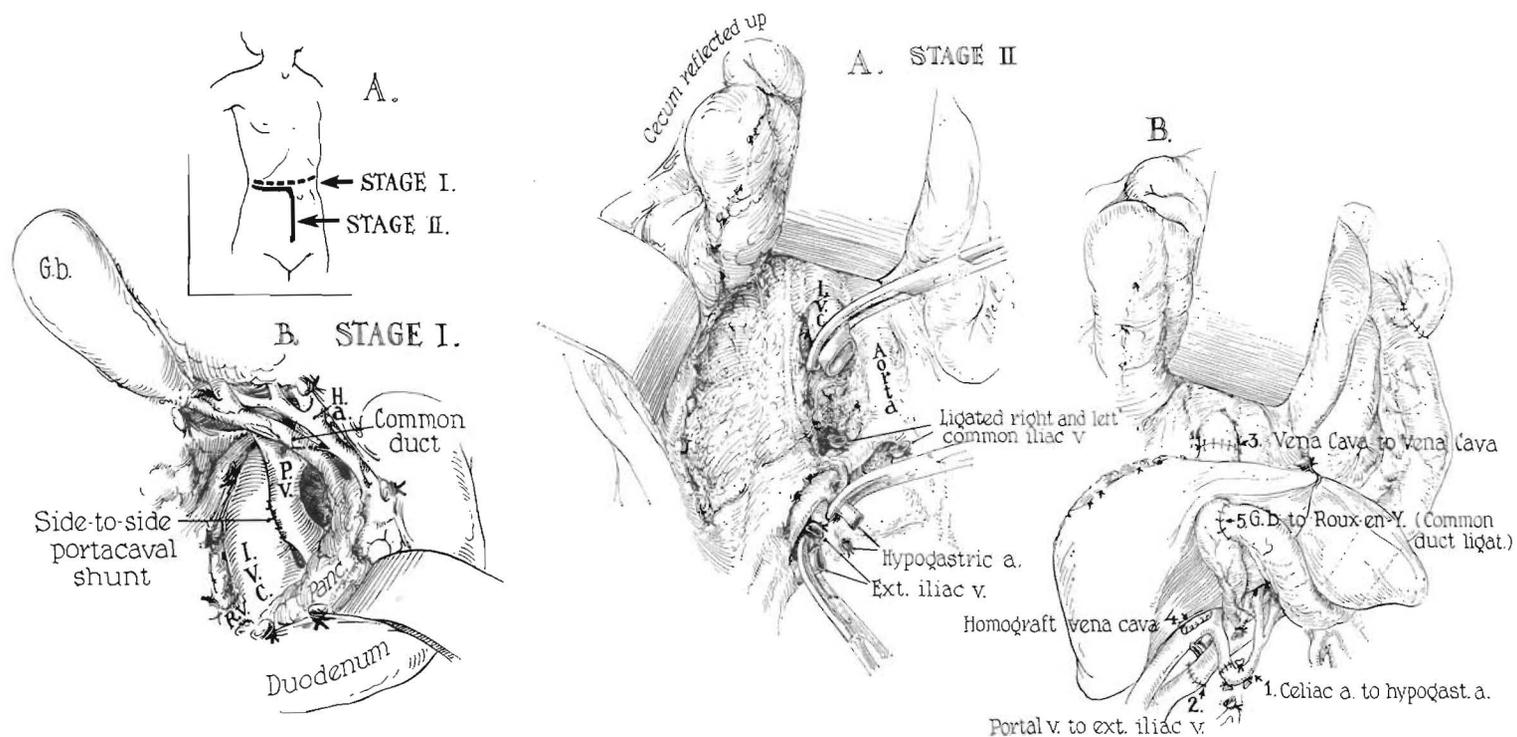


FIG. 35—Technic of auxiliary liver transplantation. Similar operations were used for 2 adults with alcoholic cirrhosis. *Stage I* (left)—A portacaval shunt was performed transabdominally for emergency control of variceal hemorrhage. *Stage II* (right)—One of several days later, transplantation was carried out utilizing part of the Stage I incision (inset). (A) Operative field before implantation of the homograft. (B) Completed transplanation. The celiac axis of the homograft is anastomosed to the hypogastric artery (as shown) or to the side of the terminal aorta. The portal venous inflow is from the external iliac vein; the homograft suprahepatic inferior vena cava is anastomosed to the transected recipient inferior vena cava. Alternately, the portal vein may be revascularized from the distal end of the transected vena cava. Roux-en-Y internal biliary drainage to the jejunum is used. (By permission of Arch. Surg. (Chicago) 93:107, 1966.)

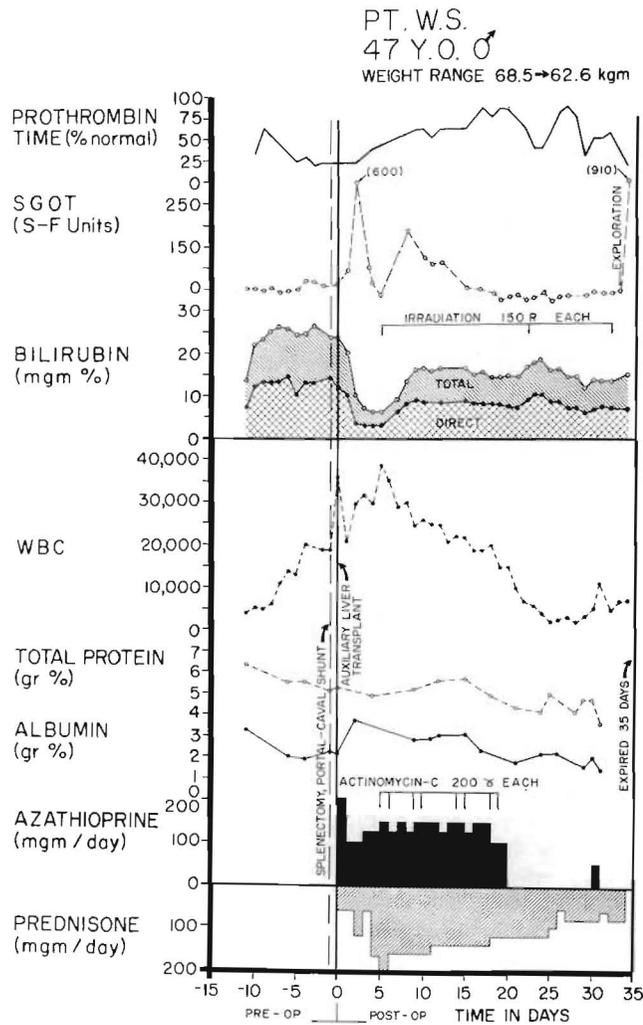


FIG. 36—Clinical course of a 47-year-old recipient who received an auxiliary hepatic homograft from a 12-year-old donor. The early rise in SGOT is probably ascribable to ischemic injury to the homograft. Improvement in liver function, as evidenced by the recovery in prothrombin time and the reduction in serum bilirubin, followed in the immediate postoperative period. However, a rejection crisis was diagnosed at 4 days after which jaundice deepened, although never to the preoperative level. Leukopenia developed during the third postoperative week. The white count remained depressed despite discontinuance of azathioprine and the patient died of sepsis on the thirty-fifth day. Exploration on the thirty-first day was for gastrointestinal bleeding, which, at autopsy, was proved to be due to invasive moniliasis of the small bowel; vagotomy and pyloroplasty were performed. (By permission of Arch. Surg. (Chicago) 93:107, 1966.)

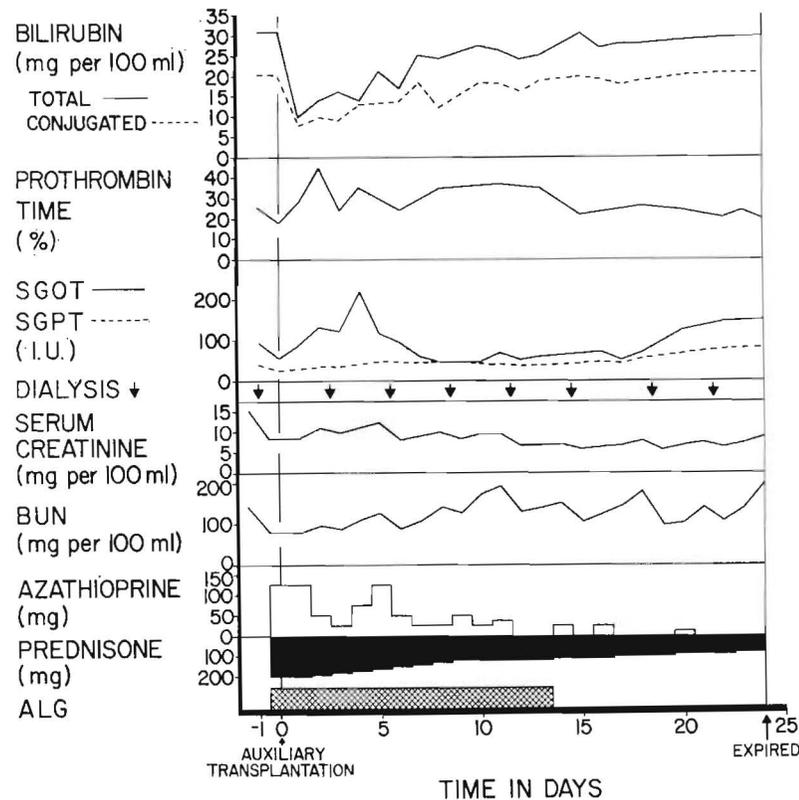


FIG. 37—The course of a patient with Laennec's cirrhosis and hepatorenal syndrome who received a newborn auxiliary homograft. The transient reduction of jaundice was probably due to the blood transfusions during operation. The patient required emergency hemodialysis before operation and at frequent intervals thereafter. Death on the twenty-fifth day was due to hepatic and renal failure and to pneumonitis.

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