80

CHAPTER 12
HEPATIC TRANSPLANTATION

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> . . . even isolated successes in this field may be more important than a large series of negative findings. They can help in the analysis of the problem of homoplastic transplantation, and the question is no longer of the possibility of the successful survival of homoplastic grafts, but of the conditions which this entails.
>
> *V. N. Shamov*°

Despite the use of any or all of the therapeutic measures now available, many patients with liver disease cannot be effectively treated. Children with intrahepatic biliary atresia, end-stage cirrhotic patients, and those with unresectable hepatic malignancies have no hope of cure. Their requirement is theoretically simple. They all need a new liver, an hepatic homograft, usually in conjunction with excision of their own diseased organ.

Direct though this concept may be, the actual performance of liver replacement is enormously complicated, and it is possible that the scope of the problem has not yet even been fully delineated. Nevertheless, there are reasons to hope that hepatic homotransplantation may soon become practical. In this chapter, the principles of hepatic transplantation will first be recounted as they have been defined in laboratory studies, both in untreated animals and in those provided with immunosuppressive therapy. Then, the clinical application of this procedure in five patients will be described. The last experience, although ultimately unsuccessful, has served to provide clearer insight into the problem and to direct attention to those similarities and differences between experimental animals and man.

° Shamov, V. N.: Homoplastic Transplantation of the Body Tissues. Experimental Medicine, page 7, Kiev, 1936.

THE HOMOGRAFT IN UNTREATED DOGS

Requirements of Surgical Technique

Historically, knowledge of whole-organ liver transplantation is of recent development. Goodrich and his associates[4] published the first detailed studies of canine hepatic homotransplantation in 1956. Working without any provision for protection of the liver from ischemia, they transplanted it to the pelvis of recipient animals. Four years later, Moore and Starzl and their associates[9,13] reported extensive studies of hepatic homotransplantation with excision of the dog's own liver and orthotopic placement of the graft.

The actual installation of a hepatic homograft involves the application of well-established surgical techniques. The recipient liver is excised with ease, providing the portion of the inferior vena cava which passes through and behind the liver is included with the specimen. Similarly, insertion of the homograft is not a difficult technical exercise, involving as it does only anastomoses of multiple vascular channels and provision for internal biliary drainage by cholecystenterostomy (Fig. 12-1)

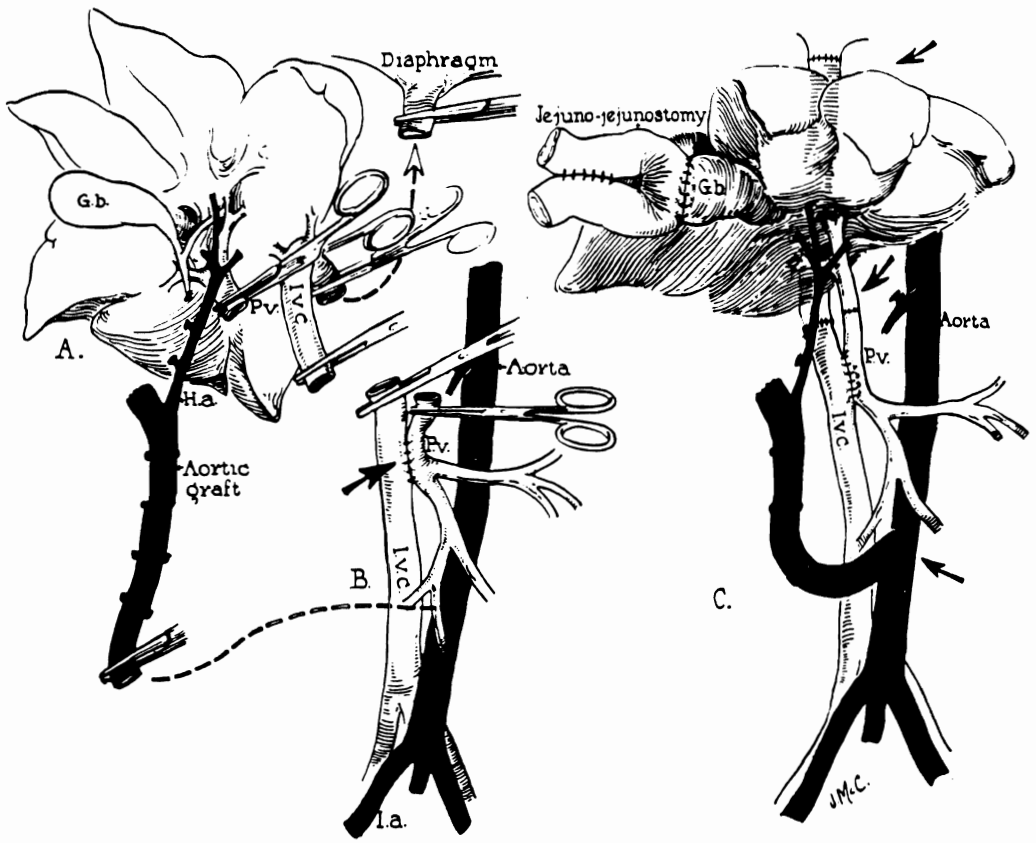

Fig. 12-1. Technique of canine hepatic transplantation. *A*. Donor liver ready for transfer. Note that the aorta, celiac axis, and hepatic artery are removed in continuity and that the segment of inferior vena cava behind the liver is part of the homograft. *B*. Recipient bed with liver removed. Portacaval shunt has been performed. *C*. Homograft in place. The portacaval shunt is usually taken down and the portal and caval defects are repaired. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 111:733, 1960.)

or by choledochocholedochostomy. The arterial blood supply can be reconstituted, either with an end-to-end hepatic arterial anastomosis or by in-continuity removal of the donor aorta, which is then attached to the side of the recipient midabdominal aorta (Fig. 12-1), thereby avoiding the necessity of a small-vessel anastomosis.

More specific problems have, however, limited the rate of success with which experimental hepatic homotransplantation has been performed. The first of these involves provision for egress of blood from the large venous pools drained by the portal vein and the inferior vena cava, since these vessels must be occluded during recipient hepatectomy and the transplantation. Inadequate diversion leads to sequestration of blood in the splanchnic and inferior vena caval drainage beds, resulting in hypotension and the invariably lethal complication of hemorrhagic gastroenteritis.

Outflow from the stagnant venous pools is accomplished with external shunts of siliconized plastic tubing. The two venous systems can be decompressed individually with bypasses running from the portal (via the splenic) vein and the inferior vena cava (via the femoral vein), respectively, with rostral insertion of the tubing into the jugular veins. We have found, however, that it is often more expedient to perform temporary portacaval anastomosis (Fig. 12-2), converting the

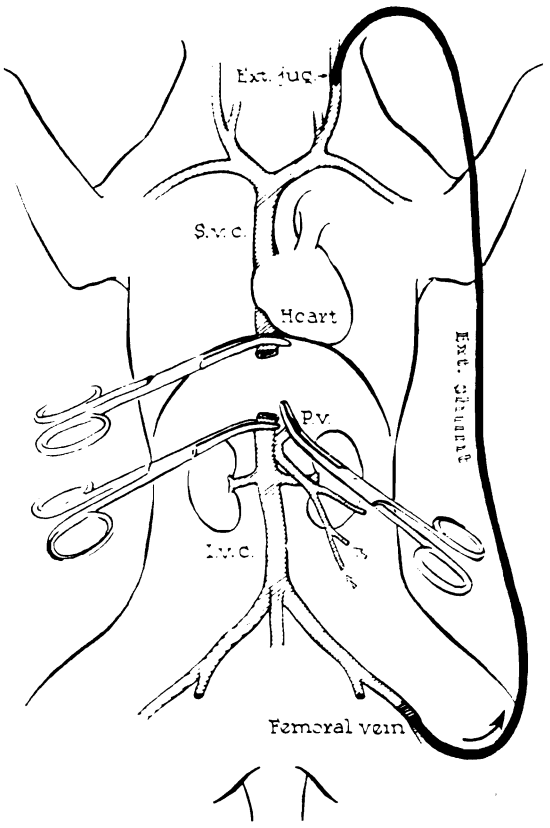

Fig. 12-2. Decompression of the portal and vena caval systems, which have been connected with a portacaval anastomosis. An external bypass is inserted from the femoral vein to the external jugular vein. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 111:733, 1960.)

splanchnic and systemic systems into a common venous pool, and then to use a single bypass to connect the inferior vena cava to the jugular system. After completion of the transplantation, the temporary portacaval anastomosis may be taken down, with lateral repair of the respective vessels.

A second specific requirement involves the protection of the homograft from the effects of ischemia during its removal and transfer, a problem which is treated in detail further on in this chapter, under "Methods of Homograft Preservation." At present, it is sufficient to say that the canine liver is so exquisitely sensitive to total anoxia that deprivation of its blood supply for more than 20 or 30 min in a normothermic state leads to irreversible damage. Once instituted in dogs, the injury follows an inexorably fatal and species-specific course. Acute vascular changes occur, probably consisting of spasm of postsinusoidal venous stopcocks which normally regulate outflow. As a consequence, blood can enter the liver but it cannot freely leave. The organ becomes swollen and purple, a syndrome referred to as "outflow block." Portal venous pressure mounts. Secondary hemorrhagic gastroenteritis follows, a terminal complication which cannot be effectively treated at this time even with a permanent portacaval shunt. Histologic sections of such livers show intense congestion and acute parenchymal injury (Fig. 12-3). Outflow block does not occur in the human liver, at least not with the severity described for dogs, so that the requirement for a perfectly preserved homograft is probably not so stringent in clinical application as it is in the dog.

Because of the prominent role of acute vascular reaction of the hepatic vascular bed in the determination of success or failure, the possibility was investigated of reconstituting the vascular supply of the graft by alternative methods. In some dogs, the nonhepatic splanchnic flow was permanently diverted to the inferior vena cava, as with an Eck fistula (Fig. 12-4*B*). In others, a reverse Eck fistula was employed, with consequent augmentation of the venous component of hepatic blood flow (Fig. 12-4*A*). Although survivals could be obtained with these modifications, the best results were obtained with restoration of normal venous pathways (Fig. 12-4*C*).

The Course in Dogs with Untreated Hepatic Homografts

Animals receiving a well-preserved homograft frequently enjoy remarkably good health for the first few days after operation. They awake promptly from barbiturate anesthesia and can eat within 48 hr. Serum bilirubin, alkaline phosphatase, and glucose levels are normal. Stools are brown. Bile can be collected from indwelling choledochal drainage tubes. Kukral[5] has demonstrated that hepatic pro-

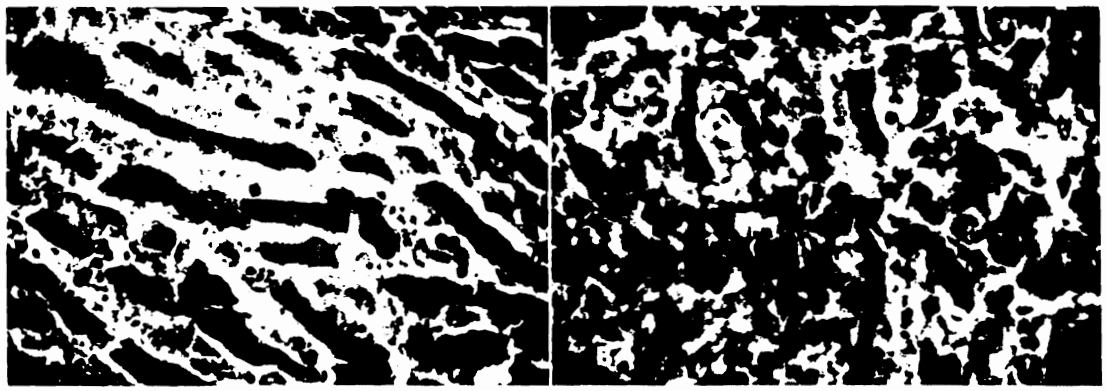

Fig. 12-3. Histologic changes in hepatic outflow block. *A*. After 10 hr, showing dilated sinusoids, congestion, and moderate loss of parenchyma. *B*. Another homograft after 36 hr. Note congestion and disorganization of architecture (hematoxylin and eosin, ×240). (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 111:733, 1960.)

tein synthesis is normal or above normal during this period.

By the third to fifth day, however, evidence of rejection invariably develops. Bile production ceases. Stools become clay-colored. The urine turns dark and contains large quantities of bilirubin. Serum alkaline phosphatase and bilirubin levels rise rapidly (Figs. 12-5, 12-6), the principal fraction of the latter being the direct or conjugated component. The early biochemical picture is thus quite indistinguishable from that seen in obstructive jaundice, a sequence that may be relevant in considering the mechanisms of rejection, as will be discussed later. At a somewhat later time, a tendency to hypoglycemia is observed (Fig. 12-7), this usually being a preterminal finding.

Although the onset of rejection in dogs fol-

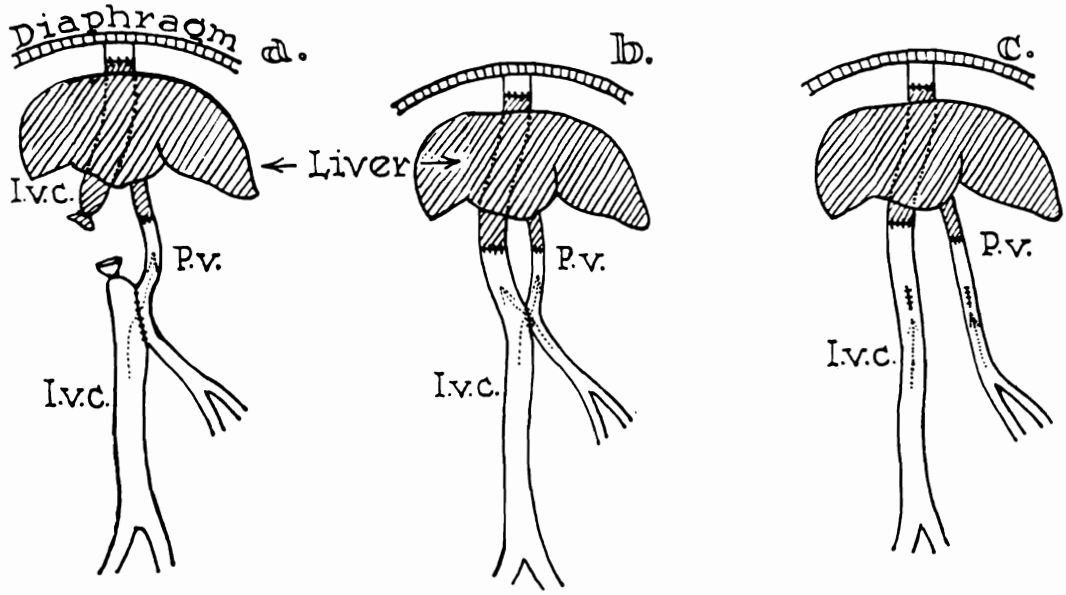

Fig. 12-4. Methods of venous reconstruction. *A*. Reverse Eck fistula. *B*. Anatomic reconstruction with small portacaval shunt. *C*. Complete anatomic reconstruction with closure of preliminary portacaval shunt. (*From Starzl et al., by permission of Surg. Gynec. & Obst.* 111:733, 1960.)

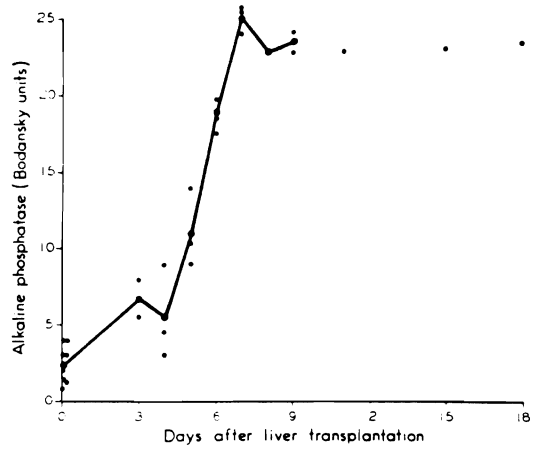

Fig. 12-5. Alkaline phosphatase levels in eight untreated dogs who received hepatic homografts. Note marked rise after fourth day. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 112:135, 1961.)

lows transplantation at a very constant interval, there is great variation in the subsequent severity and rapidity of the process. Most of the animals die within 2 to 5 days after the appearance of jaundice, but survival for as long as 21.5 and 35 days has been observed by us in the untreated animal. In one such dog, there was evidence of partial spontaneous reversal of well-established jaundice (Fig. 12-8).

Similarly, there are variations in the severity of the pathologic alterations, which are not dependably related to the time after transplantation. Thus, some homografts have good preservation of architecture even after 10 days, and others have almost total destruction at this time. Nevertheless, it is possible to reconstruct the serial histologic changes of the liver homograft which is under immunologic attack.

The first alteration consists of a mononuclear cell infiltrate in the periportal areas (Fig. 12-9*A*), consisting chiefly of small lymphocytes and plasma cells. Frequently, microscopic collections of bile are also observed at this time, suggesting intrahepatic biliary cholestasis. The degree of functional derangement may be well advanced at a time when these histologic changes are still minimal. At a later stage, loss of hepatocytes is prominent, in addition to accentuation of the mononuclear infiltration—the parenchymal loss being concentrated at the periportal and centrilobular areas (Fig. 12-9*B*). In its most advanced form, disruption of architecture is so complete that only a few remnants of recognizable liver tissue are left, lost in a sea of lymphocytes, plasma cells, and debris (Fig. 12-9*C*).

These histologic changes are comparable to that observed in other tissues, with the initial round-cell infiltration and later parenchymal loss, in accordance with the classical cellular concept of homograft rejection. Certain observations, however, permit speculation that an additional related or even independent

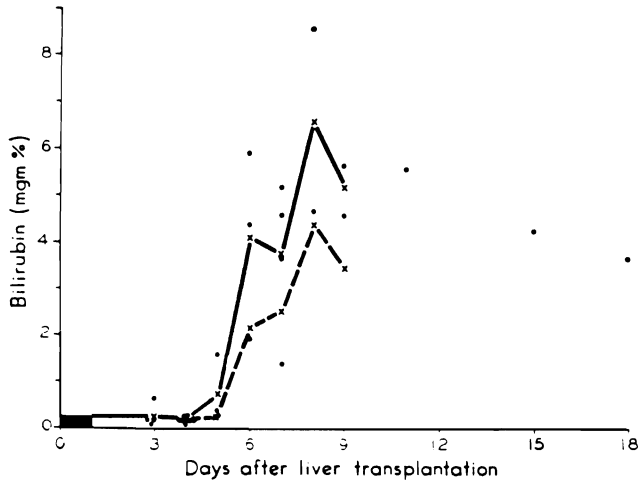

Fig. 12-6. Scattergram showing pattern of onset of jaundice in eight dogs with hepatic homografts. Immunosuppressive therapy was not employed. Dots are individual total bilirubin determinations. Solid line connects average total bilirubin for each day. Dash line represents the average of the corresponding direct bilirubin determinations. Note absence of chemical jaundice until the fifth day. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 112:135, 1961.)

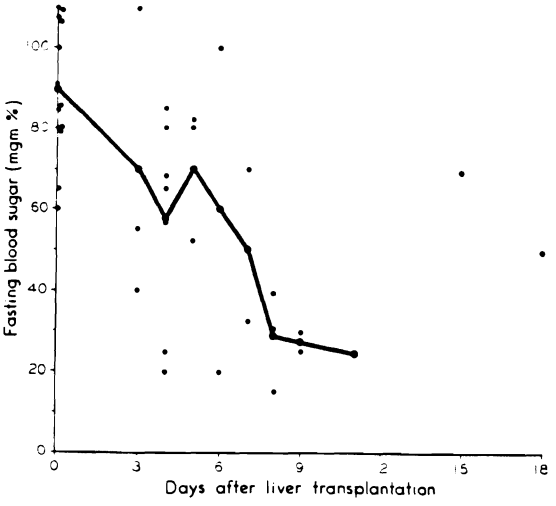

Fig. 12-7. Fasting blood sugars (dots) in 10 dogs which received hepatic homografts without immunosuppressive therapy. Solid line connects average values for each day. Note that severe hypoglycemia sometimes developed as early as the fourth day. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 112:135, 1961.)

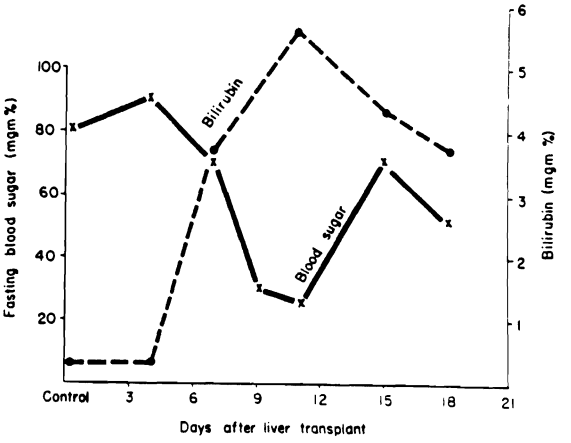

Fig. 12-8. Blood sugar and bilirubin levels in dog which lived 20.5 days after hepatic homotransplantation without immunosuppressive therapy. Note spontaneous improvement in chemistries after the eleventh day. The dog ultimately died of rupture of the arterial suture line. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 112:135, 1961.)

vascular mechanism may play an important role in tissue repudiation in general, and may in particular explain some of the phenomena encountered in hepatic homotransplantation. For example, very severe functional derangement in renal and pulmonary as well as hepatic homografts is often observed even though histologic alterations are minimal or even absent. Working with pulmonary transplants, Barnes et al.[1] drew attention to the fact that rejecting lungs often appeared to have suffered a sudden vascular calamity. Deterioration of renal homotransplant function in many cases follows a pattern consistent with that of ischemic injury. Ramos et al.[11] have

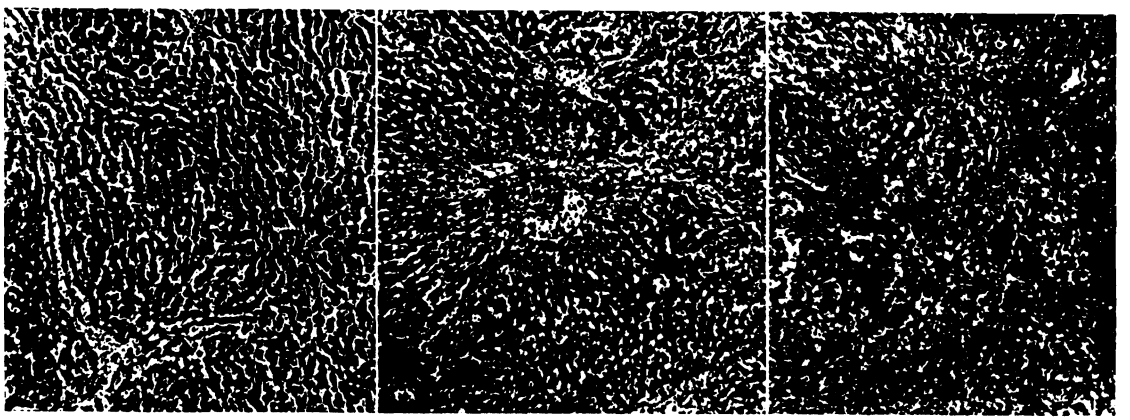

Fig. 12-9. Stages in rejection of hepatic homografts in dogs not treated with immunosuppressive therapy. *A*. Earliest finding of focal periportal round-cell infiltrate. *B*. Beginning parenchymal destruction. Note increased numbers of focal and diffuse mononuclear cells. *C*. Advanced rejection, showing almost total obliteration of normal architecture (hematoxylin and eosin stain, ×80). (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 112:135, 1961.)

shown that circulating antibodies active against small blood vessels are present within a few hours after exposure of cardiac homografts to the host. Finally, Moore[9] has demonstrated in dogs that large areas of parenchyma in the rejected liver are frequently devascularized at the time of the rejection.

It seems reasonable to believe that these observations have a related explanation with all tissues. It is necessary only to envision a common immunologic reaction in which the small vessels are the target, as described by Edgerton, Peterson, and Edgerton[3] in studies on skin grafts. The cell infiltrations which tend to concentrate at the portal triads, the humoral rejection substance recently described by Najarian,[10] or still other unknown factors could each be the responsible agents for impairment of blood flow at the time of rejection. No matter what the explanation, an early arteriolitic lesion could conceivably result in selective damage to the intrahepatic biliary collecting system, with the consequent early development of biochemical changes simulating obstructive jaundice.

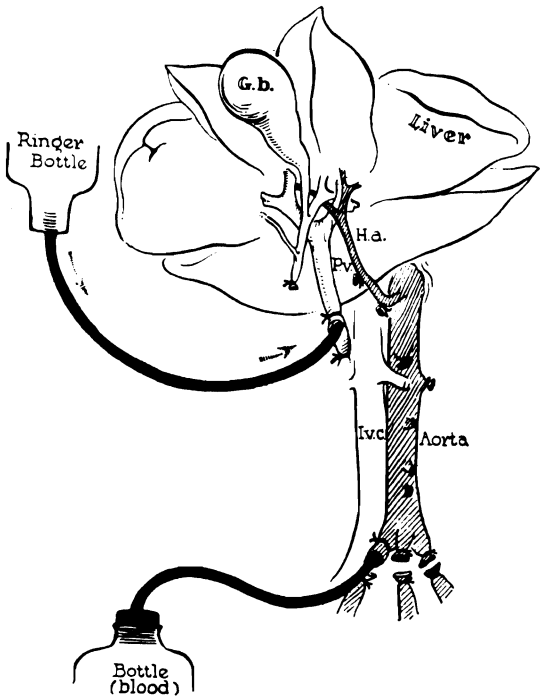

Fig. 12-10. Preparation of donor liver in the dog. Exsanguination from the aorta is carried out concomitantly with intraportal infusion of chilled lactated Ringer's solution. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 111:733, 1960.)

METHODS OF HOMOGRAFT PRESERVATION

In animal work, the most effective method of homograft preservation has been with a simple technique of hypothermia. The donor animal is cooled to 30°C before operation. The liver is prepared for removal, and while it is *in situ*, chilled lactated Ringer's solution is infused through the portal vein as the animal is exsanguinated (Fig. 12-10). A liver prepared in this way can tolerate 90 to 100 min of total ischemia with subsequent good function. Other techniques involving arterial infusion and pump perfusion are less satisfactory.

This simple method of hypothermia, satisfactory though it is for animals, is not practical for clinical use. The opportunity to procure a human donor who has been cooled prior to death would be unusual. In addition, the time necessary to remove the recipient to the operating room and prepare him for removal of his own liver would almost inevitably exceed the 2 hr which is the outside limit of ischemic tolerance in dogs. In order to improve the quality of cadaveric tissue which could be obtained for transplantation and to extend the time limitations imposed by the previously described techniques, a method for hypothermic postmortem perfusion of the donor was developed.

As soon as possible after death, catheters are inserted through the femoral artery and vein into the aorta and inferior vena cava and attached with a system of gravity venous return to an extracorporeal circuit (Fig. 12-11). The reservoir perfusate is 5 per cent glucose in water to which 200 mg heparin and 1 Gm procaine chloride per liter is added. With the first surge of the perfusion fluid from the pump, the corpse is heparinized. With the addition of a heat exchanger to the circuit, the

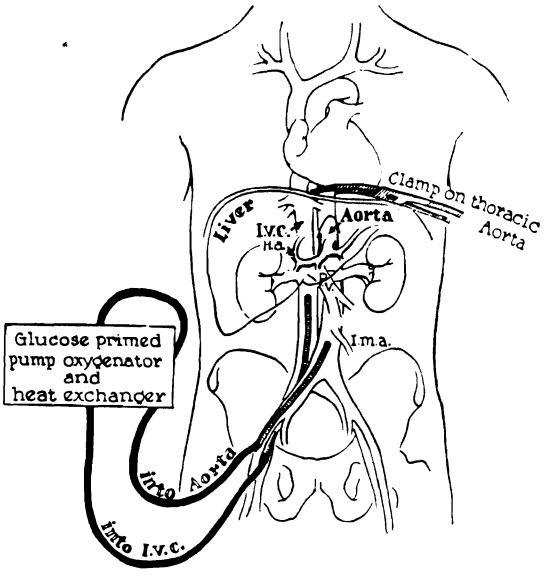

Fig. 12-11. Extracorporeal perfusion of the human cadaveric donor. The venous drainage is from the inferior vena cava, and the arterial inflow is through the abdominal aorta. Catheters are inserted into these vessels through the femoral artery and vein. Note clamp on thoracic aorta in order selectively to perfuse the lower half of the body. Glucose-primed pump oxygenator is used with a heat exchanger. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 117:659, 1963.)

cadaver can be chilled promptly. Flow rates of 30 to 60 ml/kg/min are used. The body temperature is lowered to 10 to 20°C. Selective perfusion of the abdominal organs is obtained by cross-clamping the lower thoracic aorta. If the perfusion is long, it is necessary intermittently to add blood, plasma, or electrolyte solution in order to maintain an adequate venous return.

This technique of *in situ* perfusion affords a high degree of protection to the visceral organs. Canine kidneys can be preserved for as long as 10 hr after death and then transplanted, with satisfactory renal function. The period during which hepatic tissue can thus be stored after death is much shorter, the maximum permissible period being approximately 4 hr in dogs.

Despite the utility of hypothermic perfusion, the cadaveric liver obtained with this technique has always sustained moderately severe ischemic damage by the time of its revascularization, and differentiation of this injury from that of rejection is important in planning postoperative therapy. The characteristic biochemical alterations specifically related to the use of the cadaveric liver are acute rises in serum glutamic oxalacetic acid (SGOT) and more delayed elevations of bilirubin level (Fig. 12-12), changes not observed with the more rapidly performed method of transplantation previously described (Fig. 12-12). The increase in SGOT is transient. The bilirubinemia lasts for several days.

This means of preserving cadaveric hepatic homografts has been used five times in human cases—and functioning transplants have been obtained in four. The time from death to revascularization ranged from 152 to 192 min in those organs that functioned (Table 12-1). The interval was 420 min in the unsuccessful case. In the latter instance, perfusion, which ultimately had to be used for 330 min, was not started until 15 min after death. The recipient patient died on the operating table 4 hr after installation of the homograft from a hemorrhagic diathesis. The liver had evidence of extensive autolysis (Fig. 12-13).

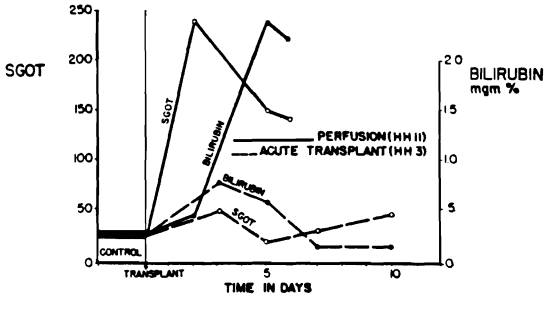

Fig. 12-12. Biochemical patterns of injury in dogs observed following transplantation of a hepatic homograft obtained from a perfused cadaver. For contrast, the course of an animal receiving a liver immediately after sacrifice of a living canine donor is included. For the cadaveric organ, total time from death to reimplantation was 140 min, as compared to 55 min in the graft transplanted immediately after sacrifice. Note that the cadaveric organ functions imperfectly. (*From Marchioro et al., by permission of Surgery*, 54:900, 1963.)

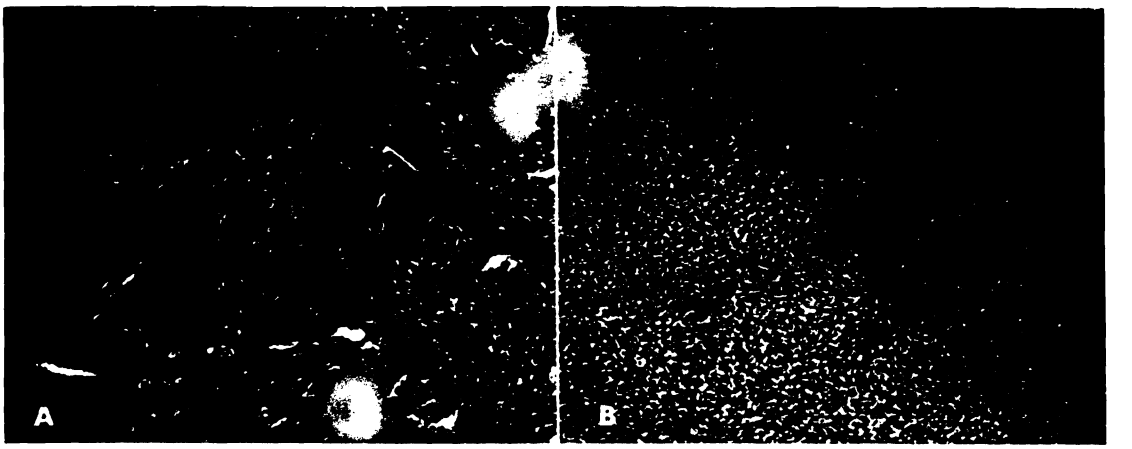

Fig. 12-13. Case 1. *A*. Patient's own liver, showing advanced biliary cirrhosis. This three-year-old child had congenital atresia of the bile ducts. *B*. Appearance of homotransplanted liver at autopsy, performed 12 hr after death. The patient exsanguinated on the operating table, 4 hr after revascularization of the homograft. Note extensive autolysis (hematoxylin and eosin stain, ×32). *From Starzl et al., by permission of Surg. Gynec. & Obst.*, 117:659, 1963.)

THE FATE OF HOMOGRAFTS IN DOGS WITH IMMUNOSUPPRESSIVE THERAPY

The invariable events that transpire after hepatic homotransplantation to the untreated dog have been described. This sequence can be remarkably altered if measures are taken to prevent rejection. In some animals, it is possible to prevent altogether the development of abnormalities in liver function tests. In others, derangements of SGOT, alkaline phosphatase, and bilirubin levels can be reversed (Fig. 12-14).

Table 12-1. HUMAN LIVER TRANSPLANTS

No.	Age		Date of transplant	Disease	Blood type		Donor death to revas., min.	Recip. survival, days	Cause of recipient's death	Cause of donor's death
	Donor	Recip.			Donor	Recip.				
1	3	3	3-1-63	Biliary atresia	A+	A+	420	0	Operative hemorrhage	Cardiac arrest at operation
2	55	48	5-5-63	Cirrhosis and hepatoma	A+	A+	152	22	Pulmonary emboli	Terminal brain tumor
3	69	67	6-24-63	Cholangio-carcinoma	O−	O+	192	7½	Pulmonary emboli; GI bleeding	Stroke
4	73	52	7-16-63	Cirrhosis and hepatoma	O+	A−	174	6½	Pulmonary emboli; congestive heart failure	Coronary
5	64	29	10-4-63	Cirrhosis and hepatoma	O+	O+	164	23	Common duct necrosis and bile peritonitis; rejection?; hemorrhagic diathesis	GSW, head (suicide)

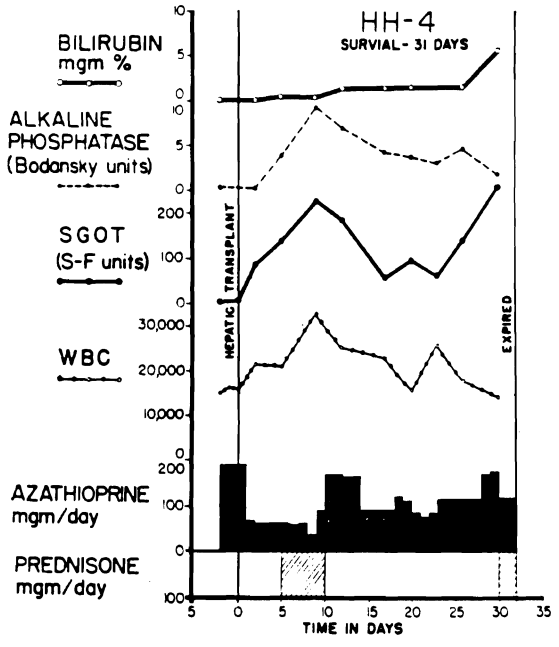

Fig. 12-14. Course of dog which received immunosuppressive therapy after hepatic homotransplantation. Note that jaundice occurred only terminally. The animal lived for 31 days. The SGOT and alkaline phosphatase levels manifested cyclic changes suggestive of parenchymal injury, but the elevations in SGOT and alkaline phosphatase were reversible. The dog died of a large perforated gastric ulcer.

Nevertheless, animals with heaptic homotransplantation have not survived for longer than 35 days with the use of immunosuppressive therapy. Even when the rejection process is entirely controlled, late deaths from perforation of the stomach and duodenum or from gastrointestinal hemorrhage have almost invariably occurred. The reasons for this are probably three in number: (1) prednisone, a drug which in high doses almost invariably produces gastrointestinal ulcerations in dogs, is freely employed and is essential in the immunosuppressive regimen used by us; (2) the method used for provision of internal biliary drainage may contribute to ulcer formation inasmuch as bile is diverted into the jejunum; (3) the increased incidence of ulcer diathesis in various hepatic diseases is well known, and it is likely that similar pathophysiologic mechanisms contribute to gastric hypersecretion during the phase of threatened rejection.

Earlier efforts to prevent rejection of hepatic homografts by total body irradiation were completely unsuccessful. The basic therapy now used consists of azathioprine ("Imuran," Burroughs Wellcome, 57-322) administered daily in a dose of 3 to 10 mg/kg (Fig. 12-14). During the early postoperative period, the drug is given in an intravenous solution; change to the oral route is made when alimentation is resumed. The quantity is guided by biweekly white blood counts, and doses are selected which do not cause leukopenia (Fig. 12-14). If rejection develops despite this treatment, 100 mg prednisolone per day is added and later slowly withdrawn as there is reversal of the process. As will be described, actinomycin C has also been used in the clinical cases, but it has not been evaluated in the laboratory since it was unobtainable at the time of these studies.

HUMAN LIVER TRANSPLANTATION

There have been six attempted human liver homotransplantations, five at the University of Colorado Medical Center and the sixth by Dr. Francis D. Moore[9] at the Peter Bent Brigham Hospital in Boston. Although the maximum postoperative survival thus far has been limited to 23 days, experience with these cases suggests that such an operation will eventually be feasible. The remarks which follow are based primarily upon experience with the five cases treated in Denver.

Selection of Donor

From information already given, under "Methods of Homograft Preservation," it is evident that a prime determinant of the outcome is the quality of tissue provided and the degree to which it has been damaged during the agonal, or postmortem, period. Consequently, a cadaveric liver is suitable only under very special circumstances in which good circulation is maintained until shortly before death, and in a setting in which extracorporeal perfusion may be instituted almost immedi-

ately thereafter. In the first patient treated by us, a three-year-old child with congenital biliary atresia (Fig. 12-13*A*), failure to adhere to these precautions resulted in the use of an irreversibly damaged homograft, with consequent immediate failure. The transplant was obtained from another three-year-old child who died in the operating room during attempted removal of a third ventricular brain tumor. Cardiac massage was carried out for 45 min before official pronouncement of death, and another 15 min was required before the perfusion catheters could be inserted. In addition, an additional 330 min of perfusion was required before the recipient patient could be brought to the operating room and prepared by removal of his own liver for receipt of the new organ. Fatal hemorrhage ensued, and the recipient patient died 4 hr after restoration of the homograft blood supply. At autopsy the liver was found to be extensively autolyzed (Fig. 12-13*B*).

The ideal donor is one in the terminal phase of a nonmalignant disease process. Patients with cerebral gliomas, massive strokes, or extensive traumatic injuries of the central nervous system are examples. In some of these disorders, part of the accepted treatment of the malady from which the patient is dying is total-body hypothermia and the prior utilization of this form of therapy is probably of great coincidental benefit in postmortem tissue preservation.

The utilization of cadaveric donors who have had a sudden death is probably not feasible. In order to obtain prompt cadaveric perfusion, it is necessary to have an entire team of surgical and supporting personnel present at the bedside at the moment of death. Permission from the family must be obtained in advance. Observations on hepatic function of the dying patient are essential. Moment-to-moment recording of urinary output during the final hours of life is of value in assessing the general circulatory adequacy of vital organs. Finally, preparation of the recipient patient must be begun several hours in advance. Thus, the most suitable candidates for cadaveric donation are those in whom death is known, with a reasonable degree of certainty, to be impending for several hours.

Because of the special circumstances surrounding both the prospective donor and his family at this time, it is imperative that the transplantation team not be involved with terminal medical care. The physicians caring for the intended donor must continue their therapy up to and including the ultimate certification of death without consideration of the events to follow. Only after death can the transplant team insinuate itself. Their role is simply that of performing an immediate, rather than delayed, autopsy.

From postmortem studies, it has been discovered that the vascular supply of the liver is almost never involved by atherosclerosis. Consequently, the influence of age on the quality of the liver homograft is not so great as with other organs such as the kidney. In our experience, satisfactory livers have been obtained from donors as old as seventy-three years. The mode of death is the factor of greatest importance in obtaining suitable tissue. An aged patient dying under the circumstances described above would be preferable to a young, healthy one in whom the conditions of death did not fulfil the general requirements cited. In all age groups, it is necessary to enquire about drinking, previous jaundice, neoplasia, or chronic infectious disease. It is possible that prospective donors who have had a chronic debilitating disease with inadequate nutrition should be excluded.

A special note should be made concerning the practice of seeking donors who have the same blood type as the recipient. With renal homografts, it has been found that the use of donors with different blood types is feasible, providing that the general scheme currently in use in blood banks is followed in which O is the universal donor and AB the universal recipient. With livers, this type of mismatch may be dangerous, inasmuch as the liver is capable of erythroclastic activity and may cause a graft-versus-host reaction manifested by autohemolytic disease. This phenomenon has been

noticed by us in canine and human studies of whole-organ splenic homografts. In one case in the Denver series of liver transplants, an O+ liver was transplanted to an A+ recipient without demonstrably harmful effects, but for the present, it would seem reasonable to restrict transfer of hepatic tissue to matched individuals.

Selection of Recipients

In the hepatic homotransplants performed thus far, four have been performed for primary malignancies of the liver; the fifth was for the treatment of congenital biliary atresia (Table 12-1). In a sixth case, treated by Moore,[9] the patient had a primary carcinoma of the colon with hepatic metastases, the primary lesion not being discovered until autopsy. For the present, the practice of limiting this operation to patients with hepatic neoplasms appears to be justified, although the therapeutic indications would become greatly extended if the operation should prove to be predictably successful. In general, hepatic transplantation should be limited to those with a single organ disease or failure. An operation of such magnitude will not be tolerated by old patients with concomitant disease of other major systems or with other important complications.

The Donor Operation

The method of hypothermic perfusion of cadavers was described in a previous section. After institution and stabilization of extracorporeal circulation, a thoracoabdominal exposure is made. The fundus of the gallbladder is immediately incised, and all bile is aspirated in order to prevent autolysis in the extrahepatic collecting system. The falciform and triangular ligaments are incised (Fig. 12-15*A*), and the liver is retracted to the left, providing access to the portion of the vena cava behind the right lobe (Fig. 12-15*B*). The right adrenal vein and the other posteriorly directed tributaries are doubly ligated and divided (Fig. 12-15*B*). The suprahepatic portion of the inferior vena cava is then freed circumferentially. At this time, it is determined that the vena cava is free posteriorly from the level of the diaphragm to the entrance of the renal veins. The liver is replaced in normal position, and the structures of the portal triad are skeletonized (Fig. 12-15*C*). The remaining gastrohepatic ligament is divided, up to the diaphragm (Fig. 12-15*C*). The liver is now ready for removal.

During the above-described dissection, the cadaver is being continuously perfused. If the dissection is completed before the recipient room is ready, further manipulations are discontinued. When a signal is received that all is in readiness, the liver is excised by transection of the vena cava at the diaphragm and just above the renal veins, and by transection of the structures of the portal triad. Care is taken to leave long stumps of the latter structures, the hepatic artery being incised below the origin of the gastroduodenal artery. Immediately after its removal, the specimen is infused with chilled lactated Ringer's solution to which procaine and heparin have been added (Fig. 12-15*D*). It is now ready for delivery.

Recipient Operation

The initial steps for removal of the recipient liver are identical to those described for harvesting the donor organ (Fig. 12-15*A–C*). The ligamentous attachments of the liver are freed, and all incoming and outgoing structures are skeletonized. When it is ascertained that the donor organ is ready, the structures above and below the liver are clamped and the diseased organ is excised.

Just prior to occlusion of the portal vein and inferior vena cava, a siliconized plastic external bypass tubing is used to join the inferior and superior vena caval systems, with insertion through the femoral and internal jugular veins, respectively (Fig. 12-16*A*). An additional external bypass was used in one case, passing from the splenic vein to the external jugular vein (Fig. 12-16*A*), but in the subsequent cases, the splanchnic system was not decompressed and no harmful result was observed. The problem of clotting in the bypass tube will

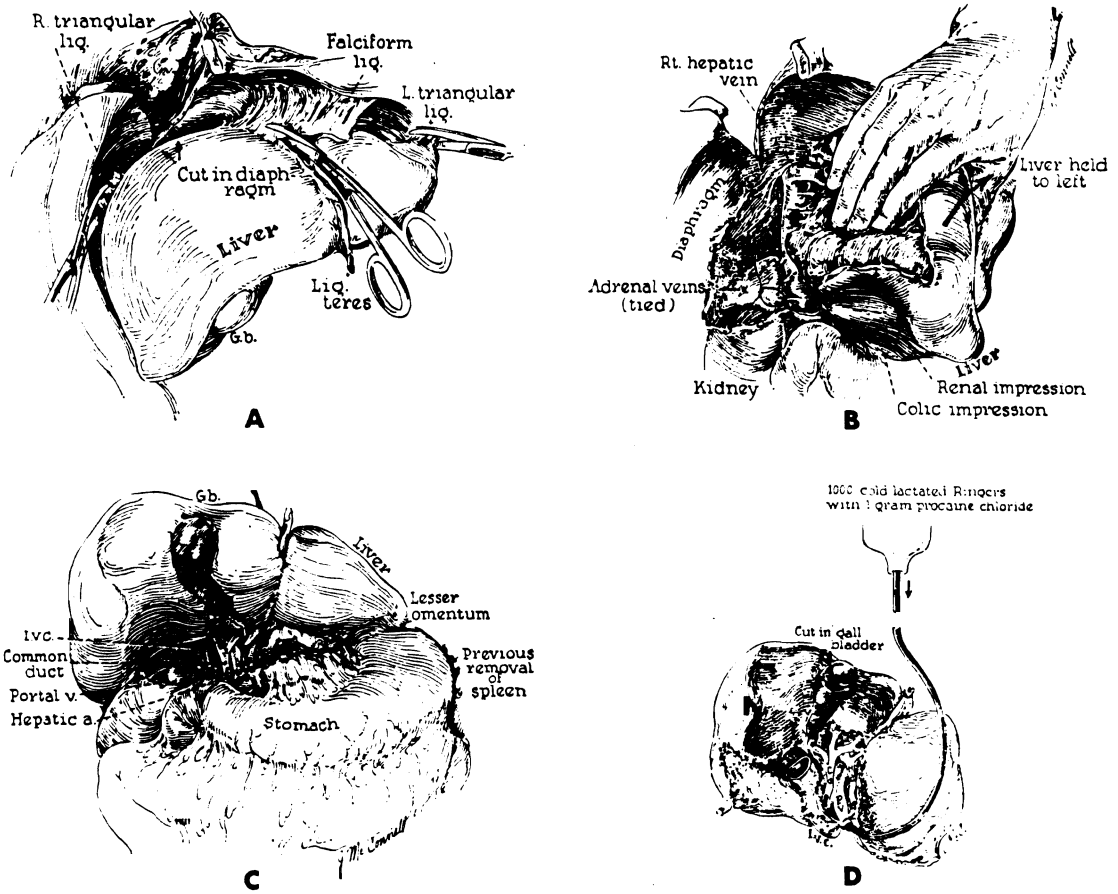

Fig. 12-15. Steps in extirpation of both the donor and recipient livers. A thoracoabdominal incision is used for the recipient patient as well as for the cadaver. *A*. Mobilization of the falciform, triangular, and coronary ligaments. *B*. Dissection of the right lateral and posterior surfaces of the inferior vena cava, ligating the adrenal veins. After completion of this maneuver it is possible to sweep the finger from the diaphragm to the renal veins without meeting resistance. *C*. Dissection of the structures of the portal triad and division of the remainder of the lesser omentum. *D*. Donor liver after removal from cadaver. Blood is washed from the donor organ by gravity perfusion through the portal vein. Note the incision in the gallbladder, employed to prevent autolysis by entrapped bile during the *in situ* dissection of the donor liver. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 117:659, 1963.)

be discussed more fully further on, under "Problems of Coagulation."

Once the liver has been removed (Fig. 12-16*B*) and a bypass system established, anastomoses of the various structures are begun. The upper vena cava is reconnected first, then the lower vena cava, the hepatic artery, the portal vein, and the common bile duct, in that order. In performing the upper vena caval anastomosis (Fig. 12-16*C*), it is necessary to exercise great care to prevent suture line leaks, particularly on the posterior row. In order to achieve a reliably water-tight posterior wall anastomosis, a double-layer technique is used, everting the first suture line (Fig. 12-16*C*). No. 4-0 silk is used for both vena caval anastomoses; 5-0 or 6-0 silk is used for the hepatic artery and portal vein (Fig. 12-16*D*). During the actual transplantation, close attention is paid to the cardiovascular hemo-

dynamics. In all but one patient, some degree of hypotension occurred at this time, but the fall in blood pressure was not alarming.

The common duct is reconstructed with a two-layer anastomosis using fine catgut and silk. The T tube is placed through the distal portion of the composite common duct, with its upper limb extending through the choledochocholedochostomy (Fig. 12-16*D*). Drains are then placed in the subhepatic space and the subphrenic spaces, and the wounds are closed after extraction of the T tube through a separate stab wound.

In four of the five cases, the above-described procedure was done in two stages. When it became evident that a donor liver would shortly be available, the recipient patients were explored and the skeletonization of all structures entering and leaving the liver was carried out and the wound closed. With sub-

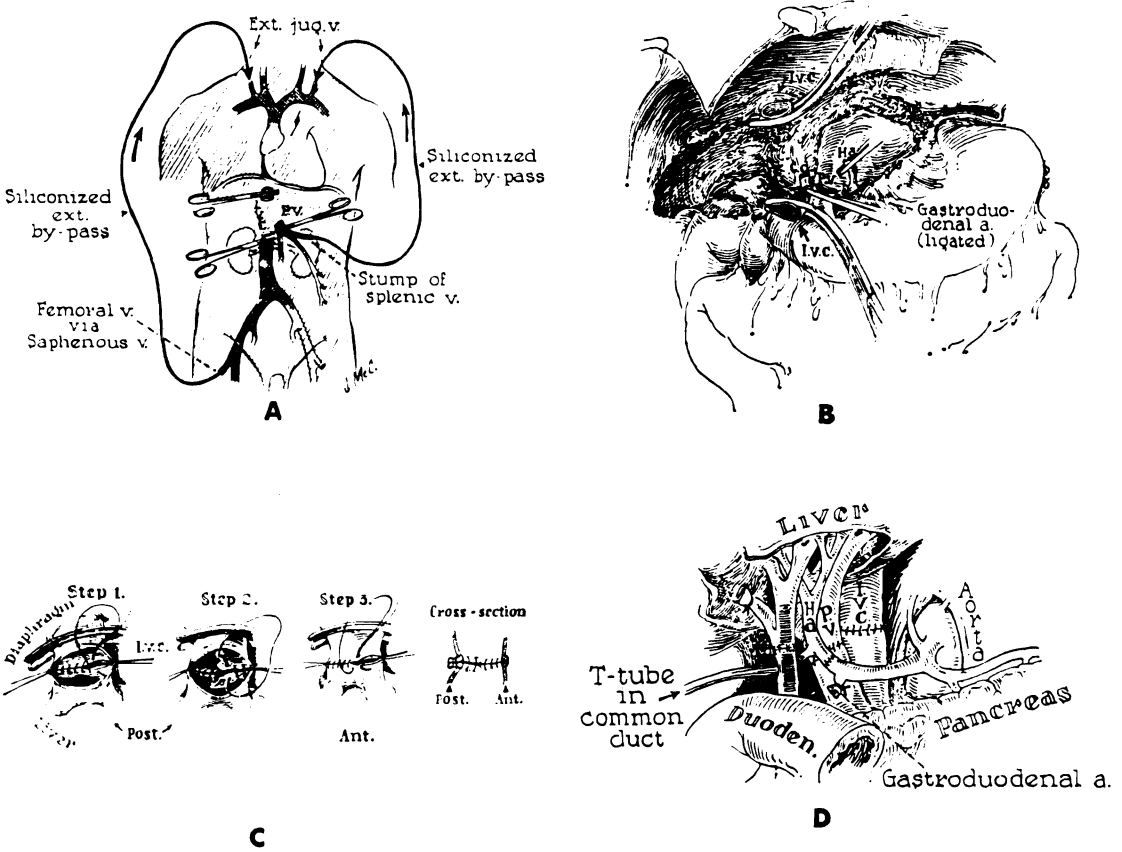

Fig. 12-16. Technique of transplantation in the recipient patient. *A*. External bypasses used for decompression of the inferior vena caval and splanchnic venous beds. Decompression of the portal vein was found to be unnecessary providing the caval bypass functioned satisfactorily and was of large caliber. *B*. Operative field after removal of the recipient patient's own liver. Note that the stumps are left as long as possible and that the hepatic artery is transected above the origin of the gastroduodenal artery. *C*. Anastomosis of the inferior vena cava at the diaphragm. Note that the cuff of the homograft is actually a confluence of the hepatic veins and vena cava. The posterior row is performed in two everting layers to ensure that no leaks occur in this area, which will be inaccessible for repair after placement of the homograft. *D*. Subhepatic operative field at completion of all anastomoses. Note that the gallbladder has been removed and that the T tube is inserted through a stab wound in the recipient portion of the composite common duct, with the upper limb passing through the anastomosis. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 117:659, 1963.)

sequent reexploration and definitive transplantation, it was necessary only to apply clamps and remove the liver without the necessity for a tedious dissection. Although the use of a staging procedure shortens the time necessary to prepare for receipt of the liver, a serious penalty resulted in one case in which the proposed donor recovered unexpectedly. It was necessary to wait for 2 weeks before a homograft could be obtained and by the time of the second operation, there were a number of annoying vascular adhesions. In the other three cases, the delay between stages was less than 48 hr.

Problems of Coagulation

In clinical hepatic homotransplantation, serious aberrations of the coagulation mechanism became manifest. These had not been observed in the canine studies. During the anhepatic interval, and for a short time after restoration of the blood supply to the transplant, there is a period of risk from hemorrhage, characterized chiefly by rising quantities of fibrinolysins and by sharp falls in plasma fibrinogen to levels as low as 30 mg/100 ml. Within a few hours after the homograft has been inserted, however, this early phase is replaced by a period of hypercoagulability, which has lasted for several days. During early convalescence, the euglobulin lysis time, which is used to measure fibrinolysin activity, becomes extremely prolonged, and in some cases fibrinogen levels also rise sharply. The surgeon is thus confronted with immediate problems of hemorrhage and with later problems of intravascular coagulation.

In three of the four patients who survived operation, the late hypercoagulability resulted in formation of venous thrombosis in the terminal vena cava and iliac veins, and all three patients died either as a direct or contributing consequence of multiple pulmonary emboli. In these three cases, the patients were given epsilon amino caproic acid (EACA) and intravenous fibrinogen during the transplantation to prevent or treat hemorrhage; this therapy may have potentiated the lethal delayed complications of coagulation.

In the last case, these clot-producing agents were not used. Instead, the patient was given 2 mg kg heparin during the time of installation of the liver. No other drug therapy was provided, not even heparin-neutralizing agents such as protamine sulfate. The penalty for this was the necessity for the transfusion of 18 units of blood. The reward was that this patient developed no late intravascular coagulation.

On the basis of the experience thus far accumulated, the wisest course would appear to be that of minimal iatrogenic alteration of the coagulation mechanism except for heparinization at the time of the operation to prevent clotting of the bypass system. In spite of the tendency for hemorrhage at this time, the overall welfare of the patient is least endangered by accepting the immediate risk of bleeding in the hope of preventing delayed complications of clotting.

Clinical Course

The first of the five patients died of hemorrhage on the operating table. The other four survived for 22, 7.5, 6.5, and 23 days. They all awakened promptly and appeared to be in relatively good condition. In all but Case 5, however, evidence of respiratory insufficiency subsequently developed, necessitating ventilatory support at some time during the course. These three patients (Cases 2, 3, and 4) were all found at autopsy to have multiple pulmonary emboli (Table 12-1).

Acute upper gastrointestinal hemorrhage occurred at some time during the course of all the patients who survived operation. This ranged from melena in Case 2 to massive hemorrhage from esophagogastritis in Case 3, hemorrhage from a previously present duodenal ulcer in Case 4, and diffuse gastric and intestinal hemorrhage in Case 5. Therapeutic gastrectomy was performed at the time of the transplantation in patient 4, and a prophylactic vagotomy and pyloroplasty were done in patient 5 at the time of the first stage.

The acute ischemic injury which follows

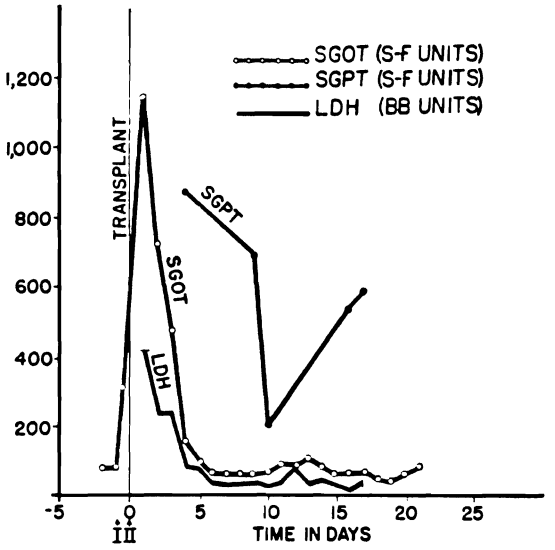

Fig. 12-17. Alterations in serum enzyme values following hepatic homotransplantation in Case 2. Note high but transient rise in SGOT level. Levels of LDH and SGPT were similarly affected. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 117:659, 1963.)

transplantation of a cadaveric dog liver has already been described. Similar findings were also noted in all the clinical cases. Rises in SGOT level to 990 to 2,040 were seen on the day after operation, with rapid return to or toward normal within 24 hr (Figs. 12-17 and 12-19). A somewhat more delayed increase in bilirubin level to 7 to 45 mg/100 ml followed (Figs. 12-18 and 12-19). Reversal of the bilirubinemia occurred 3 to 8 days postoperatively. In three of the four patients who survived operation, the improvement in hepatic function continued until the time of their death, from 6 to 22 days later. In the last case, however, steady resolution of early jaundice was interrupted on the sixteenth postoperative day (Fig. 12-19). The significance of this change is difficult to interpret because there later proved to be necrosis of the donor portion of the reconstructed common duct, with consequent biliary peritonitis.

Other parameters of hepatic function did not always follow an entirely consistent pattern. Hypoglycemia was never observed. Urea synthesis, estimated by calculation from urinary urea excretion, continued throughout the entire postoperative period. In three of the four patients studied, prothrombin times ranged from 40 to 100 per cent. In the other patient (Case 5), the prothrombin time immediately after surgery was 20 per cent and remained at this level until shortly before death. In two of the four patients, serum protein levels were well maintained until just before death, and in two others there was a slow decline.

A twenty-nine-year-old woman who survived for the longest time of any patient in the series is of special interest for several reasons. She received a very seriously damaged homograft. The donor from whom the organ had been removed was a sixty-four-year-old man who died of a self-inflicted gunshot wound of the head. He was hypotensive for several hours before death, and later analysis of a blood sample drawn during the agonal period revealed an SGOT of 2,400 units and a serum bilirubin level of 1.9 mg/100 ml. Twelve hours after transplantation of the homograft, the recipient's SGOT was 2,040 and the serum bilirubin level was 3.6 mg/100 ml. Very severe jaundice

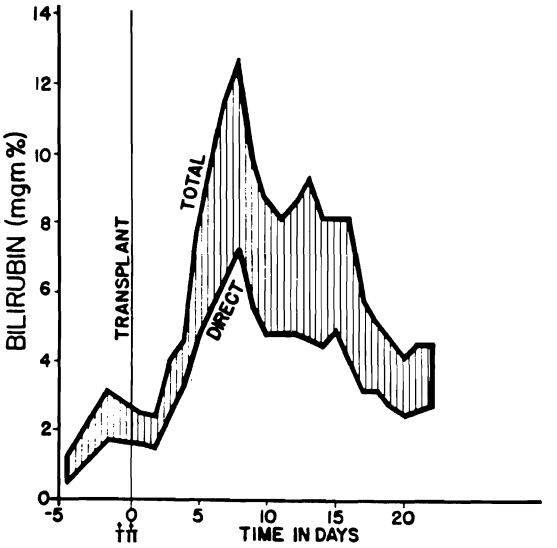

Fig. 12-18. Early changes in serum bilirubin in Case 2. Note that the early deepening of jaundice reversed in the later postoperative period. (*From Starzl et al., by permission of Surg. Gynec. & Obst.*, 117:659, 1963.)

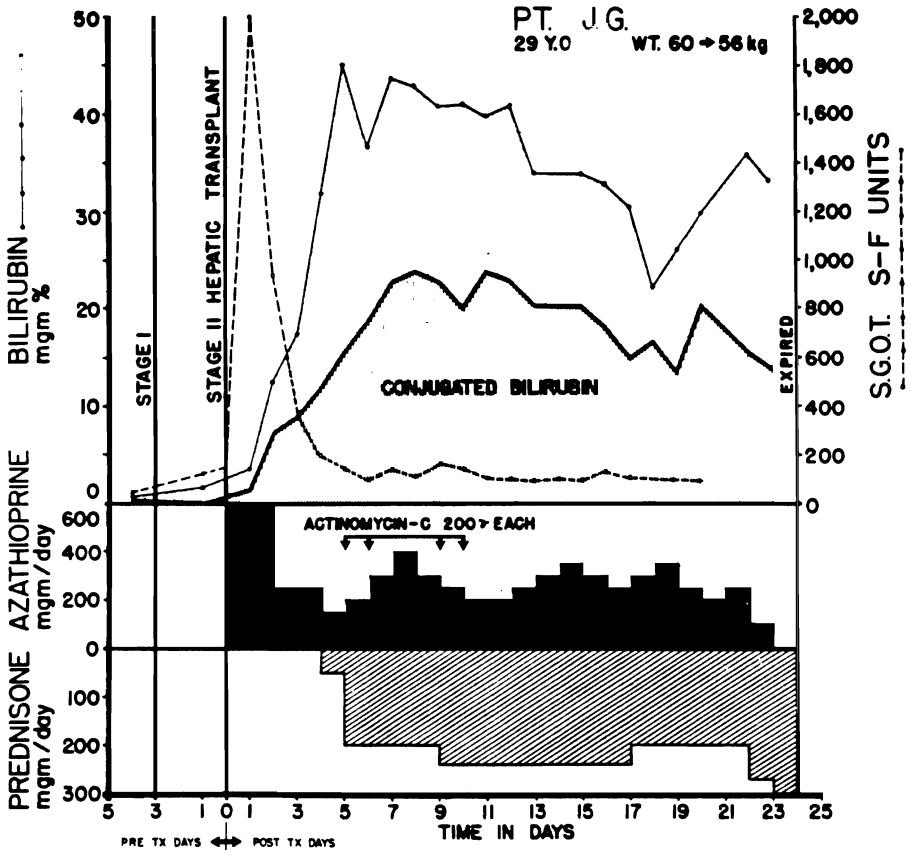

Fig. 12-19. Liver function in Case 5, before and after the homotransplantation of the liver. Note evidence of early hepatic injury with later reversal. The immunosuppressive regimen is also depicted. At autopsy, the patient was found to have necrosis of the donor segment of the common duct.

developed during the next 7 days, to a maximum serum level of 45 mg/100 ml (Fig. 12-19). Prothrombin synthesis never returned to normal. Levels of serum pyruvates and lactates were elevated throughout most of the postoperative period, especially during the last 5 days of life. Total serum protein levels began to decline in this patient almost immediately after operation, although the continuing loss of large quantities of fluid through the drain sites made it difficult to establish if this was due to failure of protein production or to losses.

Despite the evidence of severely curtailed liver function, the patient was able to walk by the fifth postoperative day and spent most of the next 10 days as a partial outpatient, visiting her home for 4 to 6 hr at a time. On the seventeenth postoperative day, she developed sudden abdominal pain and her condition deteriorated, with secondary deepening of jaundice (Fig. 12-19). Terminally, she became comatose and developed a diffuse, hemorrhagic diathesis. Final serum fibrinogen levels were 50 to 70 mg/100 ml, and the prothrombin time was 8 per cent.

The immunosuppressive regimen used in all patients was the same as that employed after the performance of renal homotransplantation. The general details of therapy have already been described in connection with canine homotransplantation. In the human cases, actinomycin C was also used, given intermittently throughout the postoperative period

(Fig. 12-19). Transient leukopenia was caused in Case 2, and the fifth patient had a terminal white blood count of 400 mm^3.

Pathologic Studies

The cause of death in Case 1 was acute hemorrhage, caused by fibrinolysins and by hypofibrinogenemia. At autopsy the liver was found to be extensively autolyzed (Fig. 12-13). An irreversibly damaged homograft had evidently been used. In Case 2, 3, and 4 multiple pulmonary emboli were either the direct or a major contributing cause of death. In Case 2, there was no other explanation for death. In Case 3, a similar complication was proved, although the brisk gastrointestinal hemorrhage which had begun 4 days after operation was also an important cause of failure. In Case 4, massive thrombosis of the mid- and terminal portion of the abdominal inferior vena cava was again noted, with multiple propagated clots in the pulmonary arteries. This patient also had acute pulmonary edema at the time of his death, which occurred suddenly 6½ days after operation at a time when his clinical condition appeared to be improving.

Only in Case 5 was there absence of intravascular clotting. In this patient, the principal abnormality was necrosis of the donor portion of the common duct, with a large defect in the anterior wall through which the upper limb of the T tube protruded. There was biliary peritonitis.

Although the hepatic homografts were all slightly enlarged, they appeared grossly to be well preserved in all but Case 5, where a 5-cm infarct in the central part of the right lobe was found. On transection, the liver tissue had a prominent lobular pattern and pouted slightly.

The livers from Cases 2 to 5 had certain common histologic abnormalities. In each instance, there was some evidence of intrahepatic cholestasis, even though the biliary drainage system was mechanically satisfactory in all but one. In the periportal region, there was a light infiltration of white blood cells, but these consisted principally of neutrophils rather than lymphocytes or plasma cells. There was some loss of parenchymal tissue adjacent to these areas, and in Case 5 there was some centrilobular loss.

Correlation of the patterns of liver function with the subsequent histologic findings suggests that the second, third, and fourth patients did not have rejection. In addition to the fact that there was improving hepatic function until shortly before death, the histologic alterations in the homografts are not diagnostic of rejection despite the focal presence of white cell aggregates near the portal triad. In Case 5, the role of rejection in the outcome is even less clear. In contrast to the others, this patient had interruption of improving heptic function 5 days before death. Histologic studies of the homograft showed a moderately severe loss of hepatic tissue, as well as the presence of periportal infiltrates (Fig. 12-20). In this case, there were more lymphocytes and a few plasma cells in this location. Similarly, it is not clear whether the necrosis of the common duct was a purely technical failure or whether the rejection process contributed to late death of this tissue.

THE FUTURE OF HEPATIC HOMOTRANSPLANTATION

In theory, the rationale for hepatic transplantation is not dissimilar to that which applies to the homografting of kidneys. The additional difficulties imposed by an operation of such magnitude, however, make it unlikely that this mode of therapy can ever be applied as freely as renal transplantation. In addition, the problem of dealing with the rejection crisis involving an organ of such complex function as the liver imposes another serious handicap.

Although the kidney is one of the vital organs, cessation or serious deterioration of its function can be tolerated for several days or even many weeks. During this time, temporary supportive measures can be carried out with the use of renal dialysis techniques. In applying the precepts extracted from experience in renal homografts to the liver, the prospect of

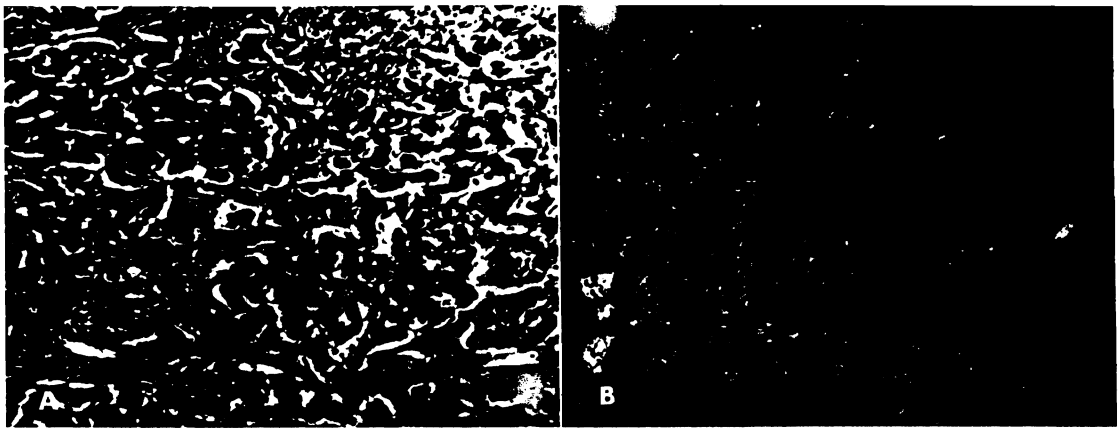

Fig. 12-20. Liver specimens in Case 5. *A.* Recipient's own liver showing primary hepatoma (hematoxylin and eosin stain, ×80). *B.* Homograft, 23 days after operation, showing focal parenchymal infiltrates and some loss of hepatocytes (hematoxylin and eosin stain, ×32).

acute temporary failure during rejection may be unacceptable, inasmuch as complete loss of function even for a few minutes could be of fatal consequence. At present, no artificial means are available by which the complex function of hepatic tissue can be performed. Perhaps this fact will promote development of better mechanical devices in the future which could be used for interim therapy. In the meanwhile, any hope of achieving consistent success with hepatic homotransplantation will depend on development of more effective ways of tempering the vigor of the rejection process which threatens the continuous function of all vascularized homografts.

The principal value of the clinical experience thus far obtained by us and by Moore has been to highlight additional problems which must now be further attacked in the laboratory. It seems inevitable that hepatic homotransplantation will eventually be successful, but not until further controlled information becomes available on more effective application of immunosuppressive therapy. Until such time, further clinical trials will continue to be purely investigative and experimental in scope.

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