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**EXPERIMENTAL AND CLINICAL OBSERVATIONS
AFTER HOMOTRANSPLANTATION
OF THE WHOLE LIVER * ****

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In this report, attention will be focused upon new or controversial aspects of homotransplantation of the liver. Although interest in liver transplantation dates from Welch's first reports almost 10 years ago (1, 2), there was at first little justification from laboratory experimentation for hope that such a procedure had a therapeutic clinical potential. In the recent past, the outlook has markedly changed.

Transplantation of the liver can be carried out in two general ways. First, the liver of the recipient may be removed and the homograft placed in its natural right subphrenic position (3-5). Survival after such an orthotopic homotransplantation is dependent upon immediate and continued function of the foreign hepatic tissue. Alternatively, recipient hepatectomy may be omitted in which case the homograft is inserted as an auxiliary organ in some ectopic site such as the pelvis, paravertebral gutter, or left subphrenic space (1, 2, 6-11). With the latter method, there is not total dependence upon the homograft; but as will be described, important physiologic problems are introduced relating to substrate competition between the two livers.

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EXPERIMENTAL ORTHOTOPIC HOMOTRANSPLANTATION IN THE UNTREATED HOST

All experiments with whole organ liver transplantation have been carried out in dogs. This animal is not expensive, has suitably large structures to permit standard anastomotic techniques, and is easy to care for. There are, however, specific disadvantages. The canine liver is peculiarly susceptible to anoxic injury as a result of a vascular response to ischemia in which there is apparently constriction of intra-hepatic venous sphincters. Blood is entrapped in the rapidly engorging parenchyma and the liver becomes swollen and cyanotic in this syndrome of « outflow Blood is entrapped in the rapidly engorging parenchyma and the intestinal tract results. These highly lethal events can largely be avoided if the homograft is cooled and if transfer can be carried out quickly. In the laboratory, the most effective means of using hypothermia is to perfuse cold electrolyte solution through the portal vein while the donor animal is being sacrificed by exsanguination (Fig. 1). Livers prepared in this way can usually tolerate 60 to 120 minutes of devascularization.

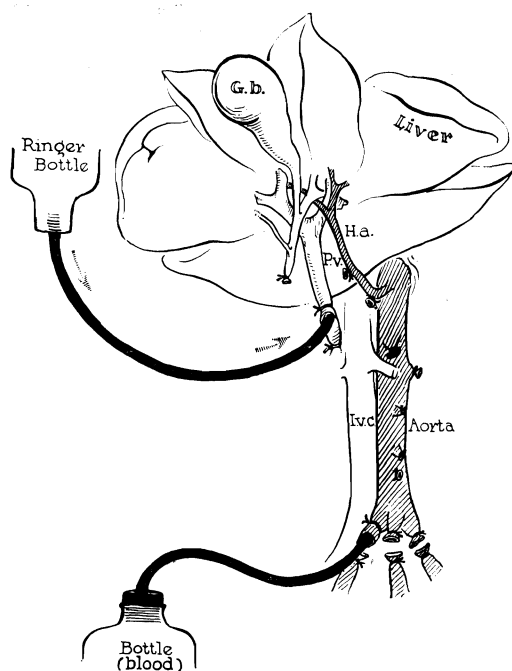


Fig. 1. — Method of further cooling a liver homograft just prior to its removal. Donor animals are operated upon with total body hypothermia of 29-31 °C. Cold lactated Ringer's solution is infused through the portal vein at the same time the donor animal is exsanguinated. (By permission of Surg., Gynec. & Obst. 111 : 733, 1960.)

During removal of the host liver and insertion of the homograft, diversion of the temporarily-occluded inferior vena caval and splanchnic systems is necessary. In our experience, this can be done most easily by first performing a temporary portacaval anastomosis after which the combined venous pools can be decompressed through a single external bypass (Fig. 2). After the homograft has been placed and revascularized, the portacaval shunt is then removed (Fig. 3).

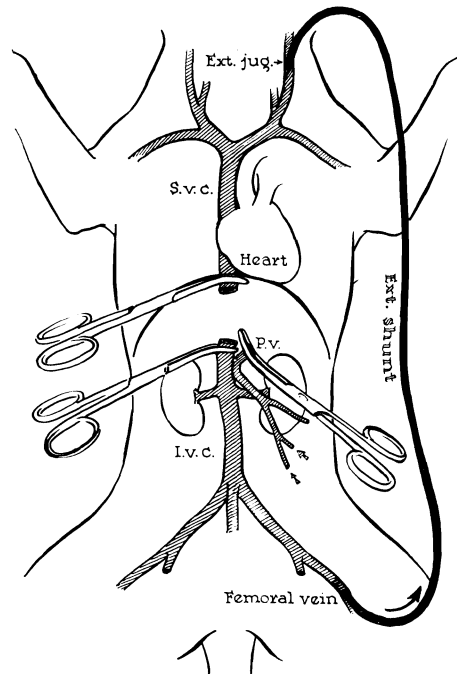


Fig. 2. — Method used for decompression of the inferior vena caval and splanchnic systems during removal of the recipient liver and replacement with a homograft. Note that a preliminary portacaval shunt has been placed. By performing this temporary anastomosis, the two venous systems are connected allowing their decompression with a single external bypass. (By permission of Surg., Gynec. & Obst. 111 : 733, 1960.)

Once the technical steps of the operation are mastered, orthotopic homotransplantation can be carried out with an acceptable risk. In the pioneer studies of Moore (3, 4) and in our own laboratories (5, 12, 13), the operative mortality was staggering, being well over 50 %. At the present time, it is less than 5 %. In a recent series of 23 control animals in which no effort was made to prevent rejection (14), all but one animal survived operation. Twenty-two of the 23 dogs lived for at least 2 days and 19 of these (86 %) lived six days or more (Fig. 4).

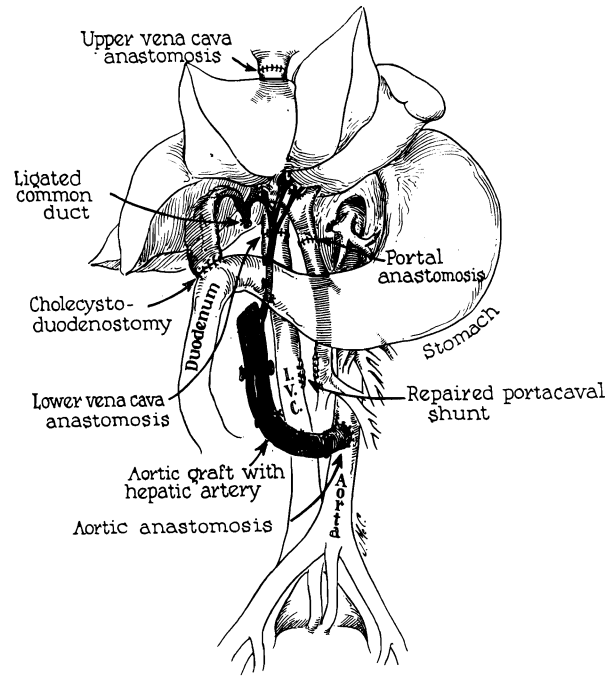


Fig. 3. — Reconstruction after orthotopic liver homotransplantation in the dog. Internal biliary drainage is with a cholecystoduodenostomy. Note that the aorta is transplanted in continuity with the hepatic artery of the homograft. (By permission of Surgery 58 : July, 1965.)

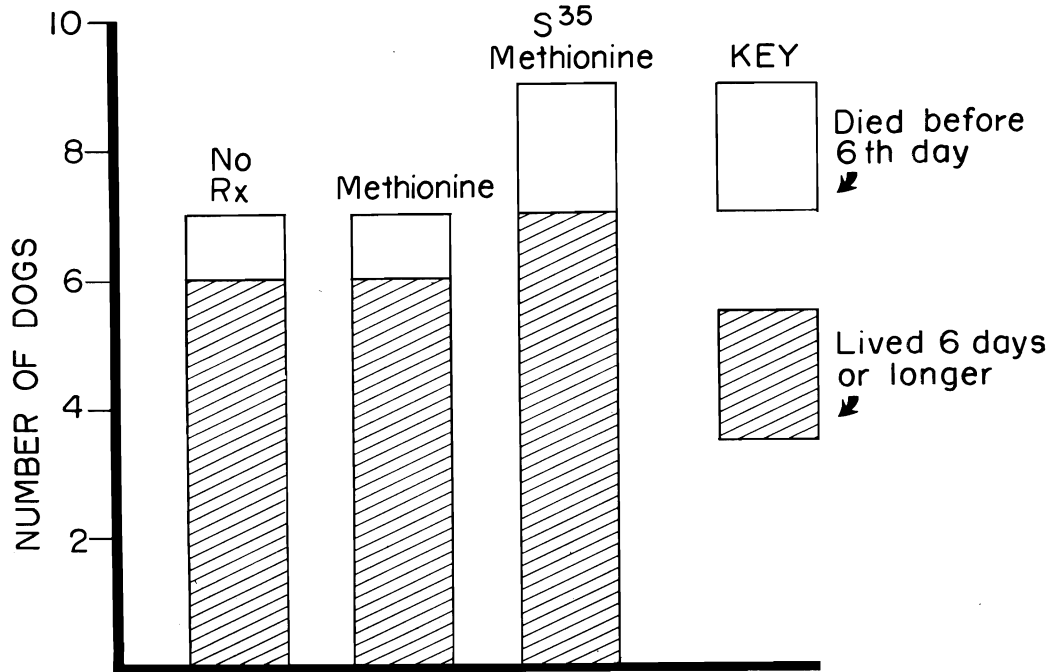


Fig. 4. — The results of orthopic transplantation in dogs not receiving immunosuppressive therapy. Seven of the animals received no treatment; 7 more were treated with methionine, given intravenously each day; and 9 received radioactive methionine. The use of methionine or its isotope did not potentiate homograft survival. The mean survival of the 22 dogs which lived through operation was 7.1 days.

In the untreated animal, the fate of the orthotopic homograft is not dissimilar to that of other homotransplanted tissues and organs. Since the liver is a vital organ without which life can be sustained for only a few hours, the functional end-point of rejection is very precisely defined by the death of the animal. Excluding the operative death, the mean survival in the above-described series of 23 animals was 7.1 days with a maximum of 10 days. In an occasional dog, protracted survival has been observed (12) as has also been noted with renal homografts.

The alterations in liver chemistries which follow orthotopic homotransplantation are quite predictable and are well correlated with the clinical course of the individual dog. After operation, there are usually 3 or 4 days of acceptable health, during which time the animals frequently resume alimentation. Progressive rises are then observed in the serum alkaline phosphatase, SGOT and SGPT, and a day or so later the serum bilirubin begins to increase. The biochemical alterations of rejection are progressive and inexorable until the time of death (Fig. 5). The animals develop

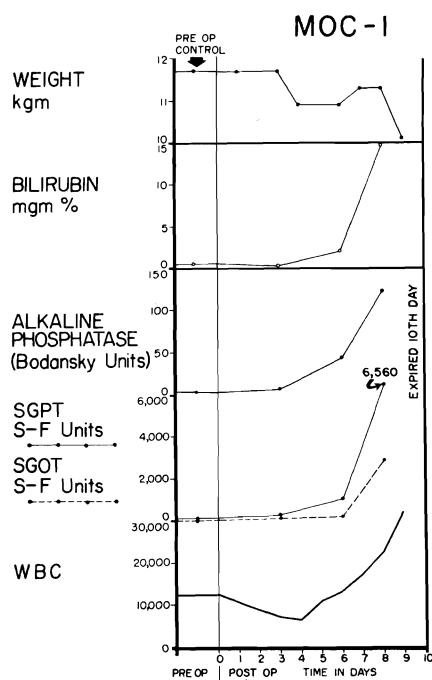


Fig. 5. — Biochemical changes after orthotopic liver transplantation to the untreated recipient. Note that a brief period of good function follows operation, but that deterioration of the biochemical pattern is unrelenting once it has begun.

dark urine and clay-colored stools, become listless and anorexic, and ultimately have unremitant terminal emesis.

Figure 6 shows the characteristic lesions of the rejecting orthotopic liver homograft—mononuclear infiltration of the portal

tracts and the area in and around the central vein, accompanied by centrilobular necrosis. Early, many of these infiltrating cells are the pyronine-positive « large lymphoid » cells of Scothorne (15) but after the sixth day these are replaced by mature plasma cells.

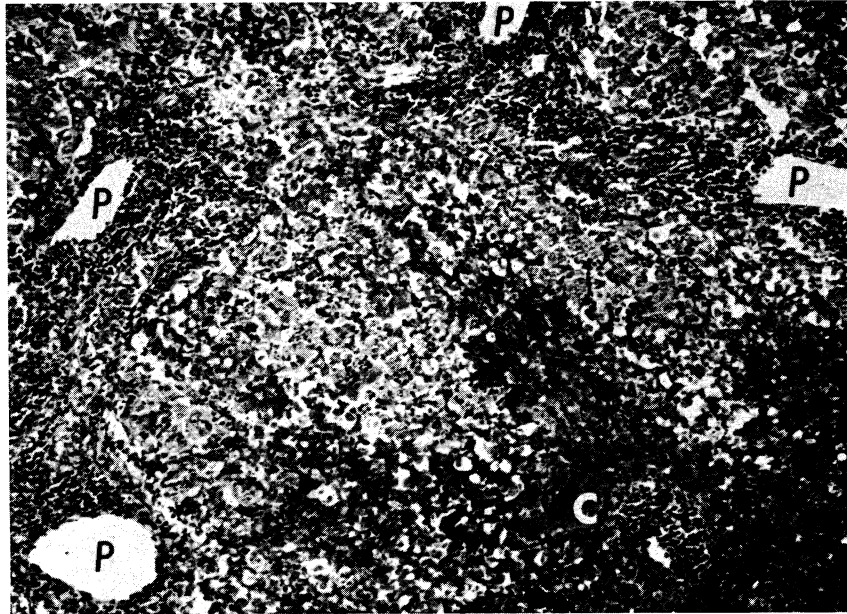


Fig. 6. — Typical rejection pattern encountered after homotransplantation to the untreated recipient. Characteristic features are host cell infiltration of the portal tract areas (P), cell infiltration in and around the central veins (C), and centrally-located hepatocyte necrosis. H. & E stain. (X 95).

The changing character of cells in the homograft is reflected by similar alterations in the host's own lymphoid organs. Lesions in the portal tract vessels are not prominent, but with electron-microscopy mononuclear cells are found adhering to and apparently injuring the central sinusoidal endothelium. If hemodynamic factors are important in liver rejection they apparently occur at this level, a localization comparable to the tubular capillary lesion of Kountz in the rejecting renal homograft (16).

EXPERIMENTAL ORTHOTOPIC HOMOTRANSPLANTATION TO THE HOST TREATED WITH AZATHIOPRINE

To date, azathioprine has been the most effective immunosuppressive agent for prolonging hepatic homograft survival. The use of this drug complicates the care of the animals in several ways. The attenuation of responsiveness to environmental antigens renders the kennel dog extremely susceptible to a variety of septic complications, the most common and lethal being pneumo-

nitis. Anemia and weight loss develop (Fig. 7). In addition, azathioprine has a specific hepatotoxicity which tends to injure the homograft at the same time it acts to protect it from rejection (14).

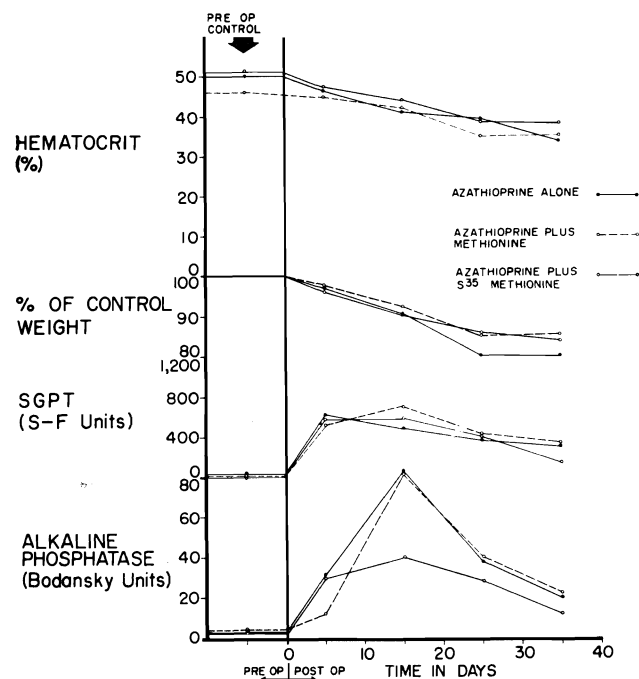


Fig. 7. — Toxicity of azathioprine when used alone, with S³⁵ methionine, and with methionine. Six dogs were in each of the three test groups depicted. Despite the severe abnormalities of liver function, jaundice did not develop. (By permission of *Surgery* 58 : July, 1965.)

The influence of this agent upon the liver function of normal dogs is seen in Figure 7. After its administration is begun, sharp rises in SGOT, SGPT and alkaline phosphatase are observed within a few days, usually without jaundice. After 15 to 30 days of continuous therapy, there is partial but usually incomplete recovery. The histologic lesion caused by azathioprine has some resemblance to that of rejection in that centrilobular hepatocyte injury of frank necrosis (Fig. 8) occurred in more than two-thirds of the animals, always, however, without cellular infiltration.

Despite the handicap imposed by the use of a liver poison to prevent liver rejection, it has been possible after orthotopic homotransplantation to obtain a large number of chronic survivors. The operative mortality was increased over that of the nontreated controls, mainly due to pulmonary sepsis. Thirty-two of the 116 dogs died during the first week. Of the 84 remaining definitive test animals, 44 lived for 25 days or longer, and 24 lived for

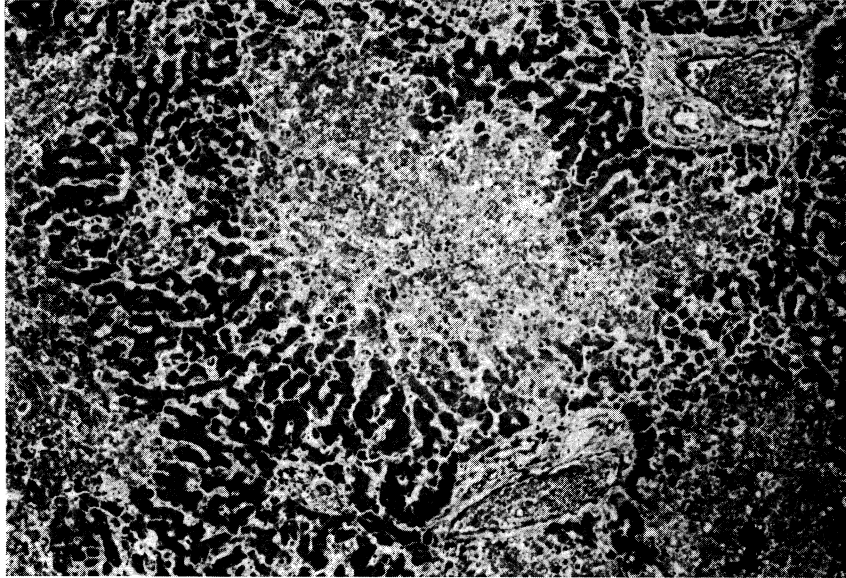


Fig. 8. — Liver of a dog treated with azathioprine for 26 days. There is centrilobular necrosis of hepatocytes but no cellular infiltration. H & E stain. (X 60). (By permission of Surgery 58 : July, 1965.)

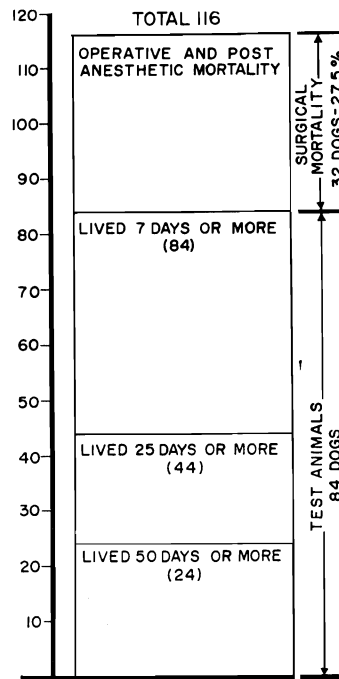


Fig. 9. — Survival after 116 orthotopic homotransplantation experiments in dogs. The mortality within the first week was 27.5%, almost always as the result of acute pulmonary sepsis. The animals which lived longer than 1 week had a better than 50% chance of living for 25 days or more and about a 30% chance of living 50 days or more. Maximum survival has been 11 months.

50 days or more (Fig. 9). Fourteen are still alive from more than 2 to slightly less than 11 months. The best results were in those animals which also received methionine or its radioactive isotope, but the variability of survival was so great in all series that statistically significant advantage of these adjuvant agents could not be proved.

After homotransplantation to the treated animal, there was a great variability in the vigor of the rejection subsequently encountered. About one-fifth of the animals never had any clinically-detectable rejection. An example is shown in Figure 10.

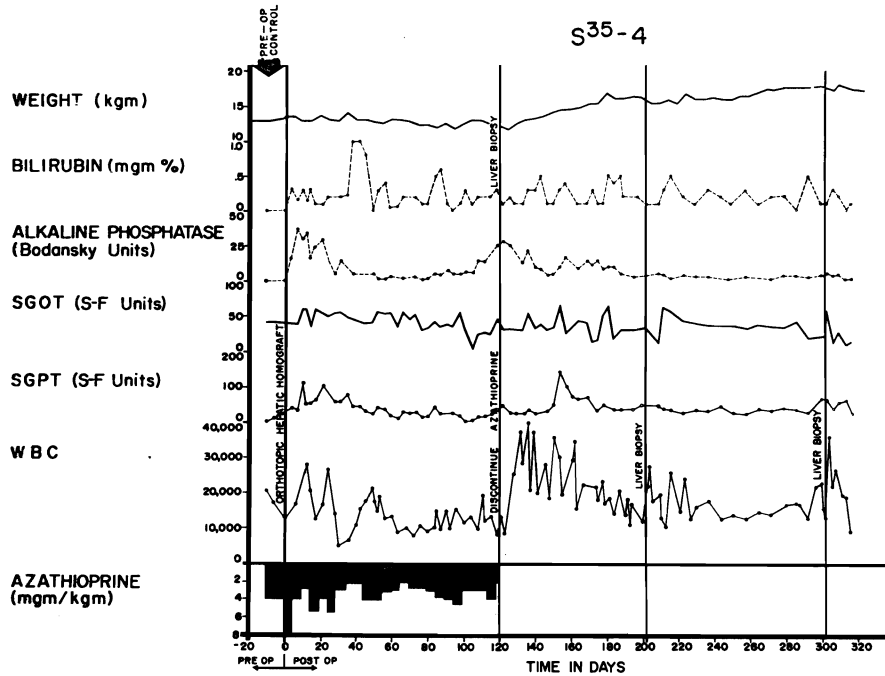


Fig. 10. — Course of an animal which never had any clinically evident homograft rejection. Note the rapid weight gain following cessation of therapy at 4 months. The pronounced leukocytosis after withdrawal of immunosuppression was commonly seen. (By permission of Surgery 58 : July, 1965.)

The dog received a homograft in March, 1964. had only minor early abnormalities in liver function, had all therapy discontinued in 4 months, and has been in good health since. In 6 such animals (Fig. 11) which had all therapy stopped at 4 months, only 1 has had a subsequent rejection and this a non-lethal one. The incidence and timing of successful discontinuation of therapy far exceeds that reported after renal homotransplantation (17-20). Moreover, none of these dogs had evidence of a late graft-versus-host reaction. In some of the dogs, red cell half-life was shortened in the early post-operative period but this did not recur after cessation of therapy (Fig. 12).



Fig. 11. — Six dogs which had all immunosuppressive therapy discontinued 116-123 days after orthotopic liver homotransplantation. Dog 6 did not have a delayed rejection but died 161 days after operation of a massively bleeding duodenal ulcer. Dog 5 had a delayed rejection which developed and reversed spontaneously while off all therapy. The others have had no evidence of delayed rejection. Dogs 1 to 5 are 11 to 6 months postoperative. All are in excellent condition.

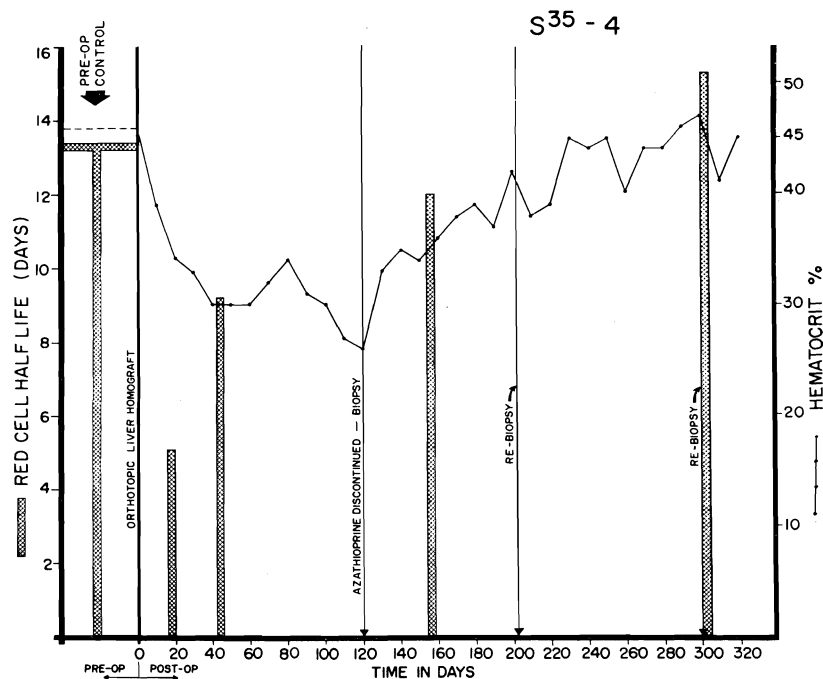


Fig. 12. — Red cell survival and hematocrits in a dog that is still alive 340 days after orthotopic transplantation. Note the sharp reduction in red cell half-life in the first post-operative month, with gradual return toward normal. Red cell survival was not altered by withdrawal of azathioprine at the end of 4 months, but the depressed hematocrit rose sharply during the succeeding months. (By permission of Surgery 53 : July, 1965.)

The biopsy of the dog whose course is depicted in Figures 10 & 12 was normal by light and electronmicroscopy after 4 months (Fig. 13 A) and remained so 6 months later when re-biopsied (Fig. 13 B). In this case, a virtually complete state of host-graft nonreactivity existed between the homograft and its host.

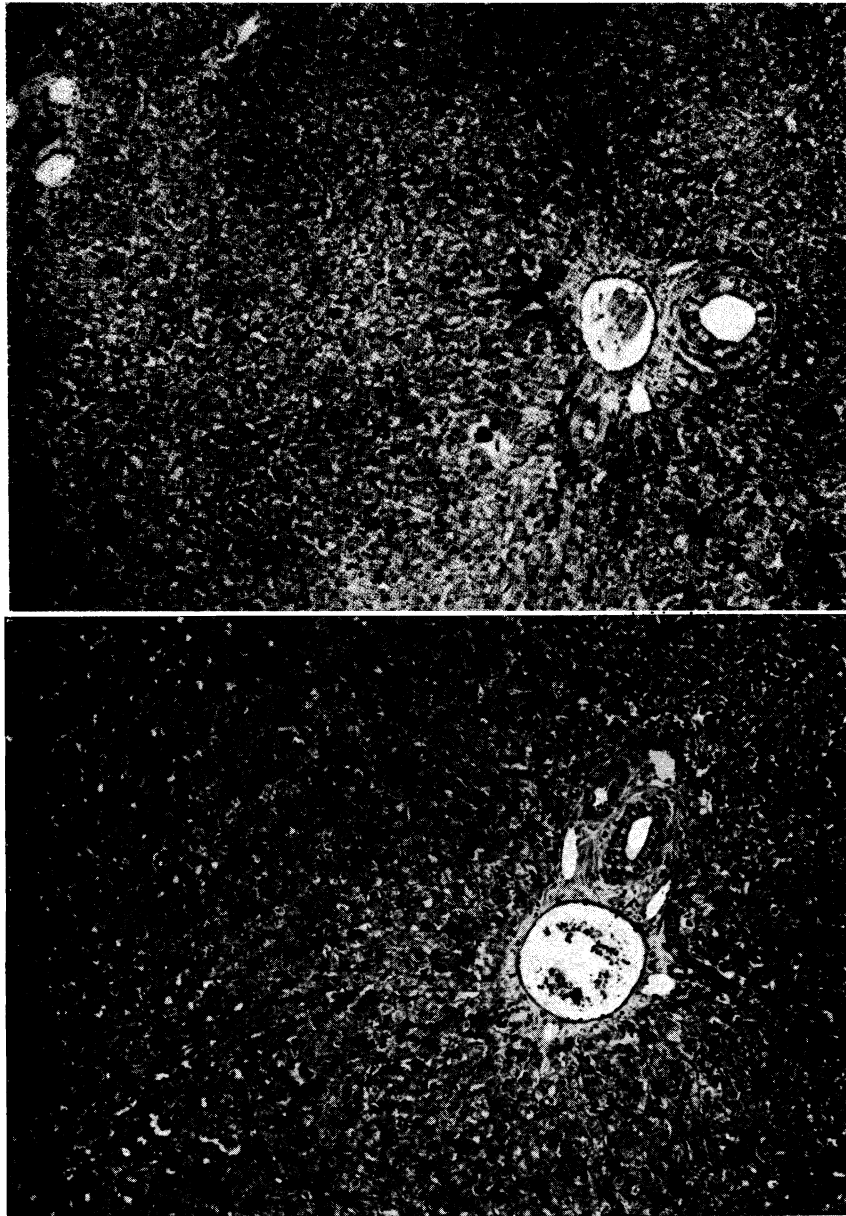


Fig. 13. — Two biopsies from an hepatic homograft. The first (A) was taken after the host had been receiving azathioprine for 120 days. There is evidence of regeneration of hepatocytes at the periphery of the lobules but no other abnormality. All immunosuppressive drugs were then stopped and 182 days later, 302 days after transplantation, sample (B) was obtained. The homograft appears normal. H & E stain. (X 90). (By permission of Surgery 58 : July, 1965.)

At the other end of the spectrum, observed in about one-third of the cases, was an inexorable rejection characterized by relentless deterioration of the liver chemistries, progressive jaundice, and death in all cases in 41 days or less (Fig. 14). The histologic features in these homograft were very similar to those of non-treated controls.

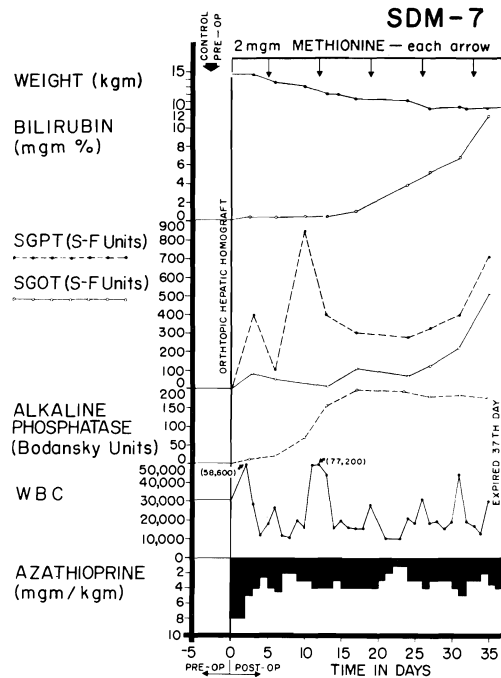


Fig. 14. — An example of inexorable rejection despite immunosuppressive therapy. Determination of the serum bilirubin was the most useful measurement for following the course after homotransplantation since the other abnormalities of liver function depicted can also be caused by azathioprine. (By permission of Surgery 50 : July, 1965.)

Finally, almost exactly one-half of the 84 definitive test animals underwent an obvious rejection which was often of great severity but which was reversible to a greater or lesser extent. Figure 15 depicts an example. After operation, this dog developed extremely poor liver function with a bilirubin that exceeded 6 mg % and collateral rises in the serum enzymes. He lost weight rapidly but as liver function improved, he began eating. The animal is still alive.

Perhaps the most interesting feature of these more than 40 examples was that intensification of immunosuppressive therapy was not used in any. This, we believe, delineates a general feature of transplantation biology which has been incompletely appreciated that rejection is subject to spontaneous remissions. This fact will make caution necessary in ascribing reversal to any preceding changes in therapy.

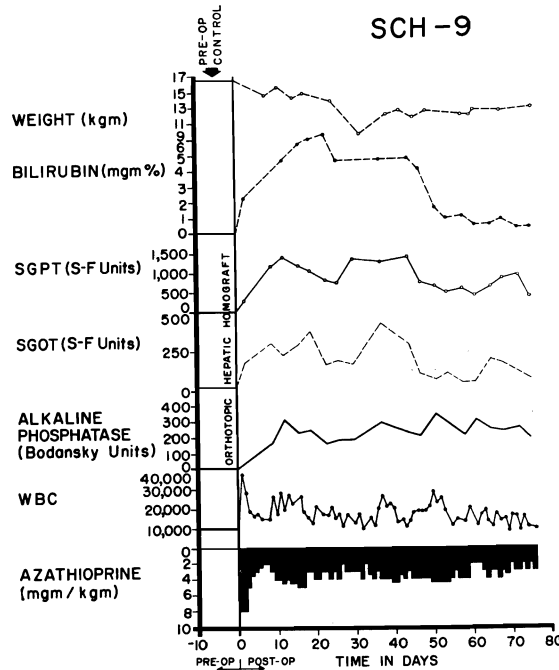


Fig. 15. — Example of a severe but reversible rejection. Note the jaundice at the peak of rejection, but with reversal of this and other abnormalities of liver function despite the fact that the immunosuppressive regimen was not intensified. This animal is still alive. (By permission of Surgery 58 : July, 1965.)

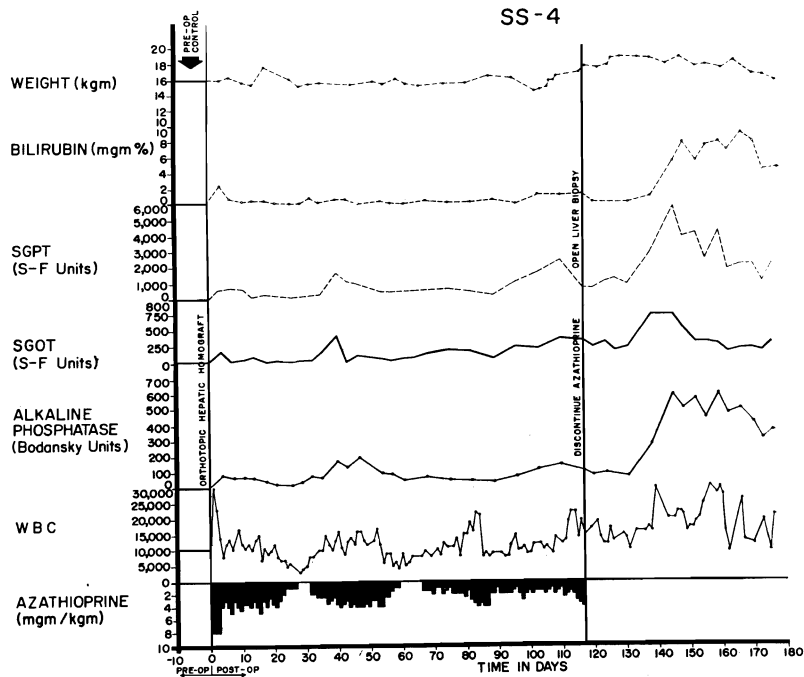


Fig. 16. — Course of an animal which did not have clinically-evident rejection during the first 4 postoperative months. After azathioprine was discontinued, there was deterioration of all liver chemistries, despite which the animal appeared healthy and had little weight loss. The late rejection partially reversed without re-institution of therapy. (By permission of Surgery 58 : July, 1965.)

The course of the animal shown in Figure 16 is an even more striking example of spontaneous reversal of rejection. Jaundice did not occur in the first 120 days after operation at which time therapy was stopped. Subsequently rejection developed, reached its functional zenith, and reversed—all in the absence of all treatment.

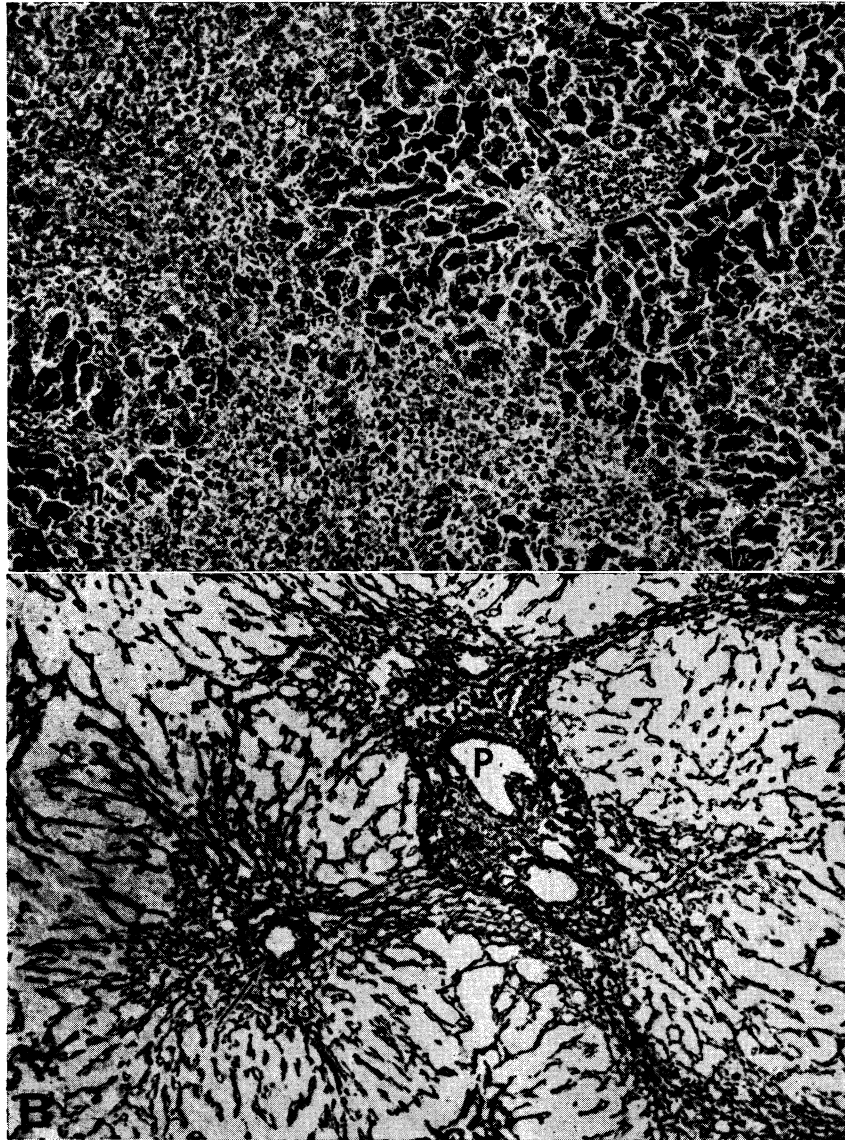


Fig. 17. — Events after homotransplantation of the liver. A) Homograft which was rejected by 15 days despite azathioprine therapy. There is widespread destruction of hepatocytes in the central and middle zones of the lobules. Only a rim of liver cells remain around the portal tract (arrow) which is heavily infiltrated with mononuclear cells. H & E stain. (X 60). B. Architectural distortion following the injury of rejection. Note the collapse and condensation of reticulin around the central vein (arrow). Few infiltrating cells are present, P - portal tract. Reticulin stain (X 60).

The pathologic correlation with the foregoing clinical observations is extremely good and permits tentative reconstruction of the serial events after homotransplantation to the treated host. Early after operation there is a more or less serious attack on the graft. If the animal dies at this time, the histologic picture is indistinguishable from that in the unmodified host (Fig. 17 A). If

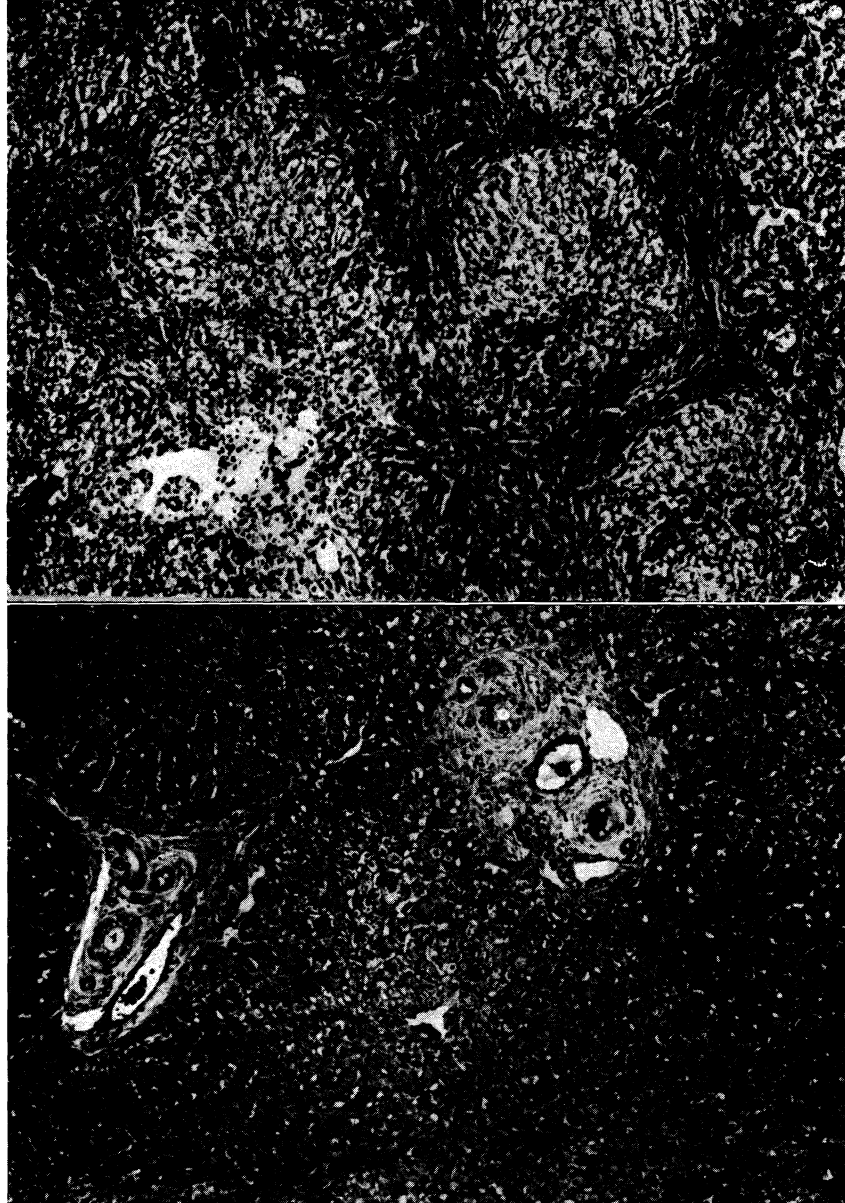


Fig. 18. — Two biopsies from an hepatic homograft. The first (A) was taken after the host had been receiving azathioprine for 121 days. The lobular architecture is distorted by thick bands of connective tissue which link portal tracts to each other and to central veins. Hepatocytes in the pseudolobules of regenerating liver contain much lipid. Azathioprine therapy was then discontinued and 77 days later, 198 days after transplantation, the second biopsy (B) was taken. There has been a striking improvement in the general liver architecture. Connective tissue bands are no longer so obvious and the liver cells look more healthy. H & E stain (X 60). (By permission of *Surgery* 58 : July, 1965).

the animals survive, many or even most of the infiltrating cells retreat from the graft, leaving large areas of necrosis.

Secondary to the necrosis there are many areas of reticulin collapse and condensation most heavily concentrated in the central areas (Fig. 17 B). From this point onward, the dominant features are those of repair in which the most affected areas acquire fresh connective tissue (Fig. 18 A). Some pyronine-positive cells often remain but rapid destruction of hepatocytes has ceased. A pseudolobular pattern often results with much connective tissue but with relatively few infiltrating cells (Fig. 18 A).

Repair may continue even after cessation of therapy. In Figure 18 A is a biopsy obtained after 4 months, at which time azathioprine was stopped. The abnormalities in this liver are evident. A substantial further improvement continued for the next 11 weeks when the biopsy in Figure 18 B was obtained of a greatly improved liver.

AUXILIARY LIVER HOMOTRANSPLANTATION

Historically, the first whole organ liver transplants were carried out by Welch (1, 2) without removal of the host's own liver and with insertion of the homograft into the pelvis by a technique similar to that shown in Figure 19 A. With this preparation, the arterial supply is physiologically normal, but the ectopic liver receives its portal inflow from the inferior vena cava instead of the splanchnic venous system. Welch (1), Goodrich (2), Mehrez (7), Hallenbeck (21), Sicular (6), Paronetto (11) and Hagihara (9) all studied variants of this preparation in animals not treated with immunosuppression. The period of bile excretion which was obtained from such auxiliary homografts in unmodified hosts was 3 or 4 days.

More recently, auxiliary transplantation has been tested in dogs treated with azathioprine (8, 21). Such auxiliary homografts were quickly found to be much more severely damaged than had been observed after orthotopic homotransplantation. The pelvic liver underwent a rapid and drastic reduction in size, usually beginning within 2 weeks after operation (Fig. 20). Histologically, the diminutive liver had marked centrilobular hepatocyte loss, but with relatively good preservation of the blood vessels and the duct system. With the dissolution of hepatocytes, there was reticulin collapse.

It was subsequently shown that this acute atrophic process resulted at least in part from the abnormal way in which the ectopic livers had been revascularized (10). If auxiliary transplantation to the treated host is carried out with a comparable technique but with portal revascularization from the recipient splanchnic venous system (Fig. 19 B), the homograft shrinkage is no longer observed (Table 1). Instead, there is a similar atrophic process in the recipient animal's own liver (Fig. 21). Under these

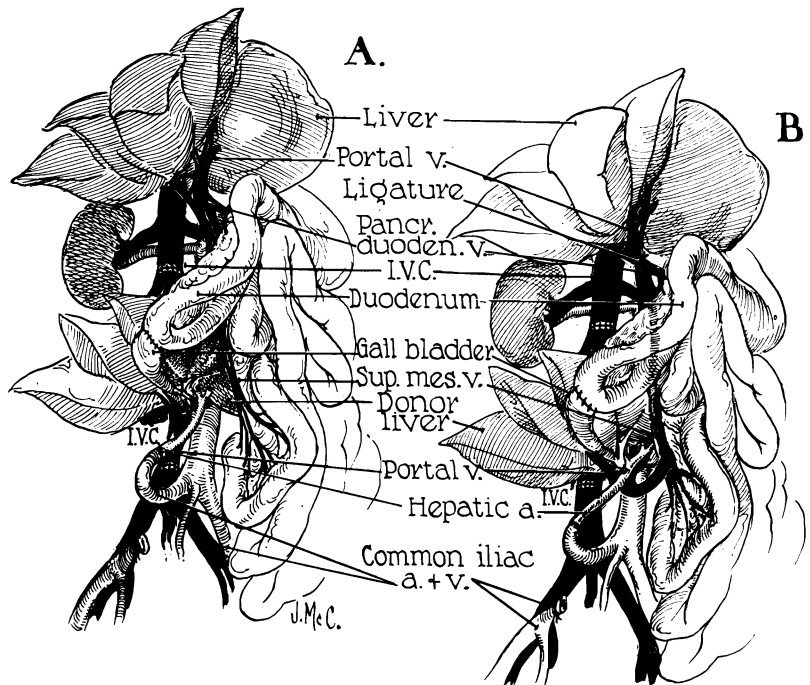


Fig. 19. — Auxiliary liver transplantation.

A) Method of Welch. Note that the portal venous inflow is from the inferior vena cava. The homograft undergoes rapid atrophy.

B) Modification of above method in which the non-hepatic splanchnic flow is diverted through the homograft. With this preparation, the homograft retains its size and the animal's own liver undergoes shrinkage. It is usually more convenient to bring the hepatic artery behind rather than in front of the portal vein as depicted. (By permission of Surg., Gynec. & Obst. 120 : June, 1965.)



Fig. 20. — Results with auxiliary liver transplantation when revascularized by the method shown in Figure 19A. Note the marked atrophy of the homograft (right) with no change in the animal's own liver (left). The general morphology of the homotransplant is quite recognizable. The two specimens were obtained at sacrifice 45 days after auxiliary transplantation.

TABLE I

RESULTS AFTER AUXILIARY HOMOTRANSPLANTATION BY THE METHOD SHOWN IN FIGURE 19 B
 IN WHICH NON-HEPATIC SPLANCHNIC FLOW IS DIVERTED THROUGH THE ECTOPICALLY-PLACED HOMOGRRAFT
 NOTE THAT THE AUXILIARY ORGAN OUTWEIGHED THE RECIPIENT ANIMAL'S CWN LIVER
 IN EVERY CASE DESPITE THE FACT THAT THE DONOR DOGS WERE ALL OF SMALLER SIZE

Dog —	Weight of Donor (kg)	Weight of Recipient (kg)	Total Survival (days)	Removal Host Liver	Survival after Hepatectomy (days)	Weight of Homograft at Autopsy (gm)	Weight of Host Liver at Autopsy or Hepatectomy (gm)
2	14.1	15.2	28	No	Not done	325	322
4	14.5	19.5	25	No	Not done	380	306
5	15.4	18.2	126	Yes	49	656	225
8	18.6	20.5	69	Yes	8	478	211
9	18.2	18.6	52	No	Not done	440	300
10	20.0	22.9	101	Yes	28	492	310

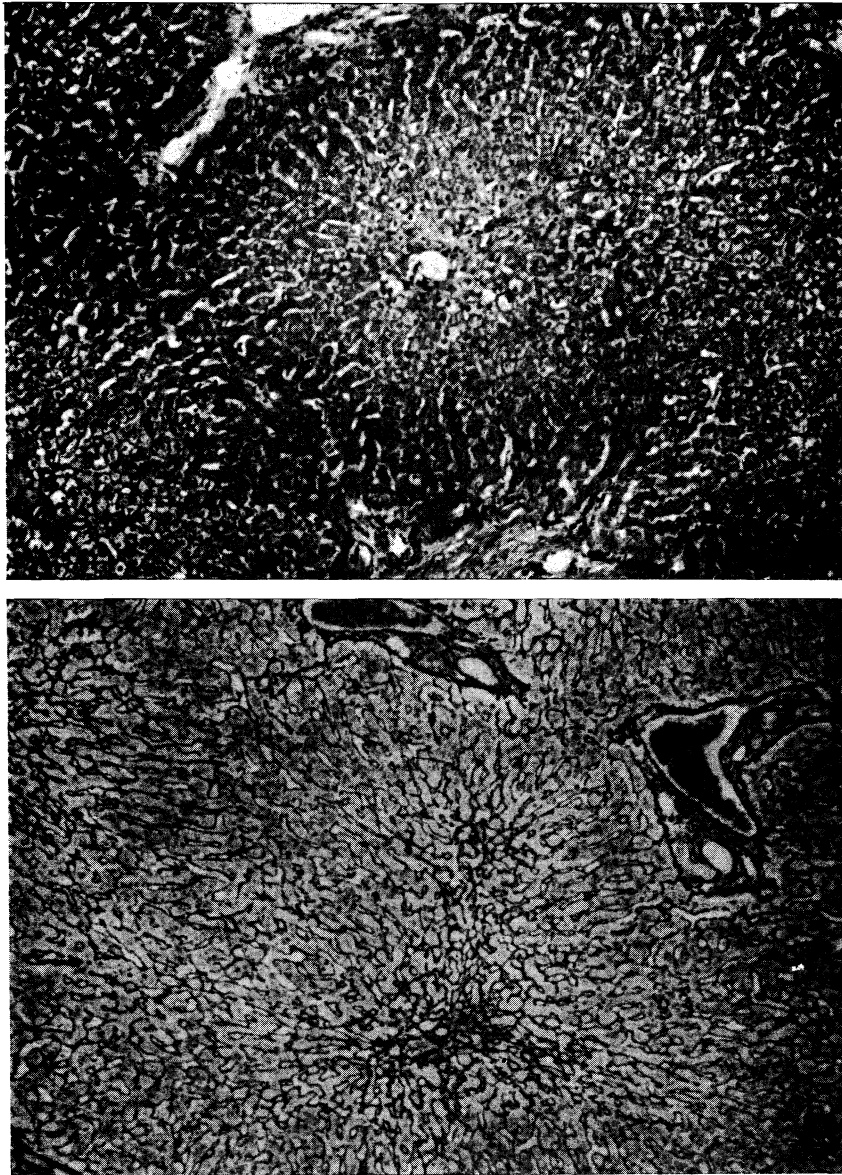


Fig. 21. — Centrilobular necrosis which results from depriving either the homograft or the recipient animal's own liver of non-hepatic splanchnic flow. The illustrated lesions were produced in the recipient's own liver in experiments in which the auxiliary homograft was revascularized as shown in Figure 19B.

A) 35 days after operation. H & E stain. (X 65).

B) Another dog 51 days after transplantation. The dense accumulation of reticulin and collagen fibers in the lower middle part of the field are around the central vein. Reticulin stain. (X 90). (By permission of *Surg. Gynec. & Obst.* 120 : June, 1965.)

circumstances, the auxiliary homograft was found to be able to sustain life inasmuch as several animals had protracted survival after removal of their own shrunken autologous liver at a second-stage operation (Fig. 22).

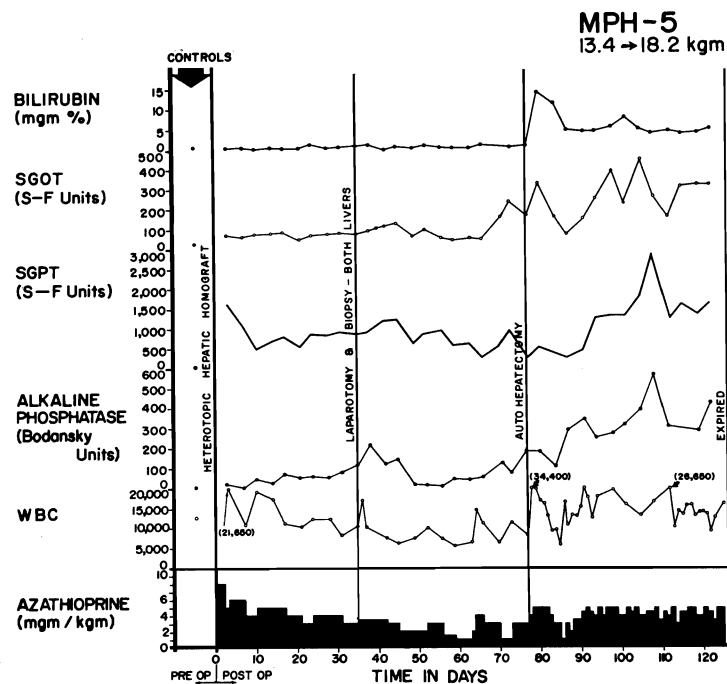


Fig. 22. — Clinical course of a dog whose homograft was vascularized as shown in Figure 19B. Note the abrupt bilirubinemia which followed removal of the dog's own liver (autohepatectomy). After autologous hepatectomy, the dog lived for 49 days with sole dependence upon the homograft, ultimately dying as the result of a wound dehiscence and evisceration which followed repeat biopsy. (By permission of Surg., Gynec. & Obst. 120 : June, 1965.)

These experiments have done much to clarify the physiologic requirements for homotransplantation of an auxiliary liver. Apparently there is a competition between the co-existing livers for some metabolite or other substance in the portal venous blood. That organ which has first access to the portal flow retains its functional and morphologic integrity. The other organ, whether it be the homograft of the autologous liver, undergoes atrophy predominantly affecting the centrilobular area.

Whether this substrate competition will prove to be of important clinical significance is not known. In the benign diseases for which liver transplantation might be contemplated, there would be pre-existing failure of the recipient patient's liver, so that it might be incapable of metabolite extraction. Should this prove to be the case, the exact method of auxiliary homograft revascularization will be less critical.

HUMAN LIVER TRANSPLANTATION

Eight attempts have been made at human liver homotransplantation, 7 in the United States and 1 in France. In 7 of these cases, the patient's diseased liver was removed and an orthotopic transplant performed; but in Absolon's case (22), the liver was rearterialized from the iliac artery and placed in the left paravertebral gutter without recipient hepatectomy. The summaries of these eight cases are given in Table 2. The indication for operation was cancer of the liver in six instances and biliary atresia in the other two.

The technical features of orthotopic clinical transplantation are similar to those in the dog, with a few important differences. First, the use of cadaveric homografts is mandatory, a fact which increases the difficulty of obtaining well-functioning and minimally-damaged tissue. In order to provide the donor liver with hypothermia and with oxygen from the time of death until its removal, a pump oxygenator has been used (23) to provide the corpse with an artificial circulation (Fig. 23). As soon as possible after death of the donor, cannulas are inserted into the abdominal aorta and inferior vena cava and perfusion begun from a glucose-or electrolyte-primed circuit into which a heat exchanger is incorporated.

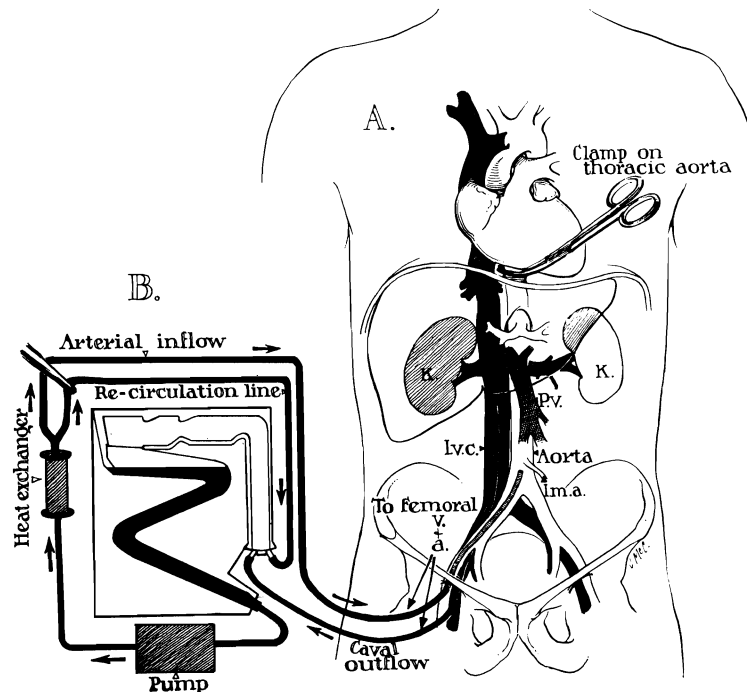


Fig. 23. — Technique of extracorporeal cadaver perfusion. Catheters are inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. The extracorporeal circuit is primed with heparinized glucose or electrolyte solution to which procaine is added. The cadaver is anticoagulated with the first surge of the pump. Temperature control is provided by the heat exchanger. (By permission of W.B. Saunders Co. **Experience in Renal Transplantation**, 1964.)

TABLE II
WORLD EXPERIENCE WITH CLINICAL HOMOTRANSPLANTATION OF THE LIVER

Case	Reference	Date of Transplant	Donor-Recipient Age - Sex	Donor-Recipient Blood Types	Recipient Disease	Cause of Donor Death	Donor Death to Revascularization	Survival	Cause of Death
1 (Denver)	8, 13, 25	3-1-63	3 M - 3 M	A / - A /	Biliary atresia	Cardiac arrest during craniotomy	420 min	4 Hr	Operative hemorrhage
2 (Denver)	8, 13, 25	5-5-63	55 M - 48 M	A / - A /	Cirrhosis and hepatoma	Terminal brain tumor	152 min	22 days	Pulmonary emboli
3 (Denver)	8, 13, 25	6-24-63	69 M - 67 M	O - - O /	Cholangio carcinoma	Stroke	192 min	7 1/2 days	Pulmonary emboli; GI bleeding
4 (Denver)	8, 13	7-16-63	73 M - 52 M	O / - A -	Cirrhosis and hepatoma	Coronary	174 min	6 1/2 days	Pulmonary emboli; congestive heart failure

TABLE II (suite)
WORLD EXPERIENCE WITH CLINICAL HOMOTRANSPLANTATION OF THE LIVER

Case	Reference	Date of Transplant	Donor-Recipient Age - Sex	Donor-Recipient Blood Types	Recipient Disease	Cause of Donor Death	Donor Death to Revascularization	Survival	Cause of Death
5 (Denver)	8, 13	10-4-63	64 M - 29 F	0 / - 0 /	Cirrhosis and hepatoma	GSW head (Suicide)	164 min	23 days	Common duct necrosis; bime peritonitis; ? rejection; hemorrhagic diathesis
6 (Moore)	24	September 1963	Not stated	Not stated	Metastatic colon carcinoma	GSW head (Homicide)	Not stated	12 days	Liver failure
7 (Demirleau)	26	January 1964	71 M - 75 M	0 - A	Metastatic colon carcinoma	Bilateral gangrene of legs	180 min	3 Hr	Operative hemorrhage
8 (*) (Absolon)	22	11-3-64	2 F - 1 M	A / - 0-	Biliary atresia	Cardiac failure post-pump	About 4 Hr	13 days	Common duct necrosis; bile peritonitis; septicemia

(*) Heterotopic transplant to left iliac system. Child died while on pump oxygenator support, and perfusion was continued until the liver was removed. Period of completely absent circulation during insertion of liver was 37 minutes.

After dissection of the homograft is completed, it is removed and further flushed through the portal vein with chilled lactated Ringer's solution (Fig. 24 D).

In the recipient patient, the problems of hepatectomy are usually greatly complicated by the presence of the disease for which the operation is performed. Hepatomegaly or portal hypertension were present in all cases thus far treated, making removal an extremely formidable procedure. The recipient operation usually requires a thoracoabdominal incision. The restraining ligaments of the liver are incised (Fig. 24 A) and the principal structures leaving and entering the liver are skeletonized (Fig. 24 A-C). This phase of the operation may be done at a separate stage from the definitive transplant.

As mentioned earlier, failure in the dog to decompress the occluded portal vein during removal of the recipient liver and placement of the homograft rapidly leads to irreversible intestinal wall damage. In the human, occlusion of the portal vein has been found to be well tolerated in such cases, presumably due to the

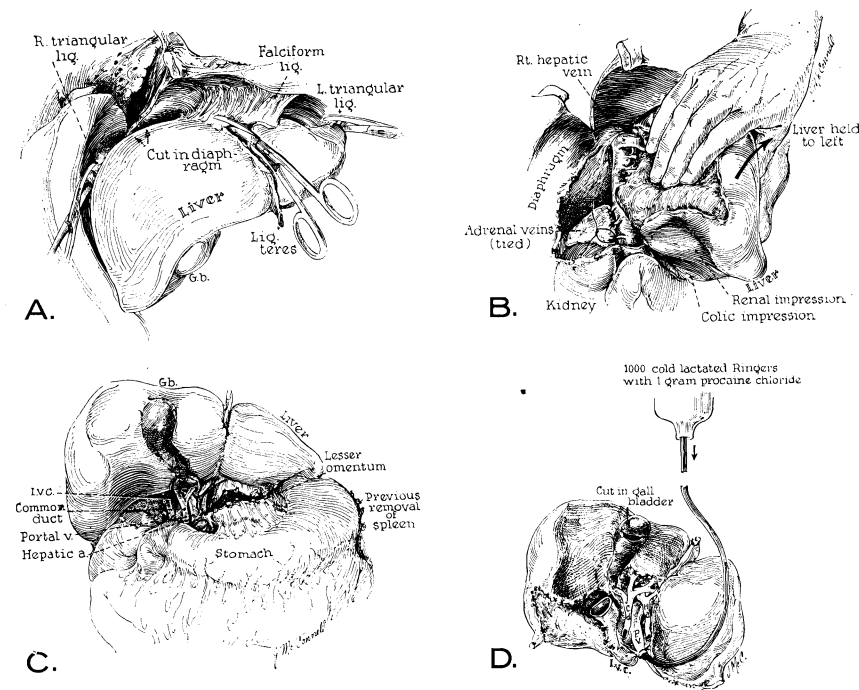


Fig. 24. — Technical steps in removal of the cadaveric homograft. All maneuvers except D are also carried out in excising the recipient patient's own diseased liver.

- A) Incision of restraining ligaments of liver.
- B) Dissection of raw area and ligation of adrenal veins.
- C) Completed dissection of the gastrohepatic ligament.
- D) Cold perfusion of the excised homograft. Note that the gallbladder is opened. Failure to remove bile may result in autolysis of the extrahepatic biliary system during the period of devascularization. (By permission of Surg., Gynec. & Obst. 117 : 659, 1963.)

much richer collateral connections with the systemic venous system. Decompression of the occluded inferior vena cava is, however, probably important (Fig. 25 A).

After the external bypass from the inferior to the superior vena cava is inserted, the diseased liver is removed (Fig. 25 B) and the homograft inserted in the normal anatomic position. Anastomosis of the supra- and infrahepatic inferior vena cava, the portal vein, and the hepatic artery is carried out with standard vascular technique (Fig. 25 C-D). Internal biliary drainage is provided by choledochocholedocostomy (Fig. 25 D) or by cholecystenterostomy.

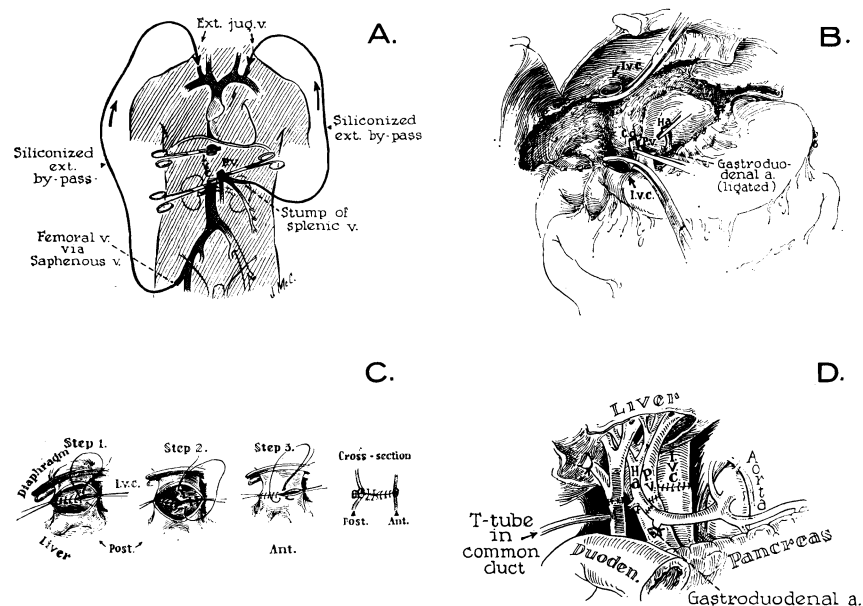


Fig. 25. — Technical steps in human homotransplantation.

A) External bypass systems used for decompression of the blocked venous pools. The external shunt from the portal system was shown to be unnecessary and only the vena caval bypass is required.

B) The operative field after removal of the recipient patient's diseased liver.

C) Anastomosis of the suprahepatic vena cava. Great care must be exercised to prevent suture line leakage since exposure of this suture line is difficult after the homograft is in place.

D) Completed anastomoses of the portal structures. Note that the T-tube is placed through a stab wound in the recipient portion of the reconstructed common duct. An alternative method of internal biliary drainage is with cholecystoenterostomy. (By permission of Surg. Gynec. & Obst. 117 : 659, 1963.)

During the actual homotransplantation, high levels of fibrinolysins have been observed in all of the cases treated in Denver, leading to fatal hemorrhage in Case 1. Within a few hours after revascularization of the homograft, this abnormal situation is spontaneously alleviated and may be followed by a period of hypercoagulability. If clot-promoting drugs such as epsilon-aminocaproic acid (EACA) or purified fibrinogen are given during the

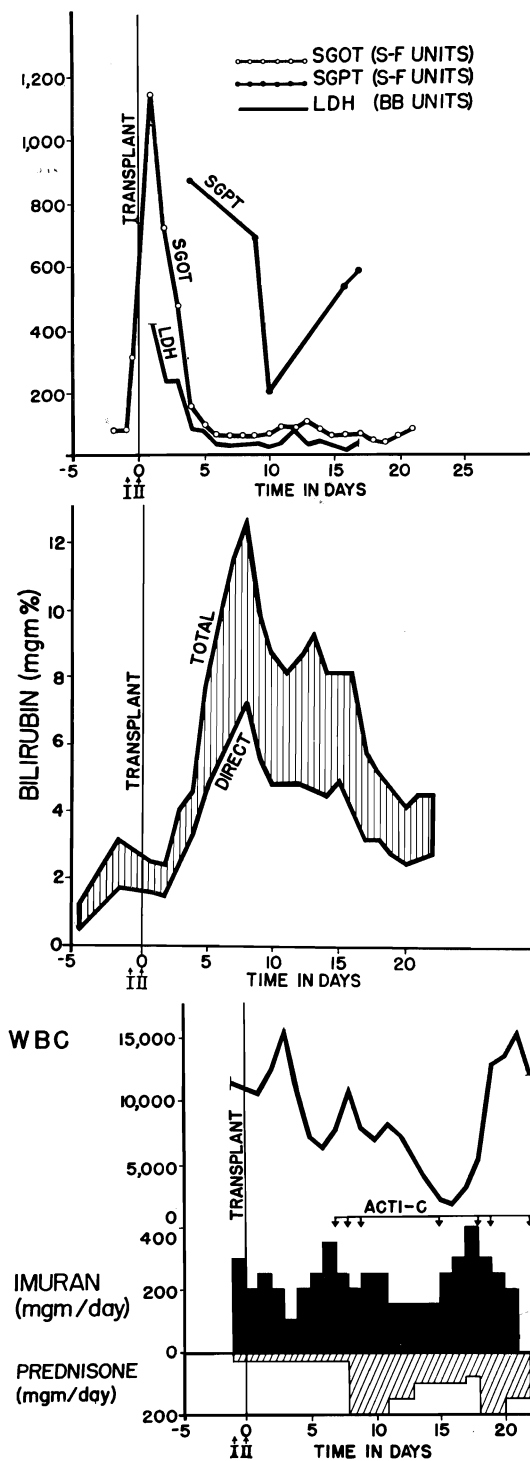


Fig. 26. — Changes in a patient who received an orthotopic liver homograft. **Upper panel** - - changes in SGOT, LDH and SGPT. Note the acute liver injury after operation which was apparently due to organ ischemia. **Middle panel** - - changes in total and direct bilirubin. The early rise in bilirubin was probably also due to anoxia rather than rejection. **Bottom panel** - - immunosuppressive therapy used. The patient died after 21 days of multiple pulmonary emboli. (By permission of Surg., Gynec. & Obst. 117 659, 1963.)

fibrinolytic phase, the penalty has been found to be subsequent intravascular thrombosis, a complication which led to or contributed to the death of 3 patients in the Denver series.

Despite the provision for preservation of the cadaveric liver, varying degrees of acute ischemic injury were detected in all of the Colorado cases, with acute rises in SGOT, SGPT, and LDH, and temporarily deepening jaundice (Figs. 26, 27). This immediate damage did not preclude early survival since it proved to be partially reversible in 4 of the 5 patients.

The immunosuppressive regimen employed differed from that described earlier for the dog in that large doses of prednisone and intermittent doses of actinomycin C were given for the clinical cases (Figs. 26, 27). Clear evidence of uncontrolled rejection was not present in the cases treated at the University of Colorado and poor terminal function was present in only one (Fig. 27). In the

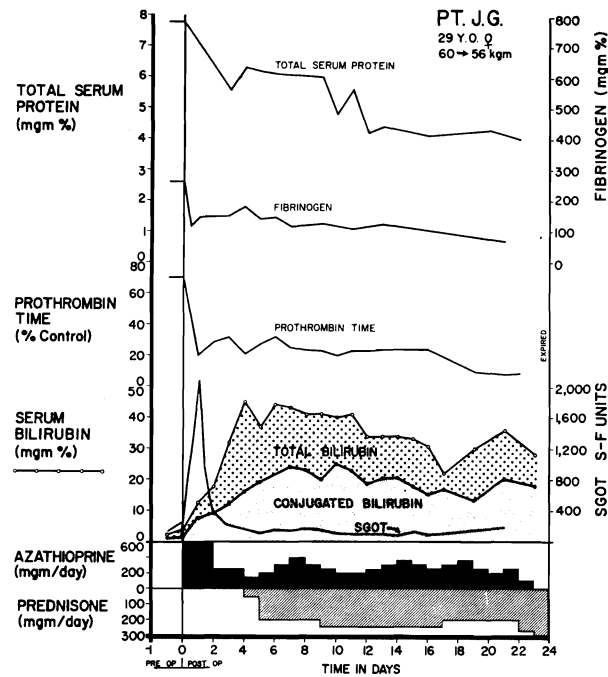


Fig. 27 — Serial chemistries in Patient 5 from the Denver series of orthotopic homotransplants. Note serious abnormalities in various measurements. The immunosuppressive therapy is depicted at the bottom. The increase in SGOT immediately after operation was the highest observed in any case. The poor liver function was probably due to severe ischemic injury. The patient died after 23 days of bile peritonitis following necrosis of the donor portion of the reconstructed common duct which thought to have occurred on the 17th postoperative day. A similar response to surgery after use of a severely-injured homograft was observed by Moore (24). (By permission of *Ann. Surg.* 160 : 411, 1964.)

last case, there was disruption of the common duct anastomosis which was probably due to inadequate blood supply of the donor portion of the reconstructed common duct.

The function obtained after Absolon's auxiliary hepatic homotransplantation (22) is of special interest since this is the only example of auxiliary human liver transplantation to date. The homograft was subjected to a minimum of anoxia since the donor patient died while on cardiopulmonary bypass. During the first

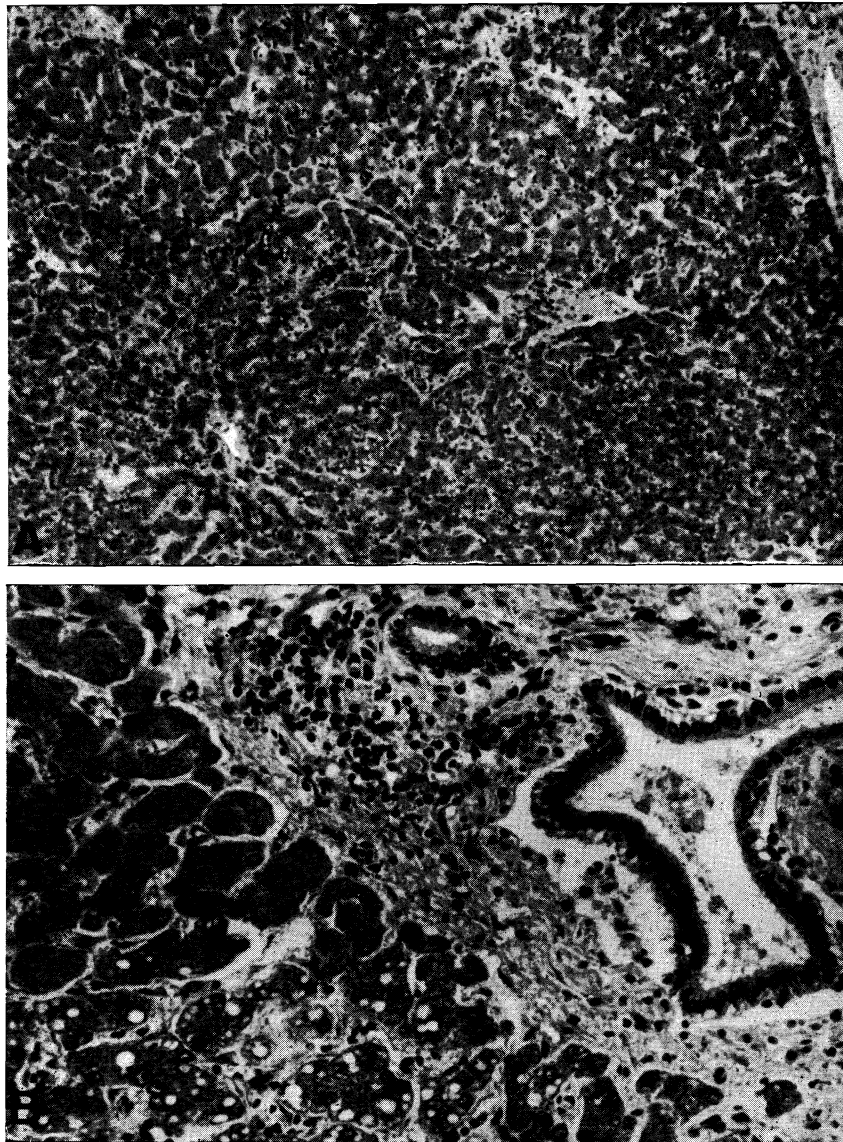
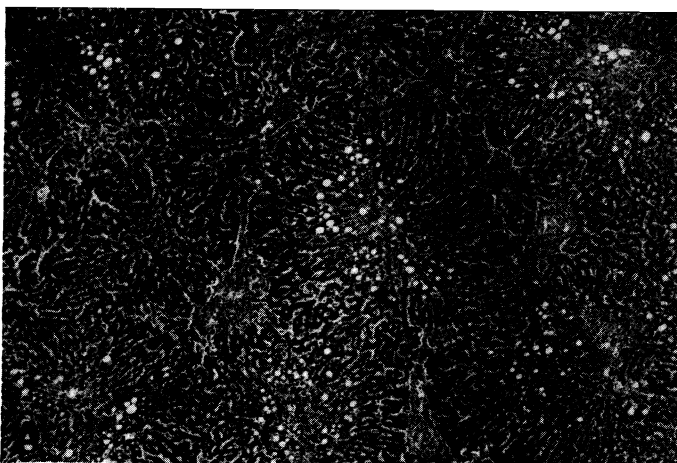


Fig. 28. — Case 4 of the Colorado series. Treated human orthotopic hepatic homograft at 6 1/2 days.

A) The lobular pattern is normal but the hepatocytes contain fine fat droplets. H & E stain. (X 60.)

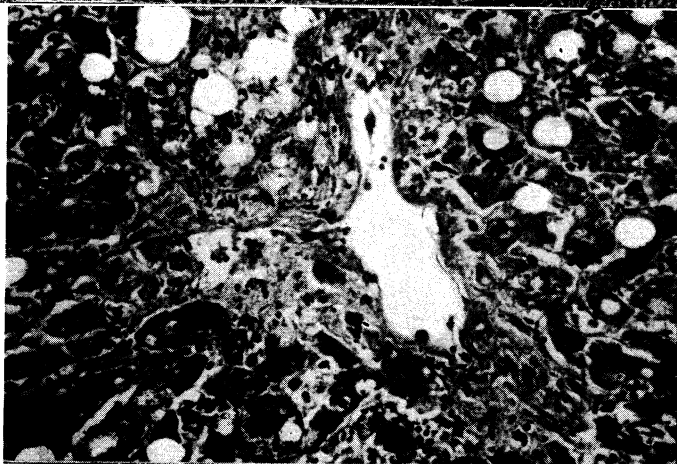
B) The portal tract is infiltrated by a small number of cells, most of which are lymphocytes. Many of the hepatocytes contain lipid droplets in their cytoplasm. H & E stain. (X 120.)



A

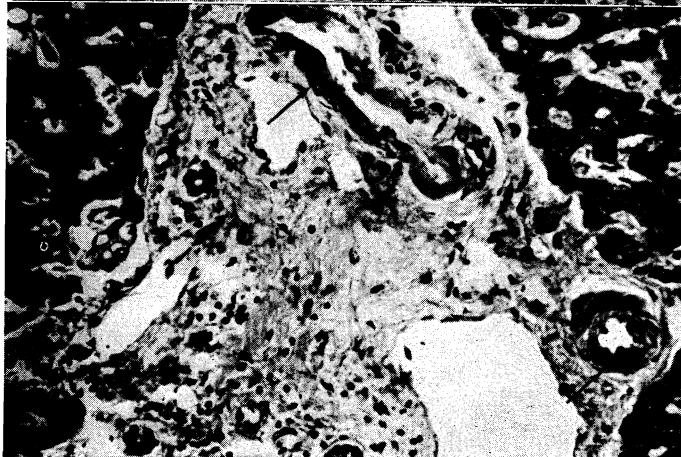
Fig. 29. — Case 3 of the Colorado series. Treated human orthotopic hepatic homograft at 7 1/2 days.

A) The cytoplasm of the centripetal and midzonal hepatocytes contains large droplets of fat. The portal tracts are conspicuous because of some bile duct proliferation and cellular infiltration. H & E stain. (X 40.)



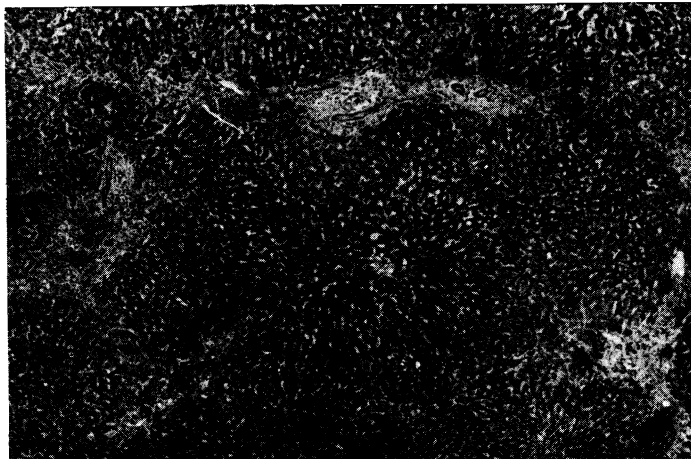
B

B) The hepatocytes immediately adjacent to the vein have disappeared and those just peripheral to this area are atrophic and contain droplets of fat in their cytoplasm. Cellular infiltration around the hepatic vein is slight. H & E stain. (X 100.)



C

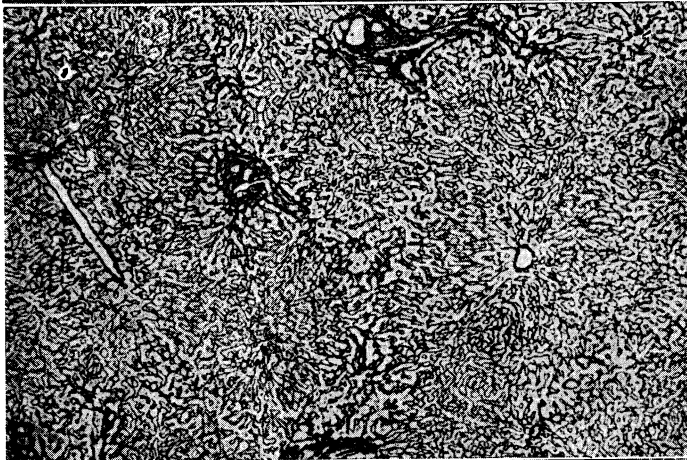
C) Three small branches of the hepatic artery (arrows) show fibrinoid necrosis of their walls. The connective tissue contains a few infiltrating mononuclear cells. H & E stain. (X 90.)



A

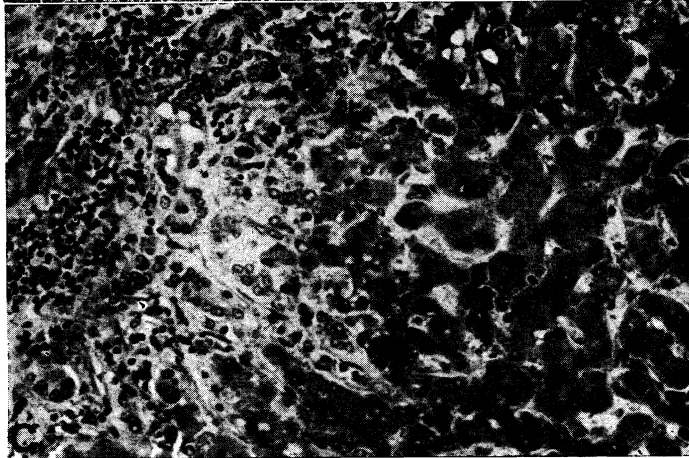
Fig. 30. — Case 2 of the Colorado series. Treated human orthotopic hepatic homograft at 22 days.

A) The centers of the lobules appear dark because the hepatocytes contain excess lipofuscin. The increase in portal connective tissue was probably present before homotransplantation. There is a patchy cellular infiltration, particularly in the smaller portal tracts. H & E stain. (X 40.)



B

B) The lobular architecture is essentially normal. Reticulin stain. (X 40.)



C

C) The portal tract is infiltrated with mononuclear cells. There is proliferation of small bile ducts. H & E stain. (X 90.)

10 postoperative days, the recipient patient, who had biliary atresia, had a fall of serum bilirubin from 22 mg % to 5 mg %. Death occurred at 13 days from septicemia and disruption of the cholecyst-enterostomy.

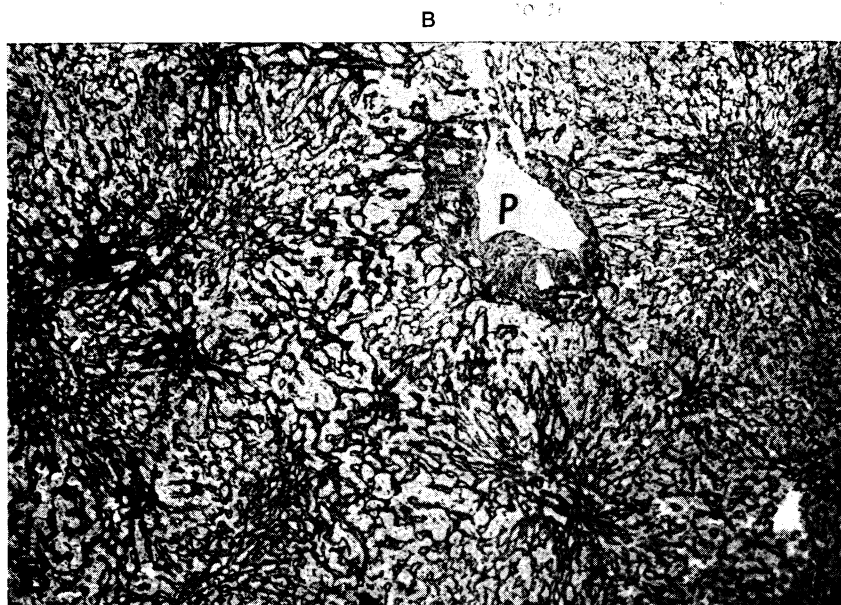
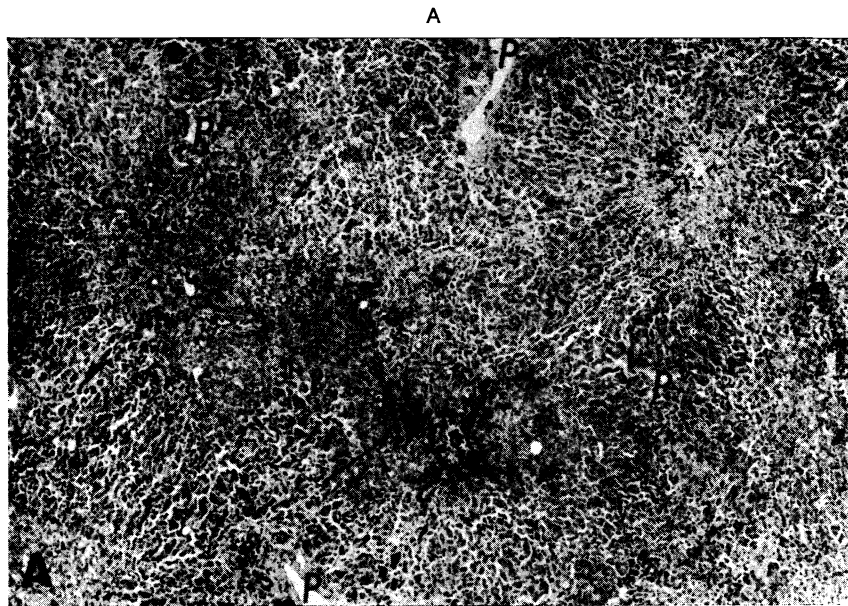


Fig. 31. Case 5 of the Colofado orthotopic series: Homograft at 23 days.
 A) There is centrilobular and midzonal necrosis of liver cells. Only those near to portal tracts (P) survive. Some hemorrhages are present in the central zones (arrow). H & E stain. (X 50.)
 B) There is collapse of the supporting centrilobular reticulin where liver cells have undergone necrosis. P - portal tract. Reticulin stain. (X 50.)

The pathologic features of the 5 human homografts treated at the University of Colorado have been previously reported (8, 13, 25) but were recently reviewed and re-interpreted by one of us (K.A.P.) in light of the vast amount of animal pathologic material which had subsequently been analyzed. One homograft was unusual (Case 1) in that the whole liver had undergone autolysis, probably due to the 7 hours of partial or complete anoxia which preceded restoration of circulation through the liver.

The other 4 cases all showed some cellular infiltration around the portal veins (Figs. 28-31). Although varying in density from one portal tract to another, it was never severe and was often mild. The larger portal tracts were rarely more than lightly infiltrated. Eighty-five to 90% of the cells were small lymphocytes, between 5 to 10% were pyroninophilic cells, and the remainder were neutrophils and the occasional eosinophile. Of the pyroninophilic cells, some were larger lymphoid types while a few were plasma cells. Only in one case were these cells present around the central veins (Fig. 29 B). There were foci of fibrinoid necrosis in the walls of several of the small branches of the hepatic artery in 2 of the homografts (Fig. 29 C). Centrilobular and midzonal necrosis of hepatocytes was the outstanding feature of the longest lived case (Fig. 31), but the others only showed atrophy and disappearance of the liver cells immediately adjacent to the central veins (Fig. 29 B, 30 A). Various degrees of collapse of the central part of the lobular reticulin framework were present in 3 of the 4 cases and were accompanied by centrilobular cholestasis.

It is interesting that of the 4 cases that survived the immediate postoperative period, there was relatively good preservation of the general lobular architecture and cell structure in 3, that only one case showed the extensive centrilobular liver cell necrosis that is so common in treated canine hepatic homografts, and that cellular infiltration was not severe in any. These histological findings support the contention that the homograft reaction played no decisive role in the death of 4 of the patients. The centrilobular and midzonal necrosis in the homograft from the patient who lived 23 days may have been due to a homograft reaction, but other factors could have accounted partly or entirely for these changes.

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SUMMARY

During the past 10 years, much has been learned about homotransplantation of the whole liver using either a replacement (orthotopic) homograft or an auxiliary organ which is inserted at an ectopic site without removal of the recipient's own liver. The available information concerning these operations has been reviewed from animal experiments, and from the handful of attempts at clinical application.

RESUME

Depuis 10 ans, de nombreuses études ont été faites concernant l'homotransplantation de foie entier, soit par un remplacement (orthotopique) en homogreffe, ou par l'insertion d'un organe auxiliaire, à une place ectopique, sans qu'on enlève le foie du receveur. Les observations valables concernant ces opérations sont revues, à partir de l'expérimentation chez l'animal et à partir des nombreuses tentatives d'application clinique.

ZUSAMMENFASSUNG

Seit 10 Jahren wurden zahlreiche Studien unternommen zur Homotransplantation der ganzen Leber, entweder als orthotopischer Ersatz durch ein Homotransplantat, oder durch Überpflanzung eines Hilfsorgans an ektopischer Stelle ohne die Leber des Versuchsindividuum wegzunehmen. Die Berichte solcher sowohl tierexperimenteller als auch klinischer operativer Versuche werden durchgesehen.

RESUMEN

Se ha hecho desde 10 años, numerosos estudios sobre el homotransplante del hígado entero, sea por reemplazo (ortotónico) en homoinjerto, ó insertando órgano de auxilio, en sitio ectópico, sin sacar el hígado del que recibe. Se pasa en revista las observaciones valables concerniendo estas operaciones, desde experimentación animal y desde numerosos ensayos de aplicación clínica.

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