HEPATIC TRANSPLANTATION

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Since the spring of 1963, a number of attempts have been made in several centers at homotransplantation of the human liver. All eventually resulted in death of the patients, the maximum survival being five weeks. These experiences and the experimental background upon which the clinical trials were based have been exhaustively reviewed in journals[20,21,25] and in a recent text.[22] Another summary does not seem justified.

Instead, an attempt will be made to identify the factors which contributed to the failures. By and large these were the same whether the operations had involved total excision of the recipient's diseased liver and its replacement with a homograft (orthotopic transplantation) or provision of a heterotopically placed homograft without recipient hepatectomy (auxiliary transplantation). The extent to which these deficiencies can be corrected will determine the feasibility of such undertakings in the future.

Faults of Immunosuppression

There is no reason to suppose that prevention of rejection is more difficult with liver than with renal or other kinds of homografts. Indeed, the converse is true. The results with orthotopic transplantation of the liver in dogs treated with azathioprine[23] have been as good or better than with kidney transplantation to comparably treated hosts. Several animals from a series of experiments conducted in 1964 are still alive from two and a half to three years after receipt of orthotopic homografts from nonrelated mongrel donors. Furthermore, a surprisingly large number of these dogs required azathioprine for only the early postoperative period. In Figure 1, the course is shown of an animal which was given azathioprine for the first four months. After cessation of all therapy, he has lived with completely normal hepatic function for more than two and a half years. Biopsies after four, eight, and twelve postoperative months were all normal.

As with canine renal homotransplantation, the use of azathioprine alone permits really long-term survival in 10 to 20 per cent of animals with orthotopic liver grafts. Obviously, effective clinical therapy cannot be provided with this single agent. Fortunately, the addition of prednisone, which has a synergistic action with azathioprine, has permitted kidney transplantation in man to be carried out with moderate success. The same drug combination in recipients of liver homografts has proved to be unacceptably dangerous.

In Denver, six orthotopic transplantations have been performed, with operative survival in five. During their postoperative intervals of six to twenty-three days, all five patients developed some evidence of sepsis, including pulmonary infection in every case. The degree of immunosuppression which can often be tolerated after the less traumatic procedure

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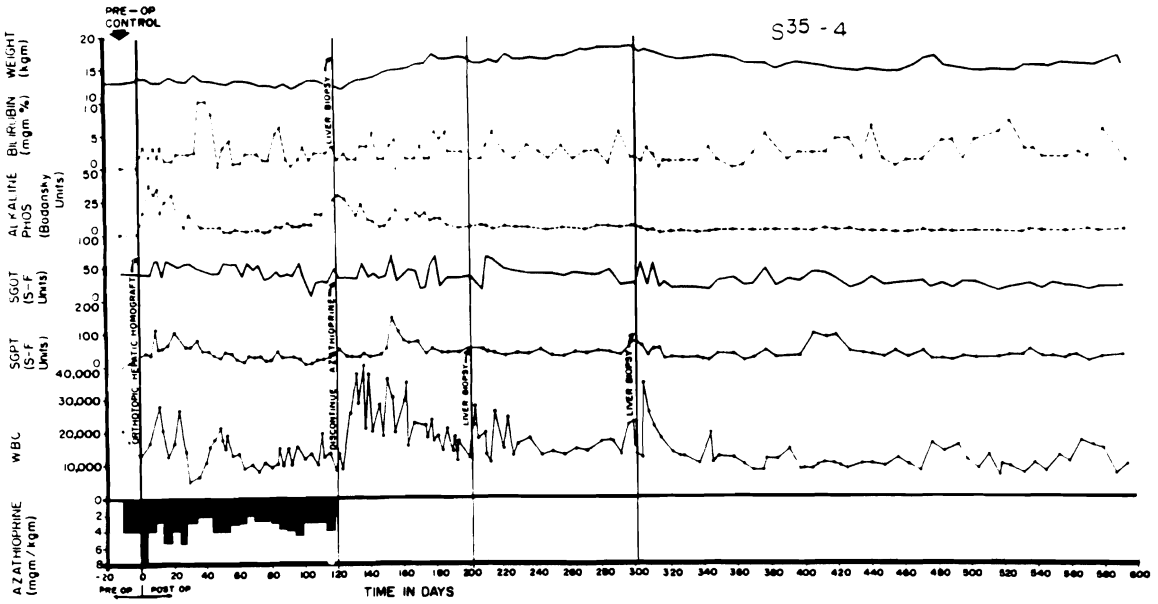

Fig. 1. — Course of an animal which never had any clinically evident homograft rejection. Note rapid weight gain following cessation of therapy at four months. The pronounced leukocytosis after withdrawal of immunosuppression was commonly seen. This animal is still alive after two years and ten months, having received no immunosuppressive therapy during the last two and a half years of this time. (By permission of Transplantation.)

of renal homotransplantation was incompatible with life in the generally older, debilitated, and feeble patients who required the much more difficult operation of liver replacement.

The same complications were encountered in the two patients who survived the operations of auxiliary liver homotransplantation at the University of Colorado. Both developed pneumonitis with pyogenic organisms and died after twenty-two and thirty-four postoperative days. Both also had infestation with unusual microorganisms which usually have low pathogenicity. For example, the patient who lived for five weeks had invasive moniliasis of the lungs as well as most of the gastrointestinal tract. Acute small bowel ulceration caused by the fungus was responsible for severe gastrointestinal hemorrhage which persisted for the last ten days of the patient's life.

These series of infectious complications have made it increasingly clear that the margin between desirable immunosuppression and toxicity is too fine to permit consistent success after clinical homotransplantation of the liver with the therapeutic regimens used in the past.

Prospects for Improving Immunosuppression

The most promising new agent in recent years has been heterologous antilymphocyte serum (ALS) or its globulin derivative (ALG). Accounts of the experimental background of these biological products (Chap. 32), and of their first testing in man (Chap. 31) are contained elsewhere in this volume. In our laboratories both ALS and ALG have been shown unequivocally to prolong the functional life of liver homografts.

A total of eighteen dogs were treated, nine with ALS and nine with ALG. Those receiving the serum had intraperitoneal injections. Therapy was generally started in advance of operation and continued for only a few weeks postoperatively (Fig. 2). The material used had a relatively low hemagglutinating titer of 1:64 to 1:256 when tested against dog leukocytes.

Subsequently, much stronger antisera were raised in the same horses by increasing the doses of immunizing antigen. With this change it became possible to extract high potency globulin from the horse serum. To date the most practical means of doing this has been with the technique of ammonium

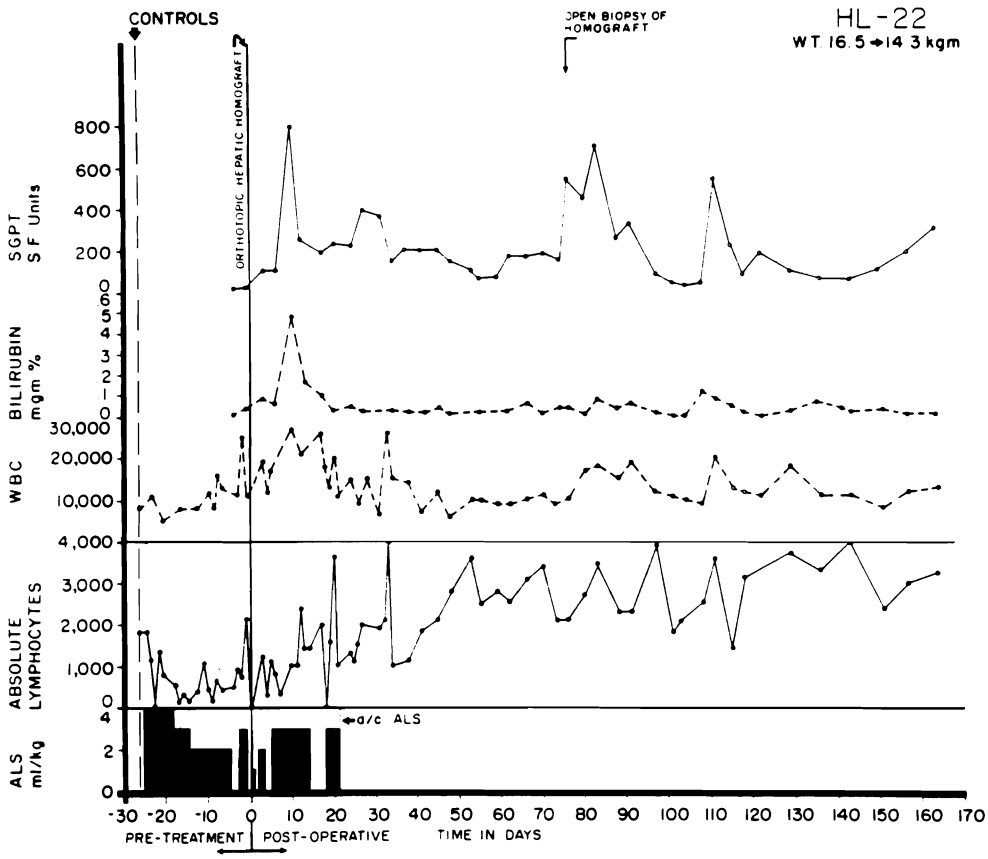

Fig. 2. — A chronologically surviving dog which was treated before and for twenty days after orthotopic liver transplantation with intraperitoneal antilymphoid serum (ALS). Note the pronounced lymphocytosis late in the postperative period. The animal is in excellent health after ten months. (By permission of Surg. Gynec. Obstet.)

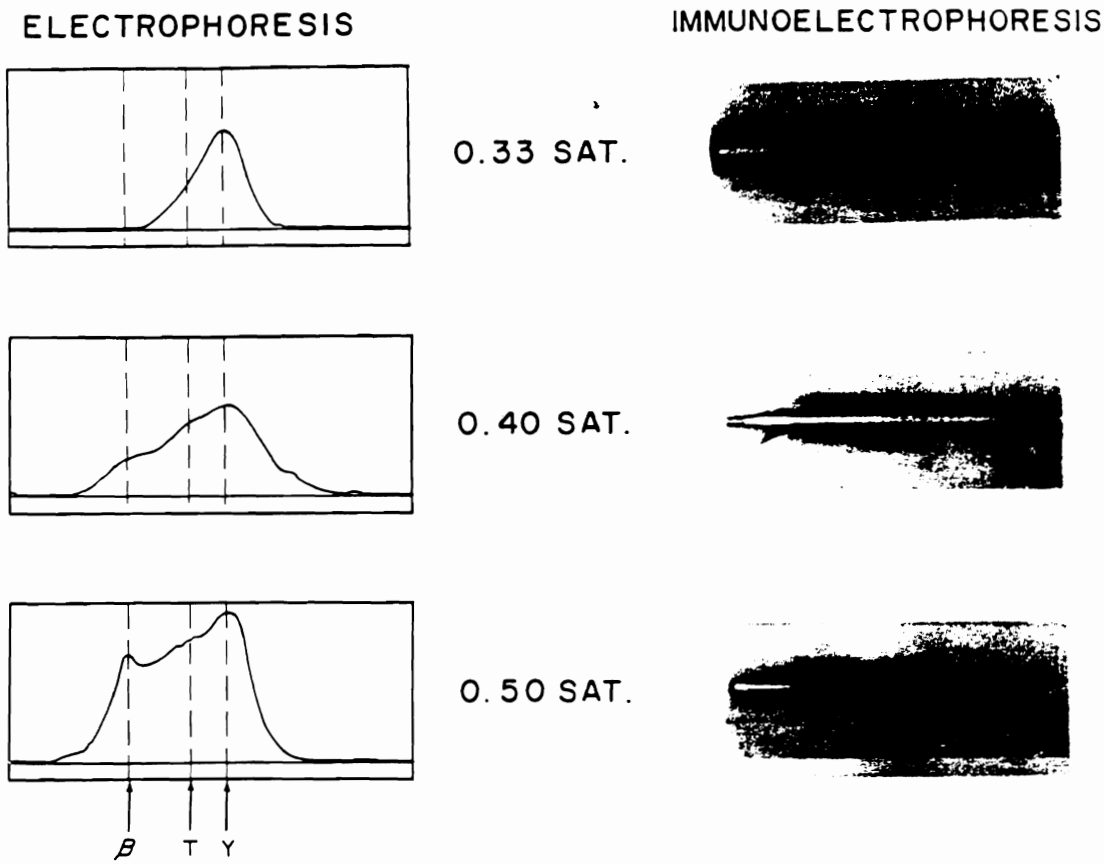

Fig. 3. — Electrophoresis and immunoelectrophoresis of the horse protein obtained by precipitating four times at different saturations of ammonium sulphate. Note the progressively heterogeneous nature of the precipitate with higher ammonium sulphate concentrations. The globulin obtained with 0.4 saturation was used clinically. (By permission of Surg. Gynec. Obstet.)

sulphate precipitation. Three different products are shown in Figure 3, obtained with precipitation at .35 saturation, .40 saturation, and .5 saturation. For testing, the globulin used was generally that prepared with .4 saturation, since there was a maximum retention of anti-white cell antibodies with a minimum of contamination with extraneous horse protein. The titer of the reconstituted globulin was 1:512 to 1:1024.

Nine animals received orthotopic transplantation while under treatment with subcutaneous injections of the horse globulin. The results in these animals are shown in Fig. 4, and compared to those obtained with ALS therapy or in untreated animals. A definite potentiation of survival was observed both with ALS and ALG. The survival figures indicated were computed with a maximum survival credit of seventy days for any dog. With this statistical ceiling, the mean survival was approximately one month in the combined groups. In actuality, however, four of the eighteen treated dogs lived for at least four months. Animals receiving no therapy died in 7.0 ± 3 (S.D.) days.

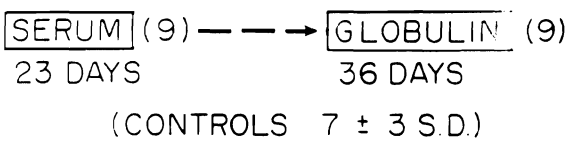

Fig. 4. — Effect of ALS (serum) and ALG (globulin) upon survival after orthotopic liver transplantation in dogs. The mean values were computed with limitation of survival credit for any dog of seventy days. A number of the treated animals had longer survival than this.

Several significant observations were made in these animals. One dog treated with ALS received therapy only prior to operation (Fig. 5). The lymphopenic response was exceedingly modest. Afterwards, there never was any evidence of rejection. The animal lived for more than six months and finally died as a result of a midgut volvulus.

The course of another dog is shown in Figure 2. This dog received intraperitoneal ALS prior to orthotopic transplantation for only the first three postoperative weeks. Here, also, the lymphopenic response was not significant, and after cessation of therapy there was a progressive lymphocytosis which has lasted for several months without late deterioration of homograft function. The dog is still alive, more than ten months after homotransplantation.

In the foregoing experiments, ALS or ALG was used as the sole immunosuppressive therapy. A limited number of additional experiments have also

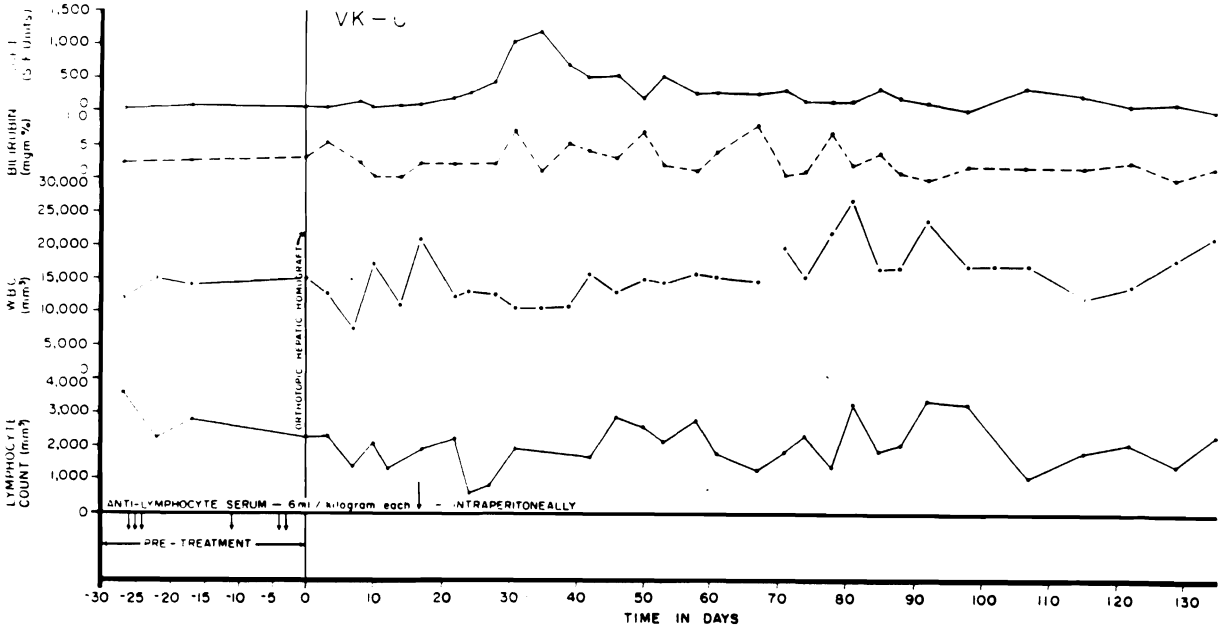

Fig. 5. — A dog that received an orthotopic liver homograft after six intraperitoneal injections of antilymphoid serum (ALS). No postoperative therapy was ever given. Note that the lymphocyte count was little changed. The dog died of intestinal obstruction six months postoperatively. (By permission of Surg. Gynec. Obstet.)

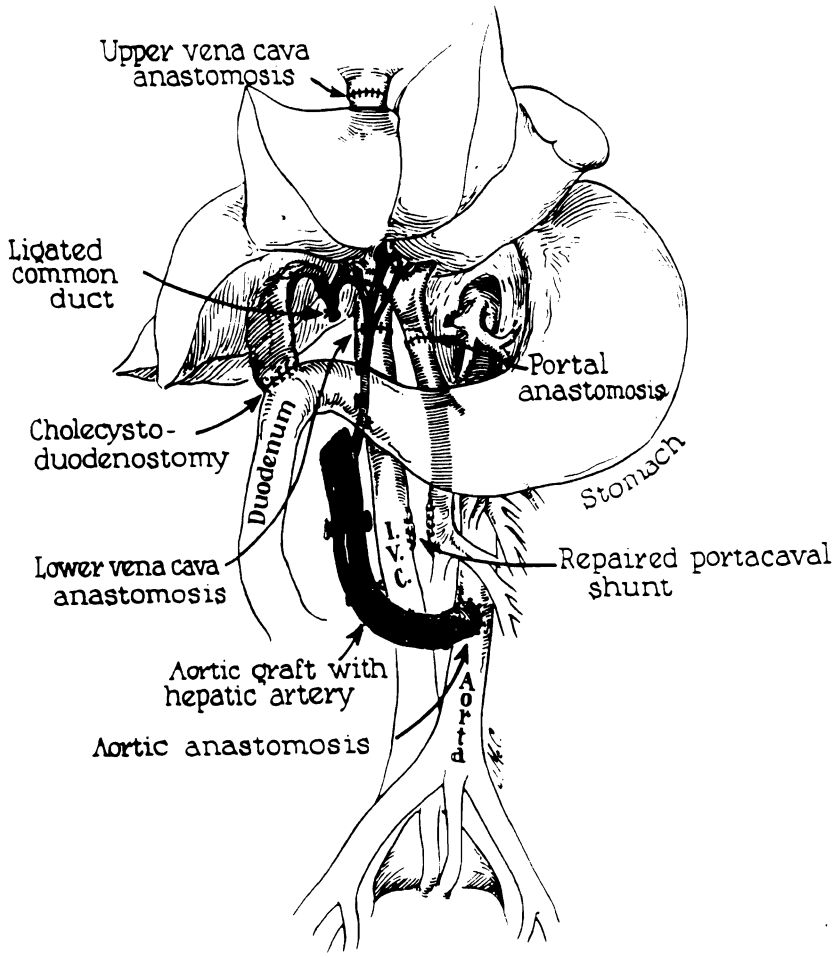

Fig. 6.— Reconstruction after orthotopic liver homotransplantation in the dog. Internal biliary drainage is with a cholecystoduodenostomy. Aorta is transplanted in continuity with the hepatic artery of the homograft. (By permission of Surgery.)

been carried out using ALG in combination with azathioprine, or with azathioprine and a short course of prednisone. Using either schedule of multiple drug therapy, there was improved immunosuppression indicating a synergistic effect of the different agents. Approximately 70 per cent of animals provided with triple drug therapy have achieved survival of at least forty days, excluding operative deaths.

A previously uncommon technical complication was seen with increased frequency with the better immunosuppression of such regimens. Since the beginning of our investigations of orthotopic transplantation, the procedure used has been that shown in Fig. 6. In the donor, a segment of the aorta was removed in continuity with the hepatic artery. It was then possible to anastomose the end of the homografted aorta to the side of the recipient's midabdominal aorta. Although this method of arterialization has hemodynamic disadvantages, clotting in the arterial system was rare.

With the improved early function resulting from the new programs of immunosuppression, a very high incidence of thrombosis of the aortic graft was encountered, killing more than two-thirds of the animals. More recently, an alternative procedure has been used. A right nephrectomy was performed in the recipient. The celiac axis of the homograft was then attached by an end/to/end anastomosis to the right renal artery. The incidence of intra-arterial thrombosis was thereby reduced to approximately 15 per cent.

Only one attempt at human liver homotransplantation has been made with the use of ALG. This was in a 28 year old man with a hepatoma and represented the sixth case of orthotopic transplantation in Denver. The homograft was obtained from a 73-year old patient who died of a cerebrovascular accident. The donor was accepted in spite of his advanced age because an unusual degree of antigen compatability with the recipient was demonstrated by van Rood's

and Amos' tissue-typing teams which were working in Denver at that time. The period from death to revascularization was 99 minutes. Although this interval is acceptable in canine experiments, there had been serious injury to the homograft. Much of the damage to the donor liver had apparently occurred in the pre-mortem stages. The recipient patient did not achieve good early homograft function and died seven days later of hepatic insufficiency.

In spite of this disappointing experience, the evidence is strong, as reviewed in Chapter 31, that ALG will make possible improved immunosuppression for homotransplantation of human tissues and organs. This clinical evidence has been obtained with the study of recipients of renal homografts, but there is no reason to think that the experience is not transferable to problems of the liver.

Histocompatibility

The desirability of improving immunosuppressive therapy is generally acknowledged. An alternative approach would be to reduce the need for immunosuppression by application of various techniques of human histocompatability analysis. Experience with both canine and human organ homotransplantation have shown beyond doubt that certain nonrelated members in either outbred population can provide tissues which elicit a relatively mild immunologic reaction, and conversely that certain members are favored recipients. In dogs, for example, 15 to 20 per cent of recipients which receive organs from randomly selected mongrel donors have a very benign postoperative course under therapy with azathioprine alone, often never manifesting overt evidence of homograft rejection. An example of such a fortunate animal has been previously alluded to (Fig. 1). At the other end of the spectrum, involving approximately one-third of the animals, rejection is only delayed for a few days or weeks. In these dogs, rejection once begun (Fig. 7) is inexorable. The histologic findings in the homografts from these unfavorable experiments are indistinguishable from those in the untreated animal.

Between the two extremes are to be found the results in approximately one-half the experiments. In these recipient animals, rejection is seen, often to a severe degree, but it is more or less reversible. It is important to emphasize that no supplementary therapy was instituted in these animals at the time of their rejection crises. Treatment with azathioprine was continued in approximately the same doses as before with ultimate improvement in liver function. The latter observations, made in more than forty animals, emphasize the important principle that rejection is a phenomenon which tends to be spontaneously reversible. It also emphasizes the caution that is necessary in attributing benefit to other therapeutic maneuvers carried out at this critical time.

Much more effort has been made to determine histocompatibility antigens in man than in dogs. Unfortunately, the location, number, and nature of human histocompatability antigens are incompletely understood. Such information may come from the investigations of human isoimmune antisera discussed in Chapter 24. Such sera have been obtained from patients who were accidentally or deliberately sensitized to homologous white-cell antigens or other tissues. The agglutination or cytolysis of test lymphocytes by these antisera imply the presence of the same or similar antigens as those which originally sensitized the donor; failure of such reactions implies the absence of the antigens.

There are indications from a number of groups that the antigens detected by these serologic methods are at least related to histocompatibility factors. The most convincing evidence has come from the pathologic studies of Porter,[14] who examined biopsies obtained from more than forty patients approximately two years after renal homotransplantation. There was a high degree of correlation between the quality of preservation of these chronically tolerated homografts and the completeness of antigen matching between the recipients and their respective donors. These findings suggested that the long-term fate of organ homografts was influenced by the degree of donor-recipient white-cell antigen conformity.

The foregoing studies supported the concept that improvement in whole organ transplantation could be achieved by prospective antigen matching. Unfortunately, efforts to identify the biologically more suitable donors by this technique have proved somewhat disappointing.[13] An increased survival was obtained in a series of patients provided with renal homografts from nonrelated donors at the University of Colorado, but the one-year mortality was still approximately 50 per cent. The results with intrafamilial renal homotransplantation were not improved at all. It has become increasingly clear that the high early mortality in such cases can only be slightly modified by the application of antigen matching techniques, and that the most urgent need is for changed immunosuppressive protocols as discussed earlier.

Organ Preservation

More effective means of either immunosuppression or histocompatability analysis will not insure the

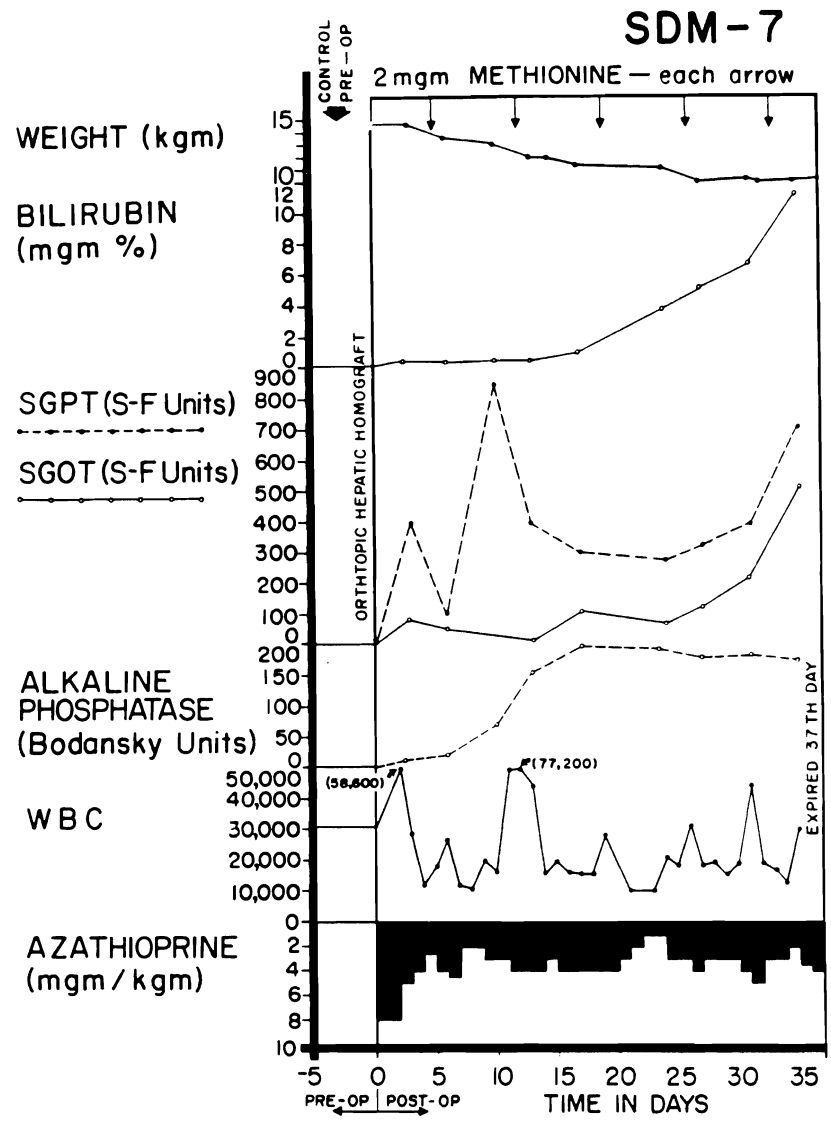

Fig. 7. — Example of inexorable rejection despite immunosuppressive therapy. Serum bilirubin was the most useful measurement for following the course after homotransplantation, since the other abnormalities of liver function depicted can also be caused by azathioprine. (By permission of Surgery.)

success of homotransplantation of the liver. The sensitivity of this organ to anoxia has created a serious problem in virtually every clinical trial to date. Invariably, there has been early postoperative evidence of ischemic injury to hepatic parenchyma with early high increases in SGOT, SGPT, and LDH (Fig. 8). Within a few days such patients have developed jaundice. These various early biochemical abnormalities were probably due to anoxic injury rather than to rejection. Although the injury was partially reversible in many instances, the quality of subsequent homograft function ranged from mediocre to poor, contributing to the ultimately unfavorable outcome.

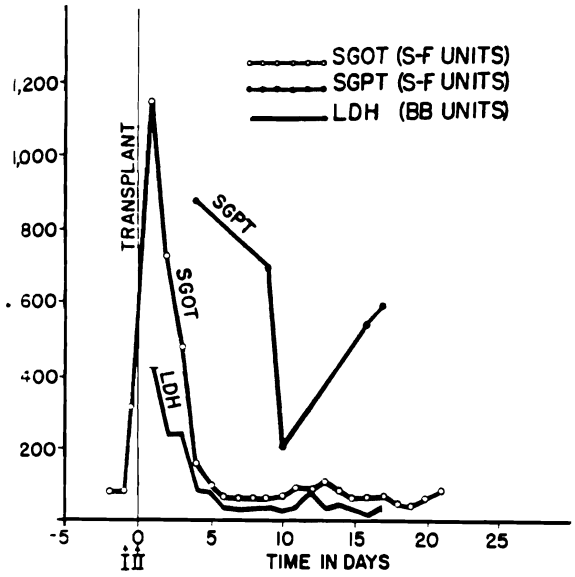

Fig. 8. — Serious injury to human liver homograft (Case 2 Colorado Series). Time from death to revascularization was 152 minutes, during 98 minutes of which extracorporeal perfusion was carried out. Note the high but reversible increases in serum enzyme values. (By permission of Surg. Gynec. Obstet.)

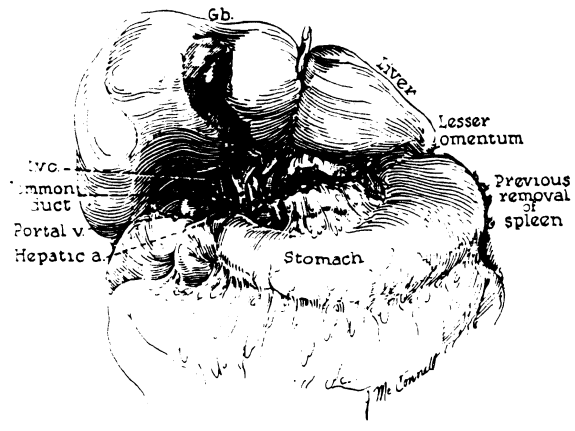

Fig. 9.— Skeletonization of diseased recipient liver at a first stage. Subsequently, the patient can be rapidly re-explored and the liver removed. (By permission of Surg. Gynec. Obstet.)

The need for haste has led to the development of compromise clinical procedures, including staging. At a first operation, all structures entering and leaving the diseased liver were skeletonized (Fig. 9). With the subsequent availability of a suitable donor candidate, it was then possible to rapidly reopen the incision and to quickly remove the patient's diseased liver. This approach is not without disadvantages. Recipients who are candidates for such operations are generally suffering from a terminal illness and can ill afford two lengthy and traumatic procedures. Moreover, the timing of the second stage is unpredictable since it is never known in advance when a donor may be expected to arrive. In one of the cases treated in Denver, there was a delay of two weeks between the first and second operation.

Methods were needed which would permit conservation of hepatic tissue for ten hours or longer. Until recently, the simplest and most effective way of ameliorating the effects of ischemia were by simple perfusion of the homografts with cold electrolyte solution (Fig. 10). In dogs, a liver so treated could be transplanted successfully after an ischemic period of two hours with a high expectation of success. Beyond this time, however, there was an exponentially increasing number of failures due to poor initial homograft function.

Methods of continuously perfusing the cadaver liver permitted only a slight extension of the acceptable postmortem time, in spite of the fact that elegant systems of perfusing dog, pig, and cow livers for other purposes had been previously described.[4,9,14] The first perfusion system which was used for preservation of liver homografts employed a heart-lung machine which was attached via transfemoral cannulas to the great vessels of the recently deceased cadaver.[10] By incorporating a heat exchanger in the circuit, both perfusion and hypothermia could be used simultaneously (Fig. 11). In dogs, this system permitted functional kidneys to be consistently obtained as long as twelve hours after death, but there was little if any demonstrable protection of the canine liver homograft. Alternatively, Mikaeloff and Kestens, using a normothermic system of isolated organ perfusion, were able to extend the acceptable postmortem time to almost six hours.[15]

The foregoing studies, as well as more recent investigations by Brown and McDermott and their associates,[3] provided little hope that immediately func-

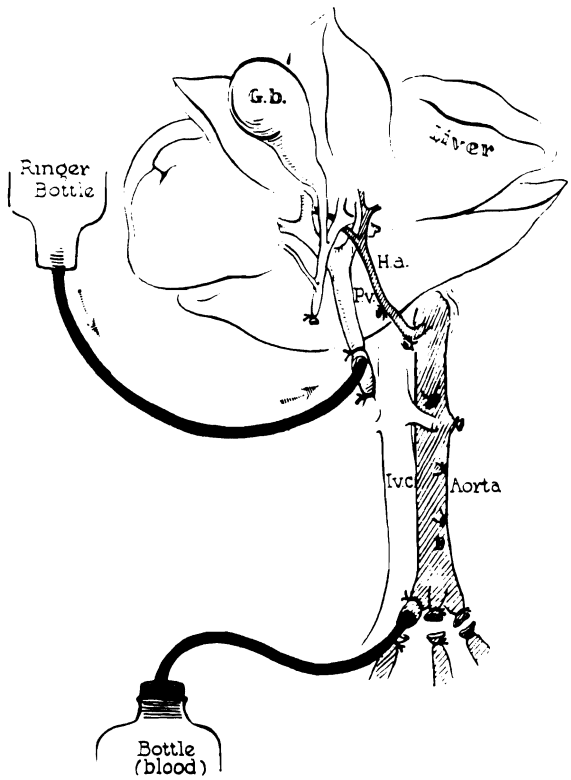

Fig. 10. — Method of further cooling a liver homograft just before its removal. Donor animals are operated on with total body hypothermia of 29 to 31° C. Cold lactated Ringer's solution is infused through the portal vein at the same time the donor animal is exsanguinated. (By permission of Surg. Gynec. Obstet.)

tioning and life-sustaining livers could be preserved even for intermediate intervals. The results recently obtained by Dr. Lawrence Brettschneider, working in our laboratories, were therefore both welcome and somewhat surprising. Five cadaver canine livers were stored using a modification of the technique developed for kidneys by Ackerman and Barnard[1]—a combination of low-flow hemodilution perfusion, hypothermia of 4° C., and hyperbaric oxygenation at 3 to 4 atmospheres. The pH was carefully controlled at 7.4.

After ten to fifteen hours, the livers were removed from the chamber and used for orthotopic transplantation to nonrelated recipients. Excellent function was evident. The animals awoke and had a postoperative convalescence indistinguishable from that of animals receiving grafts under optimal conditions. All five dogs lived for at least three days. These developments have made it clear that a method with immediate clinical applicability is already available. The certainty of being able to hold human liver homografts for many hours has solved one of the most difficult and practical problems of clinical homotransplantation.

Temporary Hepatic Support

Experience with clinical liver transplantation has shown that temporarily life-sustaining function can be expected even from very seriously damaged homografts. There is not an all-or-none hepatic response to ischemic injury as is often the case with cadaver kidneys, which may pass through a totally nonfunctional state of acute tubular necrosis.

Nevertheless, an important impediment to successful hepatic transplantation is the fact that an artificial liver for temporary assistance during a period of homograft recovery is not available. The development of such an artificial liver in the immediate future appears unlikely due to the complex and incompletely understood function of this organ.

The brilliant investigations of Eiseman, Liem, and Raffucci,[5] extended by Norman et al.[17] and other investigators,[4,29] have explored the alternative possibility of utilizing extracorporeal homologous or heterologous livers temporarily revascularized in parallel with the recipient's own circulation. The principal disadvantages of this approach are the short-term benefits which can be expected and the relatively complicated instrumentation which is required.

Nevertheless, this form of therapy, either for preoperative resuscitation of the critically ill patient or as a temporary assist procedure during recovery from ischemic injury or severe rejection, is the only means now available for the post-transplant period. Eiseman and Norman have reported definite but brief benefit in patients dying of chronic liver disease. It could be argued that the method had not received a fair trial since the nature of the original illness precluded eventual recovery.

A further application of this concept has been tested in our laboratory and in two patients.[21] In the animals, total hepatectomy was carried out. A number of hours later, homografts from nonrelated animals were revascularized in the cervical area, obtaining the arterial inflow from the carotid artery and directing the hepatic venous outflow through the external jugular vein. Such heterotopically placed grafts secreted bile and permitted a doubling of the expected survival. Detoxification of the barbiturate anesthetic was proven by the frequent necessity for re-anesthesization.

Two patients dying of acute or subacute hepatic failure have been treated with this method, a 16

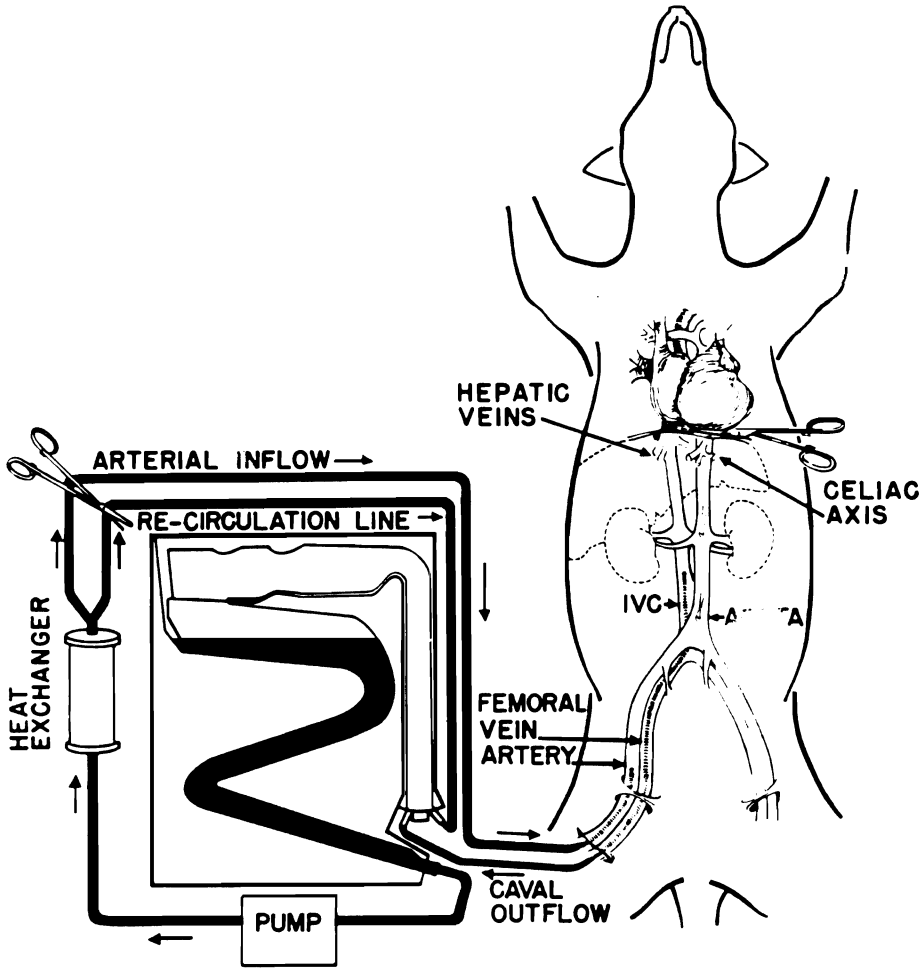

Fig. 11. — Technique of extracorporeal canine cadaver perfusion. The aorta and inferior vena cava are cannulated via the femoral vessels as soon as possible after death. Heparin and procaine are added to the glucose or electrolyte solution used to prime the extracorporeal circuit. Anticoagulation of the corpse occurs with the first surge of the pump. The heat exchanger permits rapid cooling. An identical technique has been used for humans. (By permission of Surgery.)

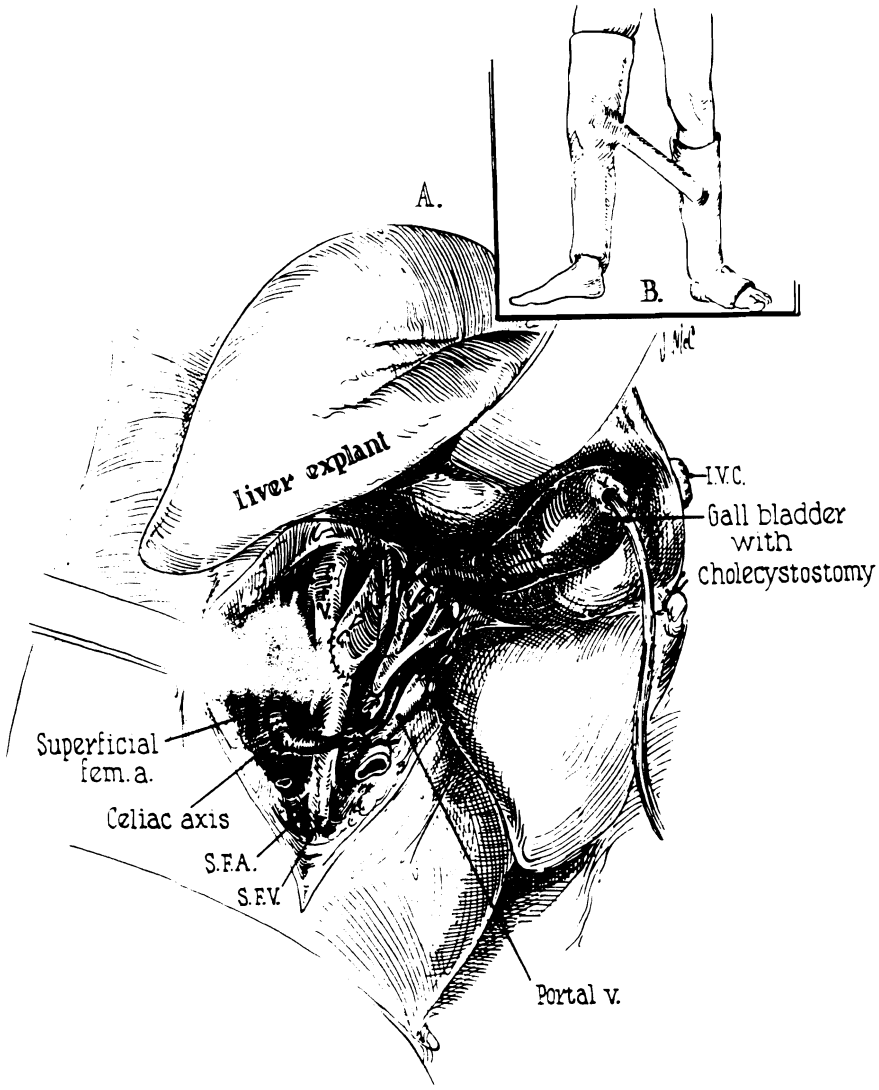

Fig. 12. — Technique of extracorporeal liver homotransplantation used in two patients. The superficial femoral artery was anastomosed to the hepatic artery, and the hepatic venous outflow was directed into the femoral system. The liver was left in situ for three and a half days. (By permission of Amer. J. Surg.)

year old boy, and a 7 year old girl. The livers were obtained from a cadaveric donor in the first case, and a blood-type compatible chimpanzee in the second. They were revascularized in the groin (Fig. 12). There was a prompt fall in the hyperbilirubinemia in both patients but with little evidence of protein synthesis. The extracorporeal livers were left in place for three and a half and one days.

Neither of the patients aroused from the preexisting hepatic coma, although this appeared to be lightened in the case of the young girl, who subsequently awoke completely several days after the liver was removed. The first patient died three and a half days after insertion of the graft, and the second child died of a massive gastrointestinal hemorrhage fourteen days after its removal.

The clinical benefit in these two cases was disappointing. It seems likely that assist procedures will be necessary for a longer period if benefit is to be derived either before or in the early period after homotransplantation.

Auxiliary Liver Transplantation

Most of the foregoing remarks have been based on experience with orthotopic transplantation. In this situation in which the sole liver tissue is represented in the homograft, there can be no question of the source of either early or late hepatic function. Consequently, the most incisive information concerning the quality of organ preservation, the efficiency of immunosuppression, the histopathologic events of rejection, and various other questions can be obtained with this experimental preparation.

Nevertheless, studies of auxiliary liver transplantation have unfolded a picture fully as interesting as, and quite different from, that which has evolved from studies of the orthotopic operation. The following remarks will review the evidence on certain controversial observations which have been made in dogs which were provided with a second abnormally placed liver.

This procedure, as first described by Welch,[30] involved placement of the homograft in the right paravertebral gutter (Fig. 13A) with rearterialization from the terminal aorta or iliac artery. Inflow to the portal vein was provided from the distal transected inferior vena cava. Subsequently, it was found in animals treated with azathioprine that such homografts were profoundly afflicted with atrophy.[31] The shrinkage usually began within two or three weeks, and reached an advanced stage within forty-five to sixty days (Fig. 14).

It was soon found that the homograft atrophy could be prevented by changing the method of revascularization. If nonhepatic splanchnic blood were diverted into the auxiliary liver (Fig. 13B), its shrinkage was averted and the atrophy now affected the host's own liver. These findings suggested that there was competition between the two coexist-

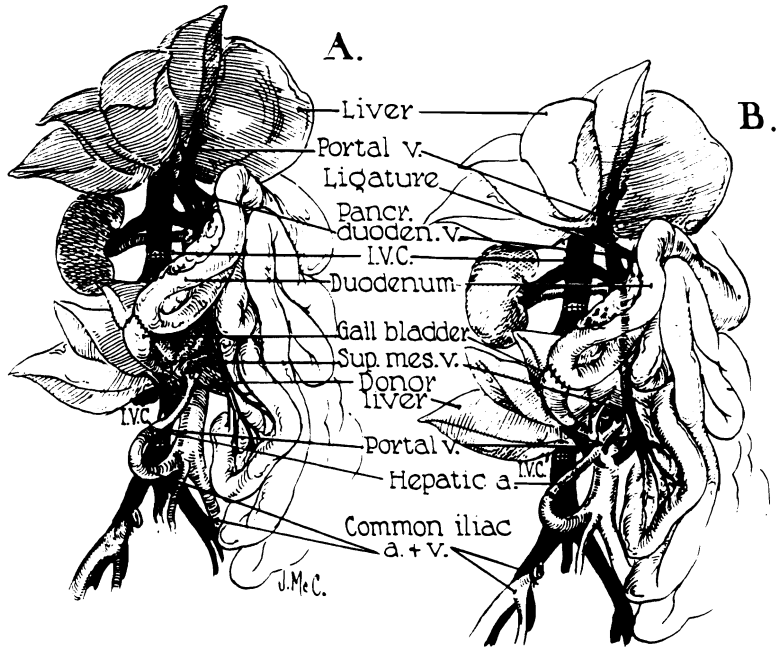

Fig. 13. — Auxiliary liver transplantation. A. method of Welch. Note that portal venous inflow is from the inferior vena cava. The homograft undergoes rapid atrophy. B. modification of Welch method in which nonhepatic splanchnic flow is diverted through the homograft. With this preparation, the homograft retains its size and the animal's own liver shrinks. 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. Obstet.)

Fig. 14. — Results with auxiliary liver transplantation when revascularized by Welch method (Fig. 13A). Note marked atrophy of the homograft (right) and no change in the animal's own liver (left). General morphology of the homotransplant is quite recognizable. The two specimens were obtained forty-five days after auxiliary transplantation.

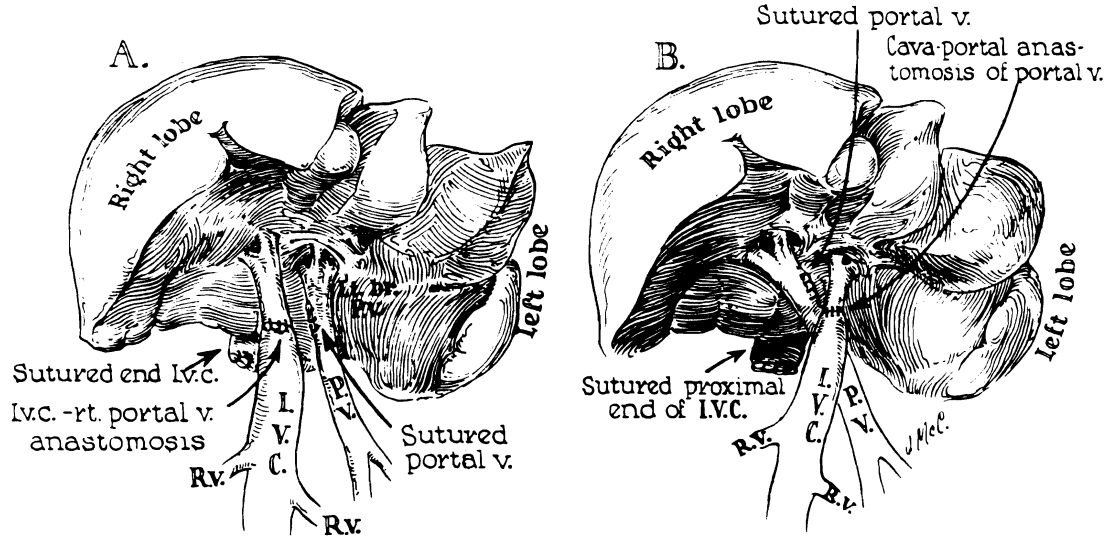

Fig. 15. — Technique of partial portacaval transposition. One part of the liver receives systemic venous blood via the inferior vena cava while the other portion is supplied with splanchnic venous blood. (By permission of Surgery.)

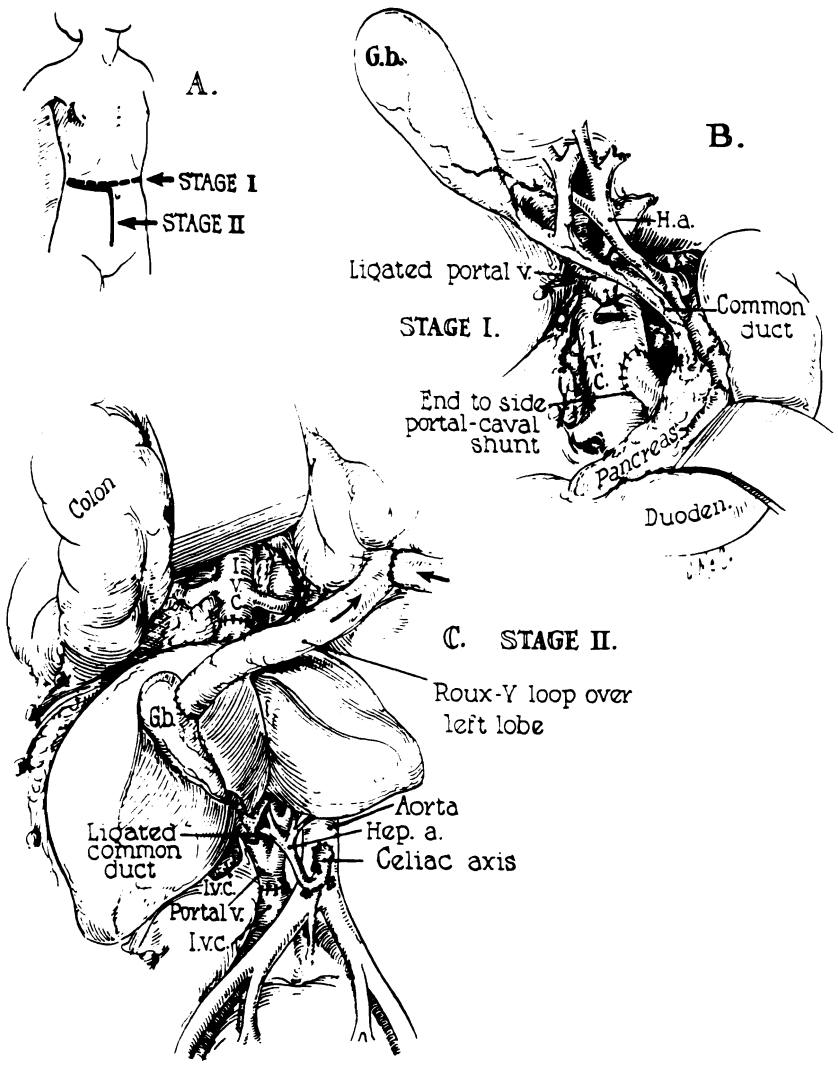

Fig. 16. — Method of auxiliary liver transplantation which has been used twice at the University of Colorado Medical Center in patients with terminal Laennec's cirrhosis. A, B, first stage portacaval anastomosis is performed. This will usually be necessary for control of variceal hemorrhage. C, Revascularization of the auxiliary liver in the right paravertebral gutter. (By permission of Pediatric Clinics of North America.)

ing livers for some substrate or substrates present in selective concentration in portal blood. The organ which had first exposure to this intestinal effluent operated at a metabolic advantage.[11]

The above experiments suffered from the imperfections that the homograft was under immunologic attack whereas the autologous liver was not, and that the host was being treated with azathioprine, a hepatoxic drug. The purer experiment shown in Figure 15 was therefore designed.[12] In this preparation, a fraction of the animal's own liver was supplied with systemic blood by means of an anastomosis of the inferior vena cava to one of the main portal branches while the other portion was perfused with splanchnic venous inflow. Blood flow was equivalent in the two hepatic components. Atrophy invariably ensued in the abnormally vascularized fraction with compensatory hypertrophy in the other part. The observations could not be supported in a preliminary report by Welborn, Lanier, and Foster[31] but were subsequently confirmed in principle by the studies of Price and his associates.[19]

These studies indicate, of course, only that the described competitive relationship can result in "starvation" of the less favorably disposed organ. Recent studies have shown that if the ability of the host liver to compete is reduced by a variety of methods, the atrophy of a heterotopically placed homograft can be partially or even nearly completely avoided. Such procedures include autologous hepatectomy,[26] ligation of the common duct,[6,7,16,28] and construction of a host Eck fistula.[6,8,27,28] Such observations have clinical applicability since the livers of patients being considered for this kind of therapy have failed and would presumably be incapable of aggressive metabolite extraction.

The kind of compromise clinical procedure which has evolved from these animal investigations is shown in Figure 16. Two patients, both suffering from Laennec's cirrhosis, have received such operations in Denver from one to four days after emergency portacaval shunt for variceal hemorrhage. As recounted earlier, both recipients died of septic complications after twenty-two and thirty-four days, respectively. However, there was unequivocal evidence of homograft function. There was no evidence of homograft atrophy in either instance.

Summary

Successful homotransplantation of the human liver depends primarily upon further refinements in immunosuppressive therapy and in organ preservation. Recent substantial progress toward both objectives, including some previously unpublished observations, has been cited. The hope that antigen matching or hepatic support procedures will be of importance in permitting at least early survival after liver transplantation seems less well founded.

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