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Avenues of Future Research in Homotransplantation of the Liver

WITH PARTICULAR REFERENCE TO HEPATIC SUPPORTIVE PROCEDURES, ANTILYMPHOCYTE SERUM, AND TISSUE TYPING

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Avenues of Future Research in Homotransplantation of the Liver

With Particular Reference to Hepatic Supportive Procedures, Antilymphocyte Serum, and Tissue Typing

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IN RECENT REVIEWS the progress already achieved in homotransplantation of the liver was summarized [*1,2*]. In principle, the feasibility of such operations has been proved since four dogs in our laboratory have lived for more than a year and a half after total recipient hepatectomy and concomitant orthotopic homotransplantation; chronic survival has also been achieved by Moore [*3*] and Mikaeloff, Kestens, and Dureau [*4*]. Moreover, important information has accrued on the alternative method of auxiliary hepatic homotransplantation, a procedure which does not involve recipient hepatectomy but which has significant physiologic disadvantages [*5,6*]. Chronic survival in man has not been obtained after either kind of operation.

Instead of reviewing this information again, an attempt will be made in the following remarks to define some of the broad areas of research which hopefully will lead to practical clinical application of these experimental procedures. Reference will be made to certain developments in renal transplantation when these are directly applicable to homotransplantation of other organs.

IMMUNOSUPPRESSION

The factor which most seriously limits development of this field is the inadequacy of present day immunosuppressive therapy. Those regimens which have made chronic survival possible after renal homotransplantation are probably no less effective in preventing liver homograft rejection; however, there is reason to believe that their use may be more hazardous largely because of the greater magnitude of the surgical undertaking. Thus, pulmonary sepsis, which is a common and often fatal early complication after renal homotransplantation, has been observed after virtually every attempt at clinical transplantation of the liver.

In addition, there may be more specific objection to the use of azathioprine and prednisone, the two most important agents currently being employed. It has been well documented in the dog that azathioprine is hepatotoxic [*7*]. The evidence that it causes similar injury to the liver in man is more tenuous [*8*]; nevertheless, a growing number of patients have been reported to have "hepatitis" after otherwise successful renal homotransplantation. Steroids can also cause injury to the liver. Fatty infiltration and even cirrhosis can be produced in animals [*9–11*] or man [*12,13*] by their protracted use in high dosage. The need for better agents has been recognized by most workers in this

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TABLE I
SURVIVAL OF DOGS TREATED WITH HORSE ANTI-DOG-LYMPHOCYTE PLASMA (ALP) OR SERUM (ALS)

Group	No.	Mean Survival (days)	Standard Deviation	Range (days)
Controls	16	11.3	4.58	5–16
Dogs with unmodified ALP	25	32.3	33.3	4–144
Dogs with absorbed ALS	6	27.2	12.95	13–49

field and has led to the evaluation of many new immunosuppressive technics.

Perhaps the most promising of these has been the development of antilymphocyte serum (ALS) or plasma (ALP). Knowledge that heterospecific antisera could destroy lymphocytes and could mitigate various hypersensitivity reactions preceded their employment for prevention of rejection as Woodruff [*14*], Waksman, Arbouys, and Arnason [*15*], Gray et al. [*16*], and Sacks, Fillipone, and Hume [*17*] have taken pains to point out. Woodruff [*14*], working with rabbit anti-rat-lymphocyte serum, was the first to allude to potentiation of homograft survival; he later reported that this effect was increased by the addition of recipient thoracic duct lymph drainage [*18,19*]. Jeejeebhoy [*20*] and Monaco, Wood, and Russell [*21*] simultaneously reported even more striking skin homograft protection and showed in addition that thymectomy added to the efficacy of the therapy. Levey and Medawar [*22*] and Monaco et al. [*23*] have shown that the second-set reaction can be partially prevented, a fact of importance in considering possible mechanisms of action [*22*].

The foregoing skin graft experiments were performed either on genetically controlled rat, guinea pig, or mouse strains, employing rabbit antiserum. Although there have been no reports of the use of ALS in outbred larger animals, trials with renal homografts are known by personal communication to have been carried out in dogs by Woodruff (Edinburgh), Calne and Medawar (London), Hume (Richmond), Monaco (Boston), Murray (Boston), and Lawson (Portland) producing the antiserum in the rabbit, sheep, cow, and horse. In our laboratories horse anti-dog-lymphocyte plasma or antiserum has been raised by the repeated subcutaneous inoculation of canine lymphocytes obtained from the lymph nodes of multiple donors. The response was followed with leukoagglutinin titers which rose from 1:4 to 1:32 to 128. The resulting ALP in unmodified form was toxic, causing death in eleven of thirty-six dogs tested. Anaphylaxis and acute anemia were common. Nevertheless, the remaining twenty-five animals pretreated with pooled ALP for two or three weeks and ultimately subjected to renal homotransplantation and bilateral nephrectomy had significant prolongation of life. Postoperatively, one to four ml. per kg. per day of antiserum was administered intraperitoneally, daily at first and later at intervals as long as two to four weeks. Mean survival was 32.3 days. (Table I.)

Subsequently, specimens from the same horses were prepared as antilymphocyte serum (ALS) and absorbed with dog red blood cells. Removal of most of the heteroagglutinin in this way reduced the severity of both the recipient anemia and the number of anaphylactic reactions. Six dogs received renal homografts after comparable pretreatment (Table I), with a mean survival of 27.2 days (range thirteen to forty-nine days). The retention of immunosuppressive effect suggests that the efficacy of the material is not dependent upon toxicity, an observation also made recently by several other investigators.

Unmodified ALP has been used to treat dogs after transplantation of the liver. Although few in number, the experiments indicate that prolongation of viability can also be obtained with this organ. Eight animals were provided with orthotopic homografts after complete extirpation of their own liver. Subsequent survival was six to thirty-three days (average 15.6 days), a significant improvement ($p < 0.02$) over that previously established for the untreated animal after such an operation. (Table II.) Neverthe-

TABLE II
SURVIVAL OF DOGS TREATED SOLELY WITH HORSE ALP AFTER ORTHOTOPIC LIVER TRANSPLANTATION

Group	No.	Mean Survival (days)	Standard Deviation	Range (days)
Controls	22	7.1	2.2	2–10
Dogs with ALP	8	15.6*	9.2	6–33

* One animal was still alive after three weeks.

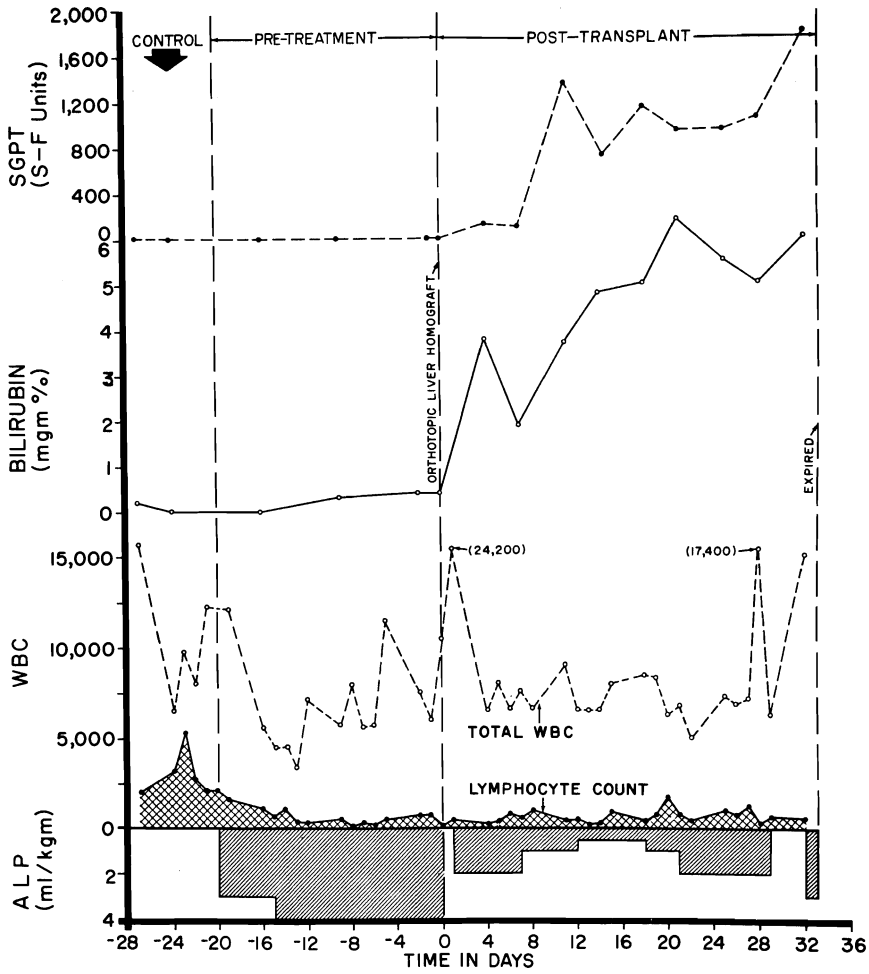

FIG. 1. Course of a dog treated solely with antilymphocyte plasma before and after orthotopic liver homotransplantation. Note the sustained lymphopenia after institution of therapy. Despite significant prolongation of life, the eventual cause of failure was rejection as reflected in the deteriorating liver chemistries.

less, the death of each animal was due to rejection. (Fig. 1.)

In the dog, results using ALS or ALP for either renal or hepatic homotransplantation are inferior to those which are attainable with azathioprine, but the hope of further improvement is well founded. The aforementioned experiments were performed with horse serum of very low leukoagglutinin titer. Since then, it has been found that titers of 1:2,400 or greater can easily be produced with proper immunization technics. In addition, Monaco and his associates [*23*] have recently reported that the active component of rabbit anti-mouse-lymphocyte serum is fully preserved in purified gamma globulin, and Woodruff [*24*] has further isolated it in rabbit anti-rat-lymphocyte serum to the 7-S fraction. Several laboratories including our own are presently isolating more or less pure and highly concentrated antibody preparations for trials, both for the dog and for eventual use in man.

The ultimate role of ALS in the immunosuppressive armamentarium is still speculative. Conceivably, it may be used alone; more likely, it can be combined with reduced doses of the currently available agents. Its unique appeal, as Levey and Medawar have pointed out [*22*], is that it is the only highly specific immunosuppressive agent available today. Further-

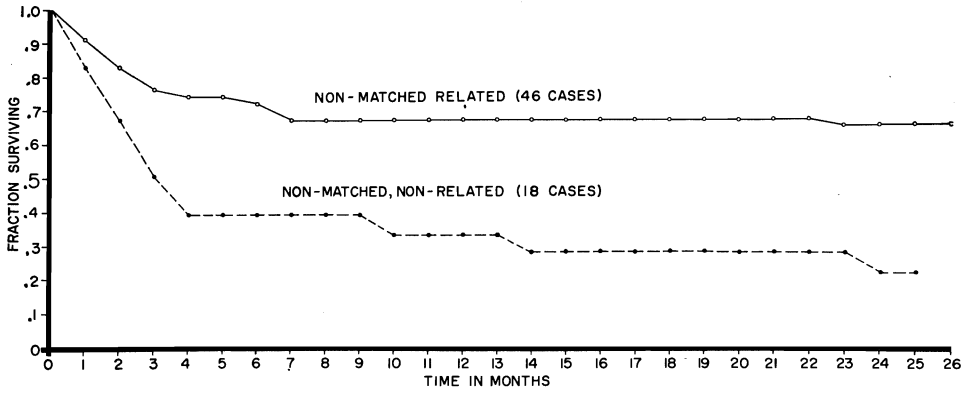

FIG. 2. Survival of sixty-four patients who received renal homografts from living volunteer donors between November 1962 and March 1964. No effort at prospective white cell antigen matching was made with these recipients and their donors. Note the poor results when nonrelated donors were used; the loss rate was heavy during the first months and has continued into the second postoperative year. The evident biologic unsuitability of randomly selected nonrelated donors is relevant to liver homotransplantation since all hepatic homografts will have to be procured from cadavers.

more, hepatotoxicity of ALS has not been observed in any of the investigations to which we have alluded.

HISTOCOMPATIBILITY

The desirability of improving immunosuppressive therapy is generally acknowledged. An alternative approach which would reduce the need for heavy immunosuppression would be the perfection of human histocompatibility analysis. A small number of either dogs or human subjects, receiving homografts from randomly selected nonrelated donors and treated with immunosuppression, have surprisingly little evidence of subsequent rejection. A similar small percentage has acute graft repudiation which is not preventable with any currently available therapy. The majority have significant rejection which can, however, be more or less favorably modified, but often at the expense of fatal drug toxicity. It is highly likely that these divergent results are due chiefly to a corresponding spectrum of chance host-donor histocompatibility.

The unacceptability of random pairing particularly when nonrelated donors are employed, as will be necessary for procurement of liver homografts, is well exemplified by the results with renal homotransplantation at the University of Colorado Medical Center. (Fig. 2.) Of forty-six patients provided with kidneys from blood relatives, almost two thirds survived for two years with continuous function of a single kidney. In contrast (Fig. 2), only four of the eighteen who received homografts from nonrelated volunteers during the same period were still alive at the end of twenty-four months. With the use of presently available immunosuppressive measures, the need is urgent in nonrelated cases to find a means of selecting a biologically suitable donor in advance, and presumably this will be advantageous even if improved immunosuppressive technics are developed.

Unfortunately, the location, number, and nature of human histocompatibility antigens are incompletely understood. It is possible that such information will come from investigations of human isoimmune antisera obtained from patients who have accidentally or deliberately been sensitized to white cell antigens. The agglutination or cytolysis of test lymphocytes by such antisera implies the presence of the same or a similar antigen as that which originally sensitized the donor, and failure of such a reaction implies the absence of the antigen. At the Seventh International Transplantation Conference, the papers of which are to be published in the December 1966 issue of the *Annals of the New York Academy of Sciences*, evidence was reviewed that many of the antisera used in Europe by Dausset, Van Rood, and Ceppellini were the same as or similar to those used in the United States by Terasaki, Payne, Amos, and others. The pooled information from these various investigators is being employed for de-

ductive genetic studies of the human antigenic profile.

The most significant reservation with this type of approach has stemmed from uncertainty that the antigenic systems being examined were related in any way to histocompatibility. The most convincing evidence that such a relation does exist derives from the studies of Terasaki and his associates [*25,26*] who retrospectively studied all cases of renal homotransplantation at the University of Colorado Medical Center in which survival of more than a year had been obtained. Chronic survival was shown to be possible with significant donor-recipient antigen mismatches, but the best clinical results were in the best matched pairs. More complete data were subsequently obtained from correlation of two year findings on biopsy in these same patients with the quality of the Terasaki match. These studies by Porter et al. [*25,27*] indicated a high degree of correlation between the state of morphologic preservation of the renal homograft and the completeness of antigen matching.

Recently, the Terasaki method has been employed for selection of donors [*28*]. Twenty-six patients were treated eleven to eighteen and a half months ago, thirteen with familial homografts and thirteen with nonrelated kidneys. Because of the limited number of potential suitable donors within a given family, the choice in the related series was not much greater than that in the earlier series of nonmatched cases previously described herein. In contrast, the availability of a large donor pool made feasible much greater selectivity for the nonrelated recipients than had previously been possible. The early results in these prospectively typed cases are summarized in Figure 3. It will be noted that after eleven months the survival in the nonrelated and related groups was exactly the same. No deaths have occurred in either group after eleven months.

These studies support the hope that typing for histocompatibility can become a useful clinical tool. As imperfect as the matching technics now are, there is reason to believe that they may provide a simple and practical means of donor screening in the relatively near future.

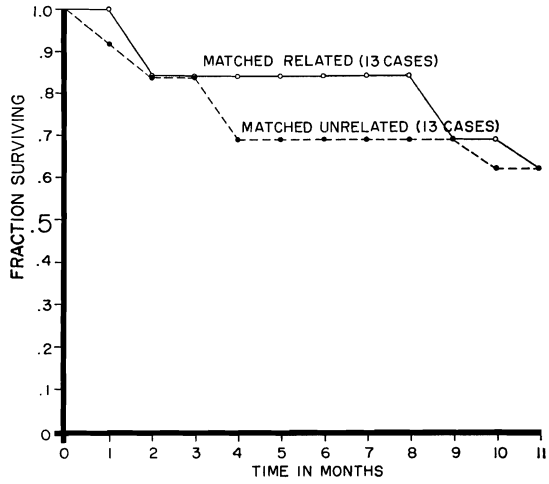

FIG. 3. Results of renal transplantation in patients whose donors were selected by Terasaki's antigen matching method. Note that survival after eleven months was exactly the same in both the related and nonrelated cases. Compare these results with those in Figure 2.

TEMPORARY HEPATIC SUPPORT

An important element in the development of renal homotransplantation has been the availability of high quality renal dialysis. These supporting technics have permitted pretransplant resuscitation of critically ill patients who could not otherwise have been subjected to operation. Furthermore, interim support is not infrequently required after transplantation either because prompt early excretion is not obtained or because of subsequent temporary failure of the homograft due to reversible rejection. Comparable procedures are not now available for patients with hepatic insufficiency. The development of 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 [*29*], extended by Norman et al. [*30*] and other investigators [*31,32*], have explored the alternative possibility of utilizing extracorporeal pig or calf livers temporarily revascularized in parallel with the recipient's own circulation. The principal disadvantages of this approach are the short-term benefit which can be expected and the relatively complicated instrumentation which is required.

A further application of this concept has recently been tested in our laboratory. Total hepatectomy was performed on six dogs under pentobarbital anesthesia. From five to seven hours later an extracorporeal liver from a nonrelated mongrel donor was transplanted to the

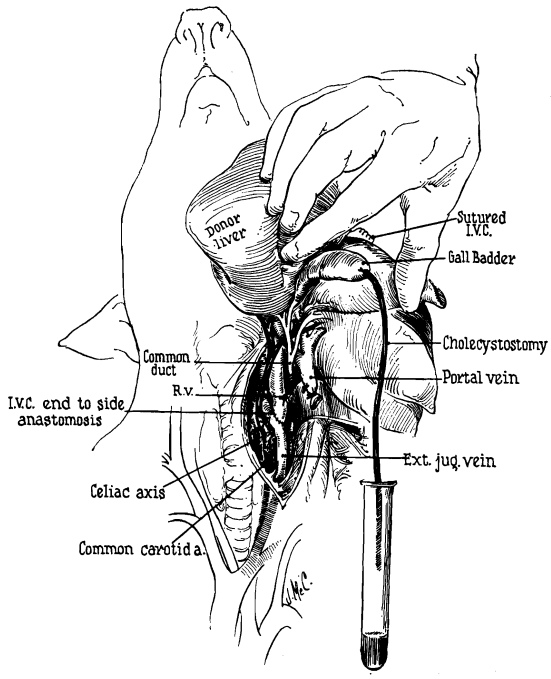

FIG. 4. Technic of extracorporeal liver transplantation in the dog. The portal vein is ligated and the hepatic artery anastomosed to the carotid artery. Hepatic venous outflow through the infrarenal inferior vena cava of the graft is channeled into the recipient external jugular vein.

neck of the anhepatic animal. The extracorporeal liver was provided only with an arterial supply. (Fig. 4.) The venous outflow was through the infrarenal inferior vena cava, the suprahepatic vena cava being closed with sutures. The liver was supported in position with moist gauze sponges.

The survival in the six consecutive experiments is shown in Table III. Total mean survival after initial hepatectomy was 30.3 hours; average survival after the extracorporeal transplant was 23.8 hours. In contrast to anhepatic animals under barbitrate anesthesia these dogs awakened promptly and required repeated reanesthetization.

TABLE III
SURVIVAL IN SIX DOGS SUBJECTED TO PRELIMINARY HEPATECTOMY AND SUBSEQUENTLY PROVIDED WITH AN EXTRACORPOREAL CERVICAL HEPATIC HOMOGRAFT

Data	Time (hr.) from Hepatectomy to Hepatic Support	Survival (hr.) after Hepatic Support	Total Survival (hr.) after Hepatectomy
Mean	6.2	23.8	30.3
Standard deviation	0.75	7.0	7.74
Range	5–7	13–31	18–38

TABLE IV
VOLUME AND BILIRUBIN CONTENT OF BILE COLLECTED FROM FIVE CERVICAL LIVER HOMOGRAFTS

Data	Time in Hours 0–6	7–12	13–18	19–24	25–30
Volume bile (cc.)					
Number	5	5	4	3	2
Mean	19.7	25.6	10.4	6.6	2.2
Standard deviation	6.6	24.8	4.5	3.6	2.8
Total bilirubin (mg.%)					
Number	5	5	4	3	...
Mean	137	187	237	245	...
Standard deviation	84	112	128	58	...
Direct bilirubin (mg.%)					
Number	5	5	4	3	
Mean	91	87	109	94	...
Standard deviation	59	16	66	23	...

Bile production was observed promptly and

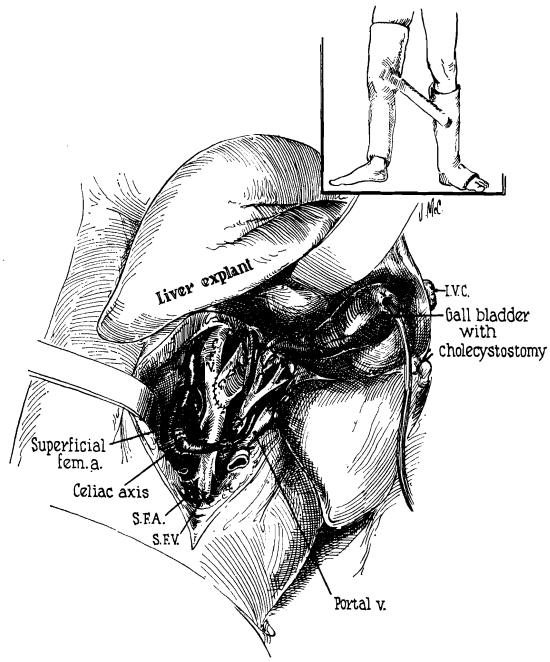

FIG. 5. Technic of extracorporeal liver homotransplantation used in case I. The superficial femoral artery was anastomosed to the hepatic artery, and the hepatic venous outflow was directed into the femoral system. The liver was left *in situ* for three and a half days.

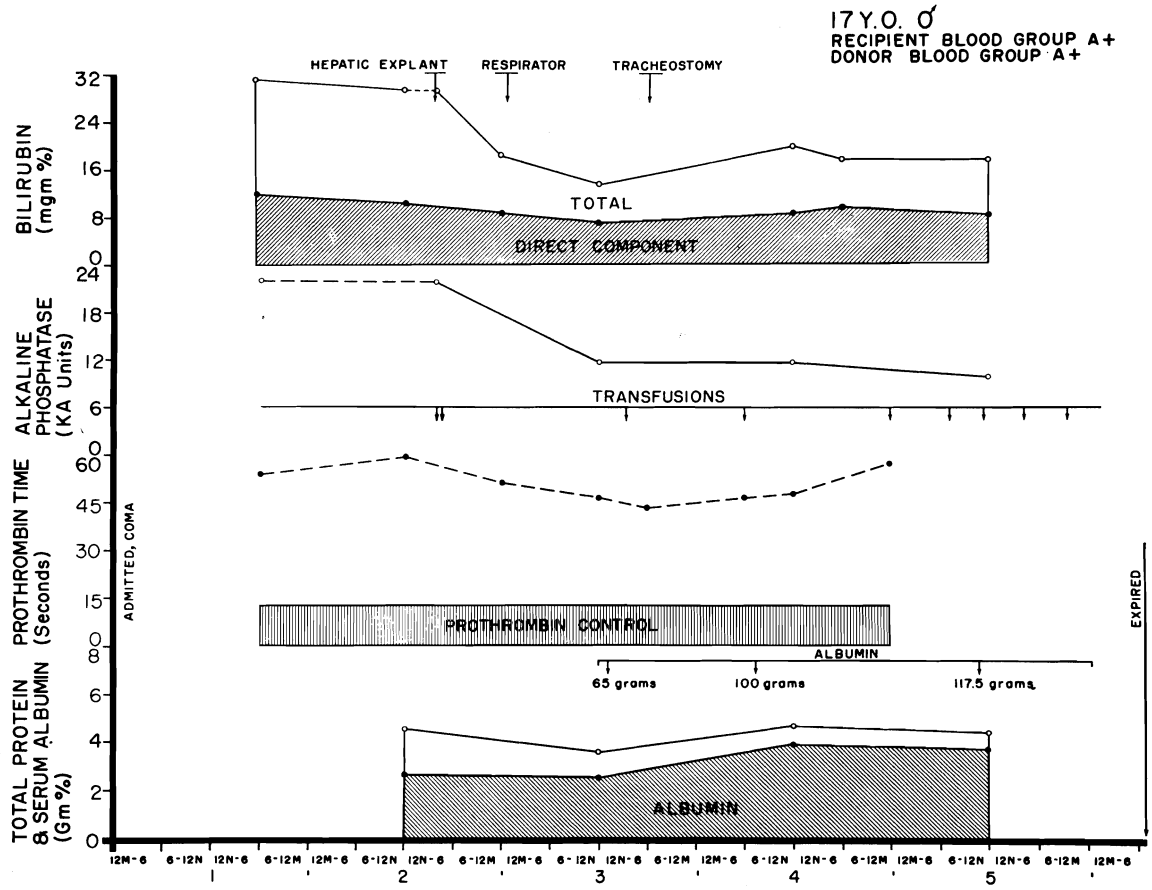

FIG. 6. Course of a seventeen year old boy dying of hepatitis who was provided with an extracorporeal liver homograft. There was prompt clearing of bilirubinemia and alkaline phosphatemia but little evidence of synthetic function.

continued for thirteen to thirty hours after revascularization. Bile flow was measured in five of the six dogs, and the average value for six hour periods as well as the bilirubin concentrations are summarized in Table IV. A sharp diminution in volume was usually observed after fifteen or sixteen hours.

Sections of the extracorporeal livers were examined at autopsy by Dr. Richard A. MacDonald. There was no evidence of rejection. The most prominent feature was sinusoidal congestion, often with atrophy and/or centrilobular necrosis of hepatocytes. In two instances the degree of congestion was extremely severe.

The demonstration that moderately prolonged hepatic support was possible without the need for special equipment prompted the use of this method for two patients dying of hepatitis.

CASE I. A sixteen year old white boy was admitted September 27, 1965 with coma and jaundice. Three weeks previously he was hospitalized elsewhere with infectious hepatitis which at first responded favorably to bedrest and diet but which subsequently became worse. One day prior to admission to Colorado General Hospital coma developed and he became deeply jaundiced.

Numerous petechiae were present over the entire body. The liver was felt two fingerbreadths below the right costal margin. There was bilateral sustained ankle clonus and generalized hyper-reflexia. Bilirubin, alkaline phosphatase, and prothrombin time are depicted in Figure 6. Serum glutamic oxalacetic transaminase was 1,700 Sigma-Frankel units. Blood type was A positive. He was treated with intravenous glucose, intragastric neomycin, enemas, hydrocortisone, arginine, vitamin K, and multiple vitamins. His neurologic status deteriorated with the development of decerebrate rigidity and bilateral Babinski reflexes.

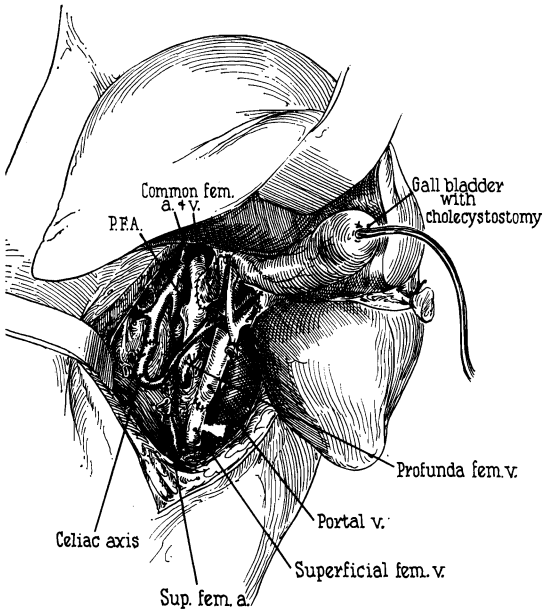

FIG. 7. Technic for extracorporeal transplantation of a chimpanzee heterograft (case II). The details are similar to those in case I except that the femoral vein was transected and the distal end anastomosed to the portal vein.

Twenty-four hours after admission an extracorporeal liver was placed in the right groin; anesthesia was unnecessary. The donor was a sixty-nine year old man who died of myocardial infarction in an adjacent hospital. External cardiac massage was conducted for forty minutes after death at the end of which time the liver was perfused with chilled lactated Ringer's solution and excised. The time from death to re-establishment of a blood supply was 155 minutes. Only the hepatic artery was revascularized. (Fig. 5.) A cross leg cast was applied to damp convulsive movement of the legs. Bile production was noted within minutes after re-establishment of the blood supply.

The biochemical changes after the procedure are depicted in Figure 6. A sharp drop in the serum bilirubin content and alkaline phosphatase occurred promptly. The slight improvement in prothrombin time was of doubtful significance. Administration of albumin made impossible the evaluation of changes in the serum protein. Due to leakage in the ductal system, accurate collection of bile was impossible.

Several observers thought there was lessening of the comatose state, but this could not be objectively documented. Nine and a half hours postoperatively he had a generalized convulsion with respiratory arrest and thereafter had to be maintained on a respirator. His subsequent course was one of progressive deterioration with the development of fixed, dilated pupils, intermittent bleeding from the gastrointestinal tract and oropharynx, and renal shutdown. His temperature was maintained at approximately 37°c. with a hypothermic blanket. He died eighty-four hours after operation. The liver retained a good color and turgor throughout.

Biopsies of the donor liver were obtained at one, forty-two, and sixty-six hours as well as at autopsy and were examined by Dr. K. A. Porter of London, England. The first specimen was normal except for some fatty infiltration of centrilobular hepatocytes. Subsequently progressive loss of centrilobular hepatocytes was noted until at autopsy only a few hepatocytes immediately adjacent to the portal veins remained alive. By this time there was moderate infiltration of the portal tracts with lymphoid cells, less than 5 per cent of which were pyroninophilic. The patient's own liver was virtually destroyed by hepatitis, with only a few residual hepatocytes.

CASE II. A seven year old girl was admitted to Colorado General Hospital on October 11, 1965 in hepatic coma. In June she had had acute viral hepatitis with subsequent incomplete clearing of the icterus. Three weeks prior to the present admission, the jaundice deepened, with rapidly developing ascites a few days later. Two days before admission she became comatose.

Petechiae were widespread. The liver and spleen could not be felt. Results of chemistries were: blood urea nitrogen 6 mg. per cent, bilirubin 18.8 mg. per cent, blood sugar 100 mg. per cent, ammonia 227 μg. per cent, alkaline phosphatase 12.4 Bessey-Lowry units, and prothrombin time 20 per cent. Plasma phenylalanine, tyrosine, and methionine were elevated. Blood type was O positive. She was treated with intravenous Swiss gamma globulin, intramuscular gamma globulin, intravenous glucose, oral and rectal neomycin, hydrocortisone, vitamin K and, multivitamins. Efforts to find a suitable cadaveric liver for extracorporeal transplant were unsuccessful.

Consequently, a chimpanzee liver heterograft was attached to the right femoral vessels twenty-four hours after admission. The chimpanzee, which had blood type O, weighed 40 pounds. The animal was cooled to 30°c. before operation. The liver was washed free of blood by perfusion of lactated Ringer's solution through the portal vein. The ischemic interval was sixty minutes. The technic of anastomosis (Fig. 7) differed from that in case I in that the portal vein was provided with a venous inflow from the distal transected femoral vein, thereby establishing a double blood supply.

For the first twelve hours the color and consistency of the liver were relatively normal. Portions of the right lobe then became turgid and discolored, a process which gradually involved most of the liver. The heterograft was removed twenty-five hours after revascularization. During this interval the serum

bilirubin dropped from 18.8 to 9 mg. per cent and the alkaline phosphatase from 12.4 to 8.4 Bessey-Lowry units. On the day after removal of the graft, the bilirubin had risen back to 22.8 mg. per cent. There was no improvement in prothrombin time.

During the period of extracorporeal hepatic support the coma lightened to an irritable and irrational state. In the ensuing week her neurologic condition was variable, but at the end of this time she had a remarkable clearing of sensorium which lasted for a few days despite no improvement in the liver chemistries. Several days later gastrointestinal hemorrhage and increasing hepatic failure developed leading to death sixteen days after admission. At autopsy she had postnecrotic cirrhosis with evidence of active hepatitis. Multiple ulcerations of the esophagus, stomach, and duodenum as well as diffuse intracerebral hemorrhage were present.

The chimpanzee heterograft was biopsied at one hour, twelve hours, and at the time of its removal. The tissues were examined by Dr. K. A. Porter. The first specimen was essentially normal. By twelve hours tiny fat droplets had accumulated in the hepatocytes. At removal several nonviable areas were located superficially, but the central portion of the liver was well preserved. Antemortem clot was present in a number of small vessels, and the main hepatic artery was completely occluded. Many normal hepatocytes were found, particularly around the periphery of the lobules. The portal tracts were lightly infiltrated with mononuclear cells, few of which had pyronine-positive cytoplasm.

Comment: The clinical benefit in these two cases was disappointing. In each case substantial clearance of bilirubin and alkaline phosphatase seemed to have occurred, but there was little or no evidence of synthetic activity despite the fact that the grafts were in place for one to three and a half days. In case II there appeared to be a chance for chronic survival, but progression of the patient's original disease ultimately led to death. In view of these experiences and those obtained by others with the porcine liver, it seems unlikely that these temporizing technics will play an important role in promoting the feasibility of liver transplantation.

SUMMARY

Three general areas of research which bear on the developing field of liver transplantation are reviewed. These are: (1) the prospects of obtaining better immunosuppression with particular reference to heterologous antilymphocyte serum; (2) the possible use of antigen matching technics as an advanced indicator of donor-recipient histocompatibility; (3) a simplified system of extracorporeal transplantation designed to provide temporary hepatic support.

ADDENDUM

The dog still alive three weeks after orthotopic liver transplantation at the time the manuscript was submitted has continued to do well and is now two and a half months postoperative. He has not received any ALS after three weeks. Another dog, pretreated with ALS, has now lived for six weeks after orthotopic transplantation; this animal has never received postoperative therapy. Both dogs now have marked lymphocytosis. The effect of ALS is therefore relatively long-lasting and does not require continuous lymphopenia.

In addition, orthotopic liver transplantation has subsequently been performed in four dogs being treated solely with concentrated gamma globulin purified from horse ALS. Three of the four dogs are in their fourth postoperative week. The evidence is thus mounting that ALS products may eventually find a practical place in immunosuppressive regimens in man.

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