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Transplantation of the Kidney and Liver

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In the interval allowed to me, I would like to say first something about renal transplantation, and then in the remaining time comment on our results in the new field of liver transplantation. My particular emphasis with both organs will be on the use of antilymphocyte globulin (ALG) and how the employment of this substance has influenced the transplantation program at the University of Colorado. In doing this I shall say nothing about the underlying animal work with antilymphocyte serum (ALS) or globulin (ALG) in which these agents were used as the sole immunosuppressive therapy, since in the clinical application we have used ALG as an adjuvant drug added to treatment with azathioprine and with reduced doses of steroids.

Kidney transplantation

First series

In order to develop some background for the way in which antilymphocyte globulin has influenced our results, I would like to briefly summarize our earlier experiences with clinical transplantation. Fig. 1 is a life-survival curve established with the series of cases treated at the University of Colorado from 1962 until March of 1964. It represents a group of patients, in which there is now a minimum followup of considerably more than four years and with a maximum followup that goes out to more than 5½ years. These are cases in which the donor-recipient combinations were selected essentially at random since there were no effective methods of histocompatibility typing at the time. The only selection that was practised, at least in most of these cases, was to insure conformity or compatibility of red blood cell types.

There were 64 patients in this original series, 46 of whom received kidneys from familial donors. The other 18 received kidneys from non-related living donors. One can see that the highest loss rate was within the first few months, and that after this time there was a fairly stable survival. In fact, in the related cases there were only 3 additional deaths after the first 6 postoperative months, 1 each in the 2nd, 3rd, and 4th postoperative years, so that in this group of cases there are still 29 out of the original 46, or some 60% of the original recipients still alive.

In contrast, there was a much higher earlier death rate after the non-related transplantations and then with a continued delayed attrition until at the present time in the 5th postoperative year, there are only 2 of these original recipients still alive (Fig. 1).

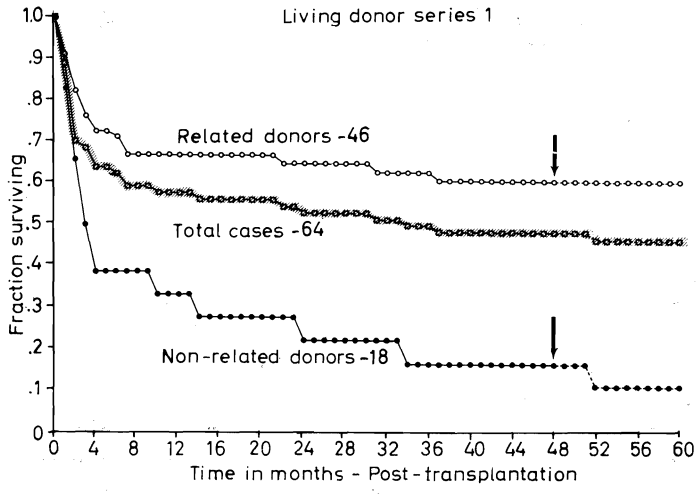

Fig. 1. Life survival curves of 64 patients treated in Denver with renal homotransplantation between November 1962 and March 1964. Preoperative histocompatibility testing was not done. As of November 1, 1968, a minimum followup of 4⅔ and a maximum followup of 6 years is available. Note the much better results with intrafamilial homotransplantation.

Second series

At the end of this experience we stopped doing transplantations for about 6 months, from March until October of 1964. The reason for this was that it had not been possible, at least in our hands, to improve the survival after transplantation. The death rate in the last half of the aforementioned original series was almost the same as in the first half.

In October of 1964 the program was reopened but with a significant change. Working in collaboration with TERASAKI, we tried to select donor-recipient combinations on the basis of serologic analysis of histocompatibility antigens. An additional 42 cases were compiled between October of 1964 and April of 1966. 25 of these new transplantations were intrafamilial. To our disappointment, the ultimate loss rate in this series was almost exactly the same as it had been previously. About a third of these recipients of consanguineous grafts died in the first postoperative year (Fig. 2). This was not particularly surprising, not only because of the limited sizes of the family donor pools but also because of our policy at that time not to exclude anyone from homograft recipiency solely because we could not find a good match. There was no statistically significant upgrading of the histocompatibility matching as determined during this period by TERASAKI.

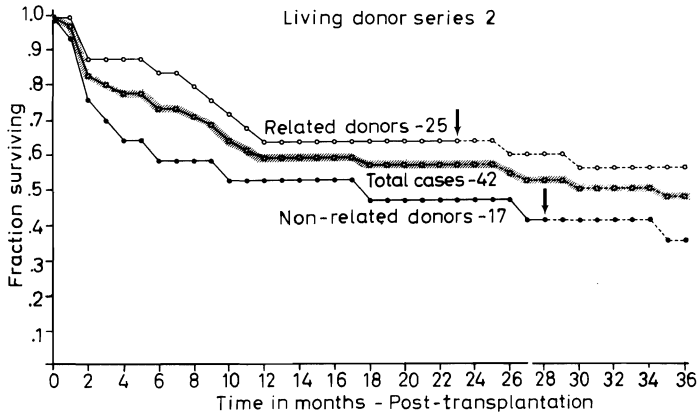

Fig. 2. Survival of 42 patients treated with renal homotransplantation between October 1964 and April 1966. An attempt was made by TERASAKI to select the most compatible donor amongst available volunteers.

In the non-related transplantations there was some improvement in survival, and now 55% of the patients lived through the 1 postoperative year (Fig. 2). In this group there had been an improvement in the histocompatibility matching since it had been possible to draw donors from a much larger pool.

ALG series

It seemed obvious to us at the end of this trial that the further improvement of results was dependent on improvements in immunosuppression. It was at this stage that ALG was introduced clinically.

Dr. PICHLMAYR and others have already discussed how ALS is prepared by immunization of a heterologous host, how the globulin (ALG) is extracted, and the fact that it can be used with intramuscular or intravenous injection. As it has already been emphasized, proper absorption of the serum, before the globulin is extracted, is an essential feature of the preparation of ALG, if it is to be reasonably safe. Dr. PICHLMAYR has also told you something about the toxicity of this ALG.

The ALG that was used from June of 1966 for the 1st year and a half of our study is shown in Fig. 3. It was prepared by ammonium sulfate precipitation and consisted of γ G, T-equine globulin, and often traces of α globulin.

The first patients in this series were treated from June of 1966 until the following December. There were 20 in all. Inclusion was not on the basis of good histocompatibility conformity or match. Of the 20 patients in the series, 1 was lost in the 2nd postoperative month from a surgical technical accident. The other 19 of these patients are still alive after a followup of some 22 to 28 months. Thus the 2 year survival with intrafamilial transplantation using ALG as an adjuvant agent was 95% (Fig. 4). Since

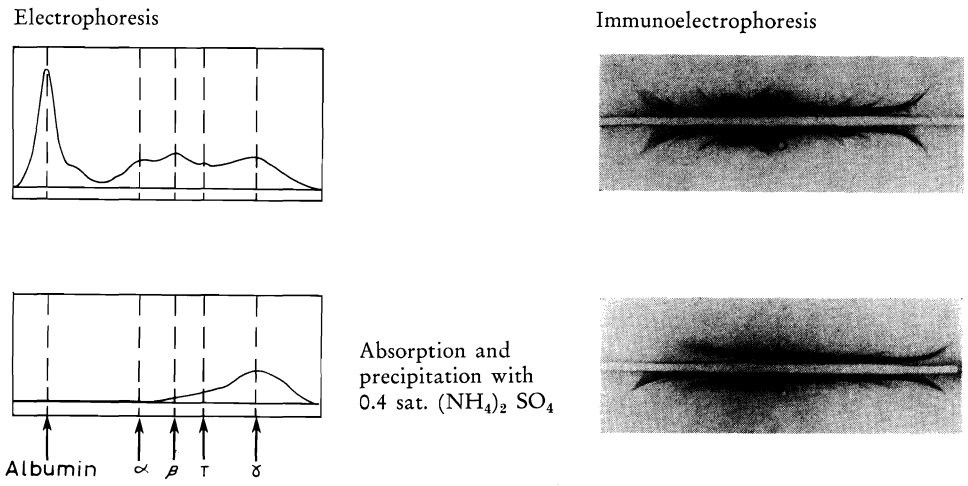

Fig. 3. Electrophoresis and immunoelectrophoresis of absorbed antihumanlymphocyte serum and the protein obtained from it by two precipitations with 0.4 saturated ammonium sulphate, two dialyses and lyophilization. The final product which was used clinically, consisted almost entirely of γ G and T-equine globulin. [By permission of Surg. Gynec. Obstet. *124:* 1 (1967).]

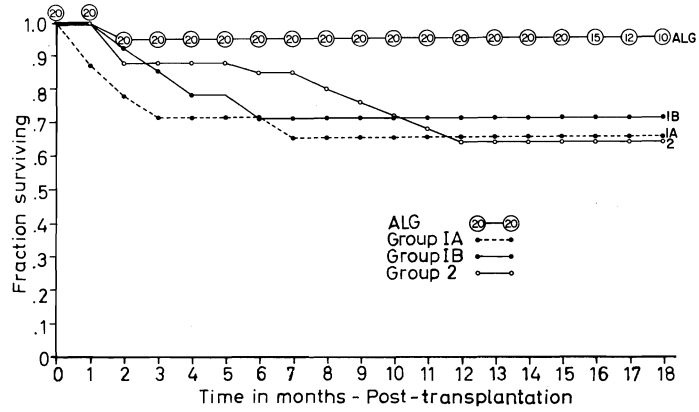

Fig. 4. Survival curve of the first 20 patients treated with antilymphocyte globulin (ALG) compared o that in 3 previous series of consanguineous transplantation at our institutions. Followups in the globulintreated group are 22 to 28 months. The numbers in the upper curve indicate the patients at risk for each monthly interval.

December of 1966, renal transplantation has become a service procedure performed by residents, by houseofficers and by fellows. It is a little painful for the senior surgeons

to now realize that the houseofficers or those in training have just as good results as those obtained by their senior colleagues.

The reason I think for the improvement in our results is that with ALG it has been possible to use smaller doses of both azathioprine and steroids. The reduction in the latter drug is probably particularly significant. All people with extensive experience in transplantation have come to realize that the real villain in the picture of renal transplantation has been prednisone rather than azathioprine. The morbidity in the ALG treated patients has been correspondingly less as the requisite steroid doses have been decreased. Coincidentally, the renal function in these cases has been better on the average than in past cases.

Liver transplantation

The first trials of liver transplantation in man were made in 1963 in Denver. From this time until the summer of 1967 there were a total of 9 such attempts in our institution, at the Peter Bent Brigham Hospital in Boston, and by DEMIRLEAU in Paris. In each of these cases, the recipient had died within 23 days or less. The causes of death were complex but they generally were due either to the failure to provide good homograft function from the beginning or else failure to retain this function for any significant period of time.

Since the summer of 1967 we have made 9 new attempts at liver transplantation with distinctly encouraging although still imperfect results. 4 of these 9 patients are alive including the 1 to whom Dr. TERASAKI alluded.

(The foregoing portion of the lecture is essentially as presented at the meeting. The following account has been largely rewritten to permit a followup report of 5 months longer duration. The statistics for the 9 mentioned cases have thus been brought up to date to October 25, 1968.)

Of the 9 recipients, 5 have died after periods of 60, 105, 133, 186, and 400 days. The other 4 are living after 3, 5, 6 1/2, 7 1/2 and 8 1/2 months. In the 9 cases the indication for operation was extrahepatic biliary atresia in 6 and hepatoma in the other 3. 7 of the recipients were children and 2 were adults.

All of the patients who have died developed the specific complication of partial necrosis of the right hepatic lobe. Autopsy studies in 4 of the 5 cases revealed selective thrombosis of the right hepatic artery.

The etiology of this complication is probably a complex one but one factor may have been mechanical. Autopsy studies have shown that failure to resuture the ligaments of the homograft to that of the host can result in a downward and medical rotation of the right lobe and a consequent kinking of the right hepatic branch (Fig. 5). In subsequent cases the falciform and triangular ligaments have been resutured and the regional hepatic gangrene has not been seen again.

So far the longest survival after orthotopic liver transplantation in man has been 400 days. This recipient ultimately died of widespread carcinomatosis from her original hepatoma. Another patient who has perfect liver function 6 1/2 months post-transplanta-

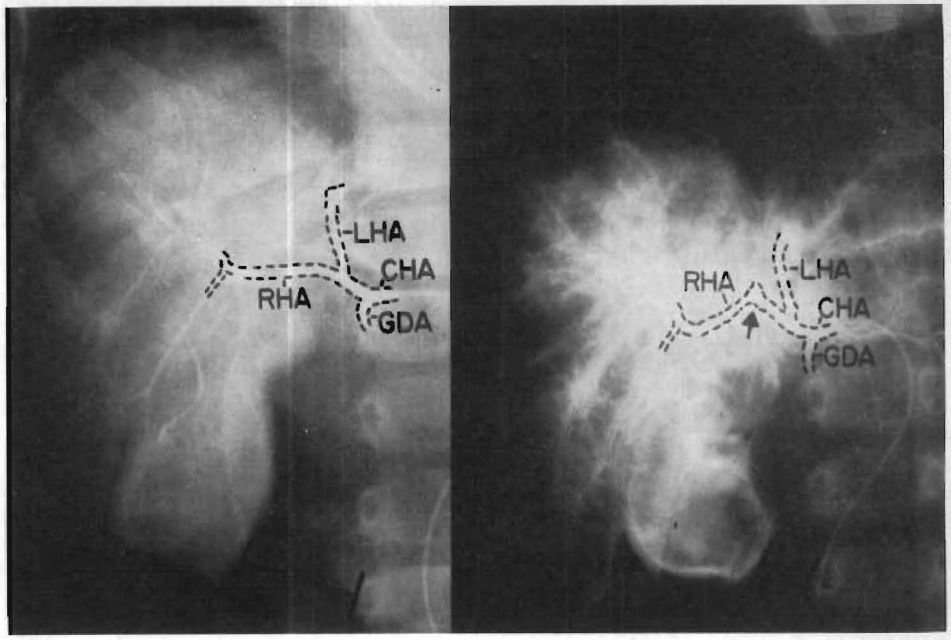

Fig. 5. Angiographic studies performed in a 5 year old child immediately after her death from head injuries. Dye was injected into the common hepatic artery (CHA) proximal to the gastroduodenal artery (GDA). *Left:* Initial injection. Note the smooth course of the right hepatic artery (RHA). *Right:* The restraining ligaments of the liver have been incised, a cholecystoduodenostomy performed, and the head of the x-ray table elevated to 60°. The right lobe of the liver has rotated down and medially. The course of the left hepatic artery is undisturbed. However, the right hepatic artery (RHA) is now severely kinked where it passes beneath the common duct. [By permission of Ann. Surg. *168:* 392 (1968).]

tion has recently developed evidence of pulmonary metastases. Thus the value of liver replacement for the treatment of hepatic malignancy is probably going to be limited by the aggressive nature of this disease.

Conclusion

The whole picture or organ transplantation has undergone an amazing transformation in the last 5 or 6 years to the point where renal transplantation as a method of treating terminal renal failure has become a spectacularly successful form of therapy.

The developments which have made this possible provide a basis in 1968 for attempts at transplantation of other vital organs including the liver, heart, and lung. Survival after orthotopic liver transplantation has already been achieved in man for more than 13 months, and more recently experience with heart transplantation has suggested that this procedure also will be of clinical therapeutic value.