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Renal Homotransplantation: 20 to 36 Months Later

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Doctor Starzl is an acknowledged leader in the area of organ transplantation. Born in LeMars, Iowa, Dr. Starzl received his education at Westminster Univ., Fulton, Mo., and a Master's, Ph.D. and M.D. from Northwestern Univ. at Chicago. His surgical training was at Johns Hopkins, in Miami, Fla., and at the VA Hospital in Chicago, where he completed training in thoracic surgery. He became Assistant Prof. in Surgery at Northwestern while with the VA Hospital. He transferred to the position of Chief of Surgery, VA Hospital Denver, early in 1962 where he began the series of fundamental and clinical efforts culminating in his recent text "Experience in Renal Transplantation."

FROM November 1962 to March 1964, 64 uremic patients were treated with renal homografts obtained from living volunteer donors. The surgical and non-operative techniques used to treat these patients were adapted from the pioneering methods described in this country by Hume,[1] Murray, Merrill and Harrison,[2] and Goodwin[3]—and in Europe by Calne,[4] Küss,[5] Hamburger[6] and Woodruff.[7]

Thirty-seven, or 58 per cent of these 64 recipients, lived for at least one year (Fig. 1). One died after 13½ months of non-renal causes. Two others died of sepsis and recurrent renal failure at 22 and 24 months, respectively. The other 34 are still alive with continuous function of their homografts for 20 to 36 months. Twenty-one of these patients have already passed the two-year mark.

The one-year survival of patients treated with homografts from blood relatives was 31 of 46, or 67 per cent. Only one patient has subsequently died; 65 per cent are still living. In contrast, only 6 of 18 patients with non-related donors lived as long as 1 year and 2 of these have subsequently died (Fig. 1).

Within the favored related group, the best results were with parent-to-offspring transplants (Fig. 2). Seventy per cent of these recipients are alive. Sixty per cent of the sibling group survived for 1 year, although one died later at 22 months; 3 patients are also well who received kidneys from an aunt, uncle or cousin.

Renal function is adequate in all of the 34 chronic survivors, and in many it is completely normal. In most instances, the requisite intensity of immunosuppressive therapy progressively declined after the first few post-operative months. In 12, however, efforts to re-

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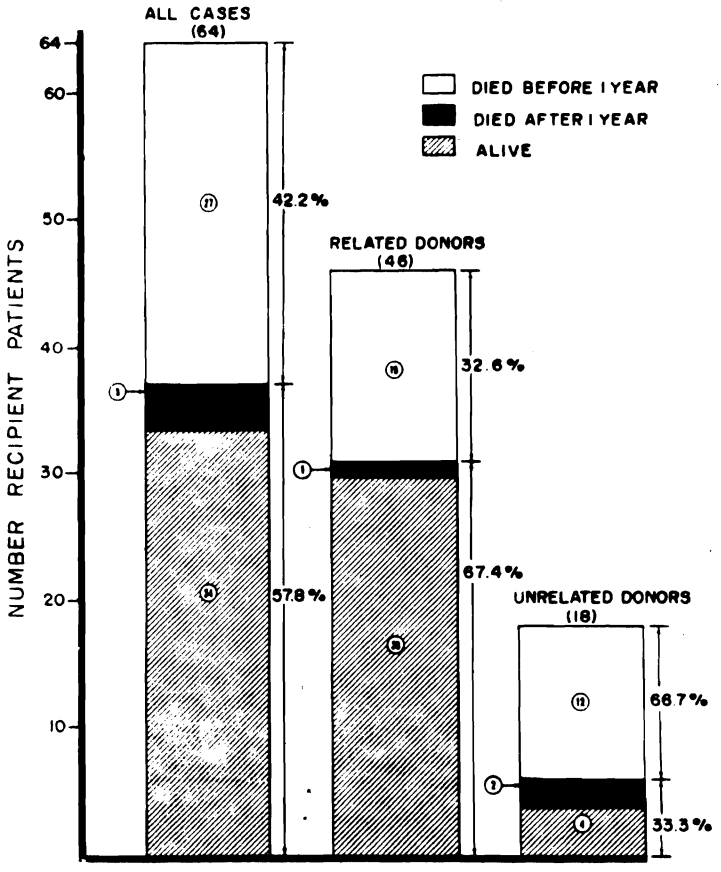

Fig. 1. Results after 20 to 36 months in 64 consecutive patients treated at the University of Colorado Medical Center with renal homografts obtained from living volunteer donors. Identical twin cases are not included. Three deaths occurred after one year. Note that almost two-thirds of the patients who received kidneys from blood relatives are alive from 20 to 36 months after transplantation. Only a third of these whose donors were unrelated lived as long as a year, and 2 of these patients died during the second postoperative year.

duce or discontinue the steroid dose precipitated a late rejection, from 4 months to more than a year after operation. Although such late rejections proved to be reversible, all but two of these patients eventually had permanent functional impairment. In such patients chronic steroid therapy will probably be required for the rest of their lives.

Several patients became jaundiced late after transplantation, possibly because of the hepatotoxicity of azathioprine. In some, the liver injury promptly receded with reduction of the azathioprine dose. However, the 3 patients who died after 1 year all had a combination of liver injury and sepsis in their terminal state. Late hepatic complications may eventually prove to be a serious threat to other chronically surviving recipients of renal homografts.

Histological Changes in Transplanted Kidneys

Specimens from 21 of these chronically tolerated homografts were subjected to pathologic examination by Dr. K. A. Porter of St. Mary's Hospital and Medical School, London; tissues were obtained by biopsy 21 to 26 months after operation. Three of the homografts were normal. In the others, there was an assortment of abnormalities which were often not associated with impairment of renal function.

There were vascular lesions which had

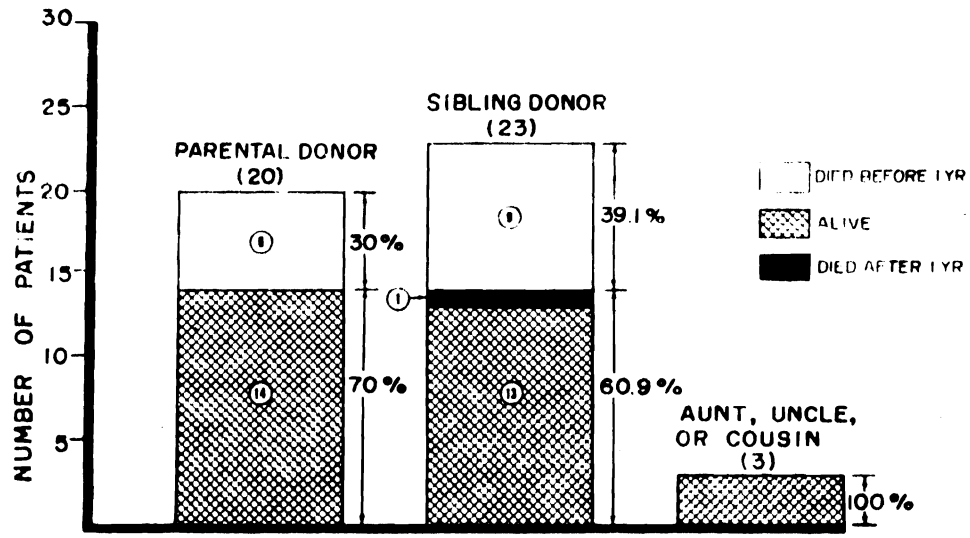

Fig. 2. Breakdown of results at the University of Colorado Medical Center in patients who received kidneys from blood relatives other than identical twins from 20 to 36 months ago. The best results were with parental donations. The late death in the sibling group was after 22 months.

many forms; fibrous intimal thickening of interlobular arteries often with rupture or duplication of the internal elastic lamina, deposition of a hyaline-like substance in the subintimal layer of afferent arterioles, and deposition of the PAS-positive hyaline material in the glomerular capillaries.

The homografts with vascular lesions often had other secondary morphologic changes; fibrosis of the glomerular tuft, periglomerular fibrosis, interstitial fibrosis, or tubular atrophy.

In addition, the majority of the homografts contained focal accumulations of mononuclear cells. Ten to 40 per cent of these cells consisted of the pyronine positive variety which are traditionally found in acutely rejecting homografts. In the chronically functioning homografts, they seem to be reasonably well tolerated.

Problems in Histocompatibility

Encouraging though these clinical results are, they have raised more practical questions than they have answered. For example, what biologic factors in these individual cases have conspired to allow success? If these could be identified, the same conditions could be established for future trials.

The most obvious possibility is that these surviving patients had accidentally achieved a good histocompatibility match with their donors. This likelihood has prompted Dr. Paul Terasaki of Los Angeles to use these chronic survivors as a test group to see if his lymphocyte typing method actually measured or was related to histocompatibility. He has approached the problem in two ways.

First, the antigen matches in the surviving donor-recipient pairs were compared to the random antigen matches actually measured in an unselected population. The results were most clear in the cases with non-related donors. These patients all had antigenic mismatches with their donors which fell into the favorable portion of a random distribution curve. It might be inferred that the patients who received poorly matched kidneys are dead.

Secondly, a correlation was also attempted in all the surviving patients between the smoothness of their recovery and the completeness of antigen matching with their donors. Although the latter correlation was crude and incomplete, the best results by and large tended to be in those patients who had received the best matches. These results suggest that the method should be given a trial for prospective donor selection.

Finally, a word may be in order concerning

the possible benefit of pretransplant thymectomy. Four patients in the total series received this extra operation prior to their transplantation. All four have had an untroubled late post-transplant course. None has required steroids for the past 1½ years and each has perfectly stable function. Unfortunately, all four of these patients also had an unusually compatible antigen match with their donors. The role of histocompatibility factors versus thymectomy in achieving these exceptionally good results cannot, therefore, be separated.

Conclusions

These results indicate that renal homotransplantation can be an effective way of treating patients with terminal uremia. Even during the developmental period of this study, the majority of recipient patients achieved a high degree of social and vocational rehabilitation —and if related donors were used the salvage rate 21 months or longer after operation is still 65 per cent. Nevertheless, the procedure is still experimental. The projected fate of patients in whom there is still evidence of low-grade host versus graft activity is unknown. The role of thymectomy or splenectomy in promoting acceptance of the homografts is not proven. Further work is required on the histocompatibility matching techniques. For the moment, it would seem wisest to regard renal homotransplantation as an effective but incompletely characterized form of palliative therapy.

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