



Published in final edited form as:

J Am Med Womens Assoc. 1966 March ; 21(3): 207–209.

The Therapeutic Potential of Whole Organ Transplantation*

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A few years ago it seemed highly unlikely that homotransplantation of tissues and organs was so soon to play a significant role in the medical armamentarium, despite an enormous quantity of research dating back more than a half century. The view persisted that the severity and perseverance of homograft rejection constituted an insurmountable barrier to the successful use of alien tissue.

Since 1962, these attitudes have undergone a remarkable change. More than a hundred patients throughout the world have had significant prolongation of life through functioning renal homografts. Long-term survival has been obtained in laboratory animals after homotransplantation of other organs including the liver, lung, heart, and spleen. Earlier unwarranted pessimism concerning the fate of homografts has been replaced by what, in some circles, may be viewed as overoptimism since the life expectancy of patients or animals with transplants tolerated over a long period of time is not yet known.

In this communication, a brief account will be given of the results of clinical renal homotransplantation at the University of Colorado Medical Center, focusing attention only upon those patients treated from 20 to 36 months ago. A brief description of the encouraging results after experimental liver transplantation will also be included.

RENAL HOMOTRANSPLANTATION

Sixty-four consecutive patients were treated with renal homografts from living volunteer donors between November 1962 and March 1964.^{1,2} Rejection was controlled with azathioprine (Imuran), prednisone, actinomycin C, and in one case with total body irradiation. The greatest risk from failure due to homograft malfunction or to toxicity from

* Aided by Grants AM 06283, AM 06344, HE 07735, AM 07772, FR 00051, and FR 00069, from the U.S. Public Health Service.

This is a condensed version of the paper presented by Dr. Starzl at the scientific session—Ed.

The following papers were presented at the 1965 Annual Meeting, November 13, in Chicago. We wish to thank Lederle Laboratories for their support.—The Editors

immunosuppressive agents is during the first few postoperative months when variable degrees of rejection are common. The phenomenon of rejection has proved to be reversible with intensification of immunosuppressive therapy. Later, the aggressiveness of therapy can very often be relaxed; nevertheless, many patients now living for a long time after operation have had continuing evidence of low-grade host-against-graft immunologic activity.

The results in these 64 patients are summarized in Table I. Thirty-seven (58 per cent) of the 64 patients lived for at least one year after operation. Three subsequently died after 13½, 22, and 23½ months. In all 3 cases, renal function was still sufficient to maintain active life, but other complications of chronic liver injury (possibly drug induced) and sepsis were the direct cause of death. The remaining 34 patients (53.1 per cent) are still alive after 20 to 36 months. Twenty-three of these patients have already passed the 2-year level of convalescence.

The best results were in the 46 cases in which the kidney was provided by a blood relative (Table I). Thirty-one of these patients (67 per cent) lived for at least 1 year; 30 (65.2 per cent) are still alive with an average survival of 28 months. In contrast, only 6 of the 18 patients (33 per cent) who received kidneys from nonrelated donors lived beyond 1 year, and 2 have subsequently died.

Kidney function is adequate in all of the currently surviving patients although in some there has been a gradual decline in the quality of renal excretion and in others continuous stable function has required the recurrent administration of potentially toxic doses of prednisone. These clinical findings suggest that future death will occur at a gradual rate due to continued low-grade rejection. This impression is strengthened by study (by Dr. Ken A. Porter, St. Mary's Hospital and Medical School, London) of biopsies taken from 21 of the homografts obtained after approximately two years' residence in their human hosts. The following are some of Dr. Porter's findings.

Three of the homografts were normal. In the others, there was an assortment of abnormalities often not associated with impairment of renal function.

There were vascular lesions which had 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 frequently 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 acute homograft rejection. In homografts functioning over a period of time such cells seem to be reasonably well-tolerated.

HOMOTRANSPLANTATION OF THE LIVER

There are two general methods for whole organ transplantation of the liver. One involves the extirpation of the host animal's own liver and replacement with an organ obtained from a nonrelated mongrel animal. The homograft is revascularized in a normal manner. Using immunosuppressive regimens similar to those employed for the kidney, survival in our laboratories has been obtained for as long as 20 months.³ Most of the general problems

encountered are comparable to those already well-defined after transplantation of the kidney.

In spite of these successful experiments, 7 efforts at human orthotopic transplantation in Denver and elsewhere have failed; maximum survival has been 23 days. These experiences have defined problems of technique, organ preservation, and control of coagulation which must be successfully managed in future trials.

An alternative method of liver transplantation, which may some day have application for the treatment of hepatic failure due to benign liver disease, is heterotopic transplantation.⁴ Here, the host liver is not removed and the homograft is placed in some abnormal location such as the pelvis, left upper quadrant, or one of the paravertebral gutters. Although the concept of heterotopic transplantation is an attractive one, since residual function in the host liver is not sacrificed, it is still not known whether this approach is a sound one. Recent laboratory investigations have shown that when two livers are present in the same animal each may be responsible for injury to the other, apparently by a mechanism of competition for nutritional metabolites. Such physiologic problems as well as those concerned with the space limitations in a recipient's abdomen make it necessary to defer judgment about the future potential usefulness of this approach. Clinical heterotopic transplantation is known to have been attempted in at least 6 institutions, with maximum survival of only 5 weeks.

SUMMARY

More than half of an original series of 64 patients receiving renal transplants, treated at the University of Colorado Medical Center from 20 to 36 months ago, are still alive. The ultimate life expectancy of these remaining patients is not known. Significant improvement in results after liver transplantation has been documented in animals, but long-term success has not yet been obtained in patients.

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TABLE I

Remits in 64 Consecutive Patients Treated with Renal Homografts Obtained from Living Volunteer Donors During the Interval from November 1962 to March 1964; Survival is to the First Part of December 1965

	No.	Lived 1 Year	Died After 1 Year	Alive
Total Series	64	37	3*	34 [†]
Related donors	46	31	1	30
Nonrelated donors	18	6	2	6

* Late deaths at 13½, 22, and 23½ months.

[†] Of these patients 23 are from 2 to more than 3 years. The other 11 are between 20 and 24 months.