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Editorial

The Past and Future of Organ Transplantation

It has now been thirty years since the first attempt was made at renal homotransplantation in man. The early efforts to apply this form of therapy to the treatment of terminal renal disease were doomed to failure since they preceded an appreciation of the problems to be encountered. Knowledge of homograft rejection was scanty, and the therapy necessary to prevent this process was not understood at all. Since that time, a rational explanation of rejection has been provided by the studies of Medawar and those of other investigators. The evidence is overwhelming that rejection is due to immunologic repudiation of the alien tissue by the host. The intensity of this reaction is related to the degree of genetic dissimilarity between the donor and the recipient. Its prevention depends to a greater or less extent upon crippling the host's capacity for immunologic response to unfamiliar antigens.

The initial attempts at potentiating homograft function by alteration of the host were made with total-body irradiation. Such therapy proved to be of value for the prevention of rejection, but the requisite dosage was so high that most of the recipient patients died from bone-marrow depression and sepsis. Despite the exorbitant risk imposed, 3 patients are still living from this pioneer era, the longest follow-up being on a young man treated almost six years ago by Murray and Merrill with a homograft from his fraternal twin. Today, American centers do not generally use total-body irradiation, although it remains an important element in the overall therapy employed by Hamburger and some of the other European authorities.

In spite of the occasional encouraging experience, the prospect of achieving significant clinical benefit from renal homotransplantation in more than the isolated case seemed remote indeed until the discovery by Schwartz and Dameshek of the immunosuppressive properties of 6-mercaptopurine in 1959 and the subsequent testing of this drug and its analogue, Azathioprine, by Calne and Zukoski. It immediately became apparent that prevention of homograft rejection could be accomplished with greater regularity and with less risk to the recipient than had been possible with total-body irradiation; long-term homograft viability was achieved in animals without the necessity of concomitant host leukopenia or agranulocytosis. During the ensuing several years, clinical efforts at homotransplantation of the kidney have proceeded with increasing regularity. By Sept. 15, 1964, almost 500 such potentially therapeutic operations were known, by virtue of their entry into the National Academy of Science Registry, to have been performed throughout the world.

The experience with clinical renal homotransplantation resulted in a number of significant observations which had not been appreciated from animal studies. It had long been assumed that rejection was one of nature's most powerful and persevering reactions, which was inexorable when once begun. It was soon learned that rejection was a reversible process and, more recently, evidence has accrued that it occasionally runs a spontaneously re-

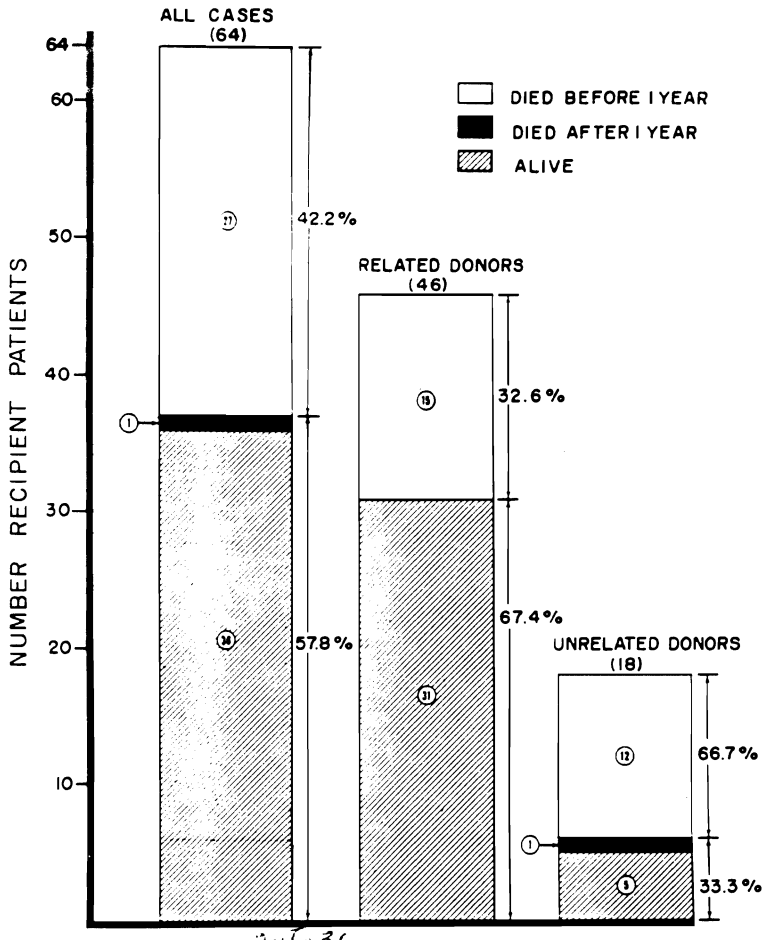

Fig. 1. Results after ~~thirteen~~ months of ~~follow-up~~ in 64 consecutive patients treated at the University of Colorado Medical Center with renal homografts obtained from living volunteer donors. Identical twin cases are not ~~included~~. ~~Only 1 death has~~ occurred after one year. Note that ~~more than~~ two-thirds of the patients who received kidneys from blood relatives are alive from ~~thirteen~~ to ~~twenty-nine~~ months after transplantation. Only a third of those whose donors were unrelated lived as long as a year.

mittent course. Although the clinical manifestations of rejection could be avoided in only a minority of cases, the adverse effects could be mitigated and reversed in most instances.

In the majority of centers the most important immunosuppressive agent used is Azathioprine. This drug, which inhibits nucleic acid synthesis, is started before or at the time of transplantation and continued indefinitely thereafter; it is a potentially dangerous agent since bone-marrow depression results from overdosage, and even in small quantities it may be hepatotoxic. Prednisone is also essential. When used alone, steroids are of little value for potentiation of homograft survival, but in combination with Azathioprine, they play a crucial role in the mitigation and reversal of an established rejection. Secondary adjuvants which have been useful are actinomycin C and local homograft irradiation.

The effectiveness of local homograft irradiation for the prevention and treatment of rejection was established by the work of Hume and Goodwin and their associates. The explanation of the therapeutic benefit is not known. During a rejection crisis, the kidney is infiltrated with cells and enlarges; the transplant wound becomes tender. After the first

dose of 150 R (at depth), the local signs are often dramatically relieved, and soon after there is frequently an improvement in the deteriorated renal function. Ordinarily, the dose is repeated on three alternate days for a total of 450 R. Further investigations are needed concerning the mechanism of this effect. In addition, more precise knowledge is required of the potential irradiation injury to the homograft which may be the penalty for this short-term benefit.

Imperfect though the currently employed therapeutic methods are, greatly improved early survival after renal homotransplantation has been reported from several centers, and it has already become possible to state with relative certainty that homotransplantation will have an increasing role in the general medical armamentarium of the future. The results with recent clinical experience have exceeded any hopes of even a few years ago. Of the first 64 patients treated at the University of Colorado Medical Center with kidneys from volunteer living donors, 37 homograft recipients lived for at least one year after operation (Fig. 1) and 36 are still alive from thirteen to twenty-nine months (mean nineteen months). Within this time limit, the results approach acceptability if homografts from genetically related donors were used; two-thirds of all those patients who received kidneys from blood relatives are still living (Fig. 1). With unrelated donors the results are poor since only one-third lived for as long as one year (Fig. 1). In our experience the best survival within the related group was with parent-to-offspring transplants, 70 per cent of the recipients still being alive (Fig. 2). In the world experience, sibling-to-sibling transfers have had the highest success rate.

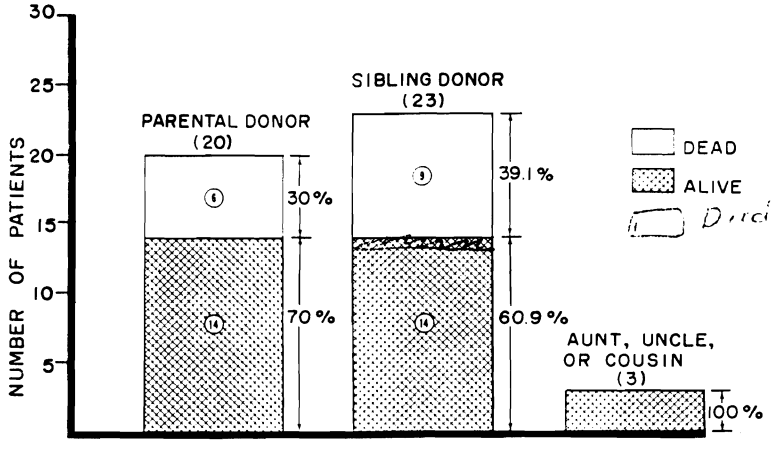

Fig. 2. Breakdown of results at the University of Colorado Medical Center in patients who received kidneys from blood relatives other than identical twins from ~~thirteen~~ 25 to ~~twenty-nine~~ 42 months ago. The best results were with parental donations; ~~in the world experience, however, sibling-to-sibling transplants have fared somewhat better.~~ The late death in the sibling group was after 22 months.

These results indicate that many uremic patients, perhaps even the majority, can be materially benefited by renal homotransplantation with relatively complete social and vocational rehabilitation over considerable periods of time. Nevertheless, workers in the field who have repeatedly warned that this treatment is experimental are not yet willing to abandon this position. The most important reason for a conservative attitude is that the ultimate life expectancy of the present crop of chronic survivors is still unknown. Barnes has attempted to answer this question with a statistical analysis of the death rate of those patients already treated and has predicted that further losses from that group of patients still living will occur at an extremely gradual rate.

Whether this is true or not can be determined only by actual observation. In the meantime there is legitimate reason for avoiding overoptimism. Not all patients who have reached a chronic stage of convalescence are well. In many, there is evidence of continued host-against-graft immunologic activity manifested in some cases by acute episodes of late rejection, in others by histologic evidence of active rejection despite perfectly functioning homografts, and in still others by a slow and insidious deterioration of function. It is possible that most of the apparently well patients are living by virtue of renal homografts which are losing a small fraction of functioning parenchyma each day. For the moment, therefore, it would seem most reasonable to regard renal homotransplantation as an effective, but incompletely characterized, form of palliative therapy. Ultimately it may be proved to be a curative procedure, but that time has not yet arrived.

Acceptance that human renal homotransplantation is still an exercise in clinical investigation may slow the widespread use of this procedure and hopefully confine its application to appropriately equipped institutions in which the clinical program is only one component of an overall transplantation effort. Under these circumstances, potentially significant discoveries in the animal laboratories can be tested on the wards with a minimum delay; conversely, observations on patients will influence the direction of basic research.

To illustrate the interdisciplinary nature of the undertaking, one need only to mention the necessity of identifying human histocompatibility antigens for improvement of future donor-recipient matching, or the desirability of establishing whether the thymus has the same role in recovery from immunologic depression in man as it apparently does in adult mice. The collaborative efforts of immunologists, surgeons, internists, and physiologists will be required to study these and many other important problems.

The potential applicability of advances in homotransplantation is, of course, not limited to the field of renal disease. In future years, it seems inevitable that other kinds of mono-organ failure will be treated with functional homografts. Already, attempts have been made in man to transplant the heart, lung, and liver. Although protracted survival has yet to be obtained in man with any of these organs, the difficulties encountered have not seemed inherently insolvable. Survival of a year or longer has been accomplished in dogs with all three types of homografts, and with livers the regularity with which long-term success can be achieved equals that reported with canine kidneys. These findings suggest that strong organ-specific antigens will not make the control of rejection more difficult and that the immunosuppressive methods will have an interchangeable efficacy with different homotransplanted tissues. This is not to imply that success will be as readily attainable as with kidneys. The problems of surgical technic are more formidable. Special physiologic problems concerning denervation and blood supply have been encountered. The necessity for use of cadaveric organs limits both the quantity and quality of supply. Finally, the secondary illness and deterioration of homograft function during a potentially reversible rejection of such organs may carry a far more serious implication than with the kidney, since effective extracorporeal hearts, livers, and lungs have not reached the stage of perfection which would allow their emergency use for several days or weeks during a postoperative rejection episode.

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