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THE FUTURE OF RENAL TRANSPLANTATION

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Cadaveric renal transplantation has not yet given optimal results. Recent introduction of cyclosporin A has, however, already improved the results of primary and secondary transplantation. In the light of the results with cyclosporin A, transplantation in the future may be offered more liberally to high risk patients, reduce the need for A, B and D matching, render living related donor transplantation obsolete and open up transplantation to greater numbers of patients.

We should take a cold look at the past before speculating about the future (Table I). Kidney transplantation as a legitimate clinical venture began in 1962 and 1963 when the first wave of chronic survivors, mostly recipients of living related kidneys, began to emerge from a handful of transplant clinics. The reason was the combined use of azathioprine and prednisone (double-drug therapy). Previously, azathioprine alone had been tried but by itself was too ineffective to hold any promise of practicality. Double-drug therapy became and has remained the standard form of therapy in more than 85% of transplant clinics throughout the world.

TABLE I. IMMUNOSUPPRESSIVE DRUG REGIMENS USED CLINICALLY

Agents	Year Described	Place	Deficiencies
Azathioprine	1962	Boston	Ineffective, dangerous
Azathioprine - Steroids	1963	Denver, Richmond, Boston, Edinburgh	Suboptimal
ALG as Adjunct	1966	Denver	Still suboptimal
Cyclophosphamide Substitute for Azathioprine	1970	Denver	No advantage except for patients with azathioprine toxicity
Thoracic Duct Drainage	1963	Stockholm	Nuisance; requires 20-30 days pretreatment
Total Lymphoid Irradiation	1979	Palo Alto, Minneapolis	? dangerous; extensive preparation; not quickly reversible
Cyclosporin A Alone	1978-79	Cambridge	Suboptimal
Cyclosporin A - Steroids	1980	Denver	

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In the long run, most of the deviations from azathioprine-steroid therapy will probably be footnotes in the history of renal transplantation including (Table I) the use of ALG as an adjunct, the demonstration that cytoxan (cyclophosphamide) could be substituted for azathioprine, the use of thoracic duct drainage as a means of preoperative lymphoid depletion, and lymphocyte depletion by total lymphoid irradiation. Even with all of these combinations, the results of cadaveric transplantation, except in isolated centers and small series, have been unacceptable. The one year survival of primary cadaveric kidneys in the United States has averaged about 50%.

CYCLOSPORIN

In 1978, Professor Roy Calne of Cambridge, England, introduced into clinical use cyclosporin A (cy A), a drug that has proven to be the most potent immunosuppressive agent yet used. Calne recommended and has continued to believe that this agent should not be systematically used with steroids¹, a point of view with which we have not agreed. In 1979 and subsequently we have shown how the optimal use of cyclosporin A is with steroids², a technique which has been adopted in all American centers where cyclosporin A is now being tried.

Cyclosporin therapy is begun orally on the day of operation. In adults, prednisone also is started at 200 mg on the day of operation and decreased by 40 mg/day so that by the sixth day, a maintenance level of 20 mg/day is reached. Further reductions are later possible at a more gradual rate. The daily starting dose of 17.5 mg cyclosporin is reduced if there is evidence of nephrotoxicity, hepatotoxicity or other side effects. A benign course with no rejection is seen in about 40% of primary cadaveric recipients.

In almost as many patients, rejection supervenes. However, the rejections are usually easily controlled and reversed with boluses of hydrocortisone or a second 5 day burst of prednisone. The incidence and severity of rejection is greater after retransplantation than after primary grafting. The presence of acute tubular necrosis postoperatively does not contraindicate cyclosporin therapy.

Between late 1979 and August 1980 our first clinical trials with cyclosporin and steroids were begun involving 57 primary cadaveric recipients and 9 patients undergoing cadaveric retransplantation. The cadaveric transplantations were performed with randomized donor selection and with no attempt to exclude immunologically or medically high risk candidates. Preoperative transfusion was not used. Largely because of learning errors, there was a 13% patient mortality. However the results of kidney

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survival were still as good or better than any previously achieved by us.

Amongst the 57 patients who received their first cadaveric transplants, the actual one year kidney survival was 80%. One more kidney was lost after the end of the first year. Now after a minimum follow-up of almost 1-1/2 yrs extending out to beyond 2 yrs, 77% of these patients remain dialysis free. One of the patients had an incidental lymphoma at autopsy which was the only such complication in this initial trial. Of the 9 patients undergoing cadaveric retransplantation, 6 have achieved satisfactory results.

Armed with this experience, a new series of cadaveric transplantations was begun at the University of Pittsburgh. The patients were treated in 1981 and follow-ups are 1-1/2 mos to a year. Thirty-eight patients received primary cadaveric grafts, almost all badly matched at the A, B, and D loci. About one-fifth of the patients were diabetics, and many were more than 60 yrs old. Thirty-five of these 38 kidneys, or more than 92% are still functioning. There was one death in the series, from myocardial infarction in a patient with good renal function. A second kidney was lost immediately because of a blood bank error whereby an A kidney was transplanted into an O recipient. The third kidney was lost in a patient who perforated her cecum a few days after transplantation necessitating discontinuance of all immunosuppression.

Similar patients, mostly in a randomized trial, were treated with conventional therapy consisting of azathioprine and prednisone during the same time. About 45% of these kidneys have already been lost, but with no patient deaths. The kidney survival divergence has been so extreme that the study was discontinued on grounds that it was no longer ethical to persist.

An additional observation confirming our earlier pilot trial in Colorado has been the good survival that can be obtained after retransplantation. In most centers cadaveric retransplantation has yielded inferior results. At the University of Pittsburgh, this had resulted in the number of retransplantations being small, only 13 in the preceding 2-1/2 yrs. Only 3, or 23%, of these 13 patients had functioning kidneys by the end of 6 mos. In the cyclosporin cases the degree of success has been almost 80% (23 of 28), in spite of the fact that at least half of these recipients had widely reacting T-warm antibodies, and in 8 patients the donor lymphocyte cross-matches with recently stored recipients serum were positive. The success rate under this circumstance, which is considered to constitute a positive crossmatch and thus to preclude transplantation in most centers, is noteworthy. However the problem of the positive cytotoxic crossmatch remains a vexing one and one which has slightly degraded the results in this retransplantation group.

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FUTURE DIRECTIONS FOR TRANSPLANTATION

From this experience which goes back more than 2 yrs I think that many tenets of what has been called the strategy of transplantation will be revised as cyclosporin-steroid therapy becomes widely used.

First I believe that the use of living related donors will become obsolete. About a dozen living related donors have died throughout the world, and although this mortality is small, it will no longer be necessary to take this risk. Second, the potential importance of matching at the A, B, and D loci will be diminished. However, the importance of preformed antibody analysis will be as great as before. Third, pretransfusion of potential recipients will be stopped. One of the penalties for this widespread practice is the development of a population of untransplantable patients with broadly reacting cytotoxic antibodies. It seems unlikely that this penalty will be desirable or necessary, and thus pretransplant transfusion will be avoided instead of being deliberated advocated. Fourth, certain high risk patients including diabetics will be easier to treat, potentially realizing the great advantage of treating brittle diabetics with the low doses of steroids that can be used with cyclosporin. Clearly candidacy criteria along other lines will also be liberalized. Fifth, the interface between dialysis and transplantation will be drastically altered. In the United States, the numbers of patients undergoing transplantation is 5% or perhaps less, of those who are on chronic dialysis programs. One of the reasons has been the understandable reluctance of nephrologists who hesitate to refer patients doing well on dialysis for cadaver transplantation, with the bad record which the latter procedure has had. Finally as movement occurs toward increasing the numbers of cadaveric transplantations, the supply of organs, which has not been as major a problem as has often been claimed in the lay press, could turn into one of crisis proportions.

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