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Transplantation

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Nineteen eighty-five and 1986 have been consolidation years in which the great advances of the early 1980s were brought closer to fruition. The single most important advance is the immuno-suppressive agent, cyclosporine, which was developed by Borel et al.¹ Clinical trials with this agent were begun in England by Calne et al² in 1978 and a year later in the United States.³ The drug was released by the Food and Drug Administration for general use in November 1983. Most commonly, cyclosporine is used in combination with steroids.³

The effectiveness of cyclosporine precipitated an avalanche of cadaveric transplantations of a variety of organs, beginning in 1980 and continuing to the present. Cadaveric renal transplantation has become increasingly accepted, not only because the results are improved over those with old-style immunosuppression, but also because the quality of life is so much better. With cyclosporine, dosage of the steroid component of therapy is far less than in past times, when azathioprine and steroids were used for early and maintenance treatment.

Although cadaveric donors have become the principal source of kidneys, some transplant surgeons still passionately defend living donation,⁴ partly because it makes possible immunologic manipulation of the recipient by the use of donor-specific blood transfusions.⁵ However, with the recognition that about 20 living donors have died in high-quality centers throughout the world, the use of living donors has been increasingly questioned.

The survival of recipients of cadaveric livers has more than doubled since 1980, a viability rate largely attributable to cyclosporine.⁶ A smaller but still significant improvement has been seen with cardiac transplantation.⁷ Heart-lung transplantation and unilateral lung transplantation, which were not feasible previously, have become commonplace.^{8,9}

The most serious limitation to use of cyclosporine is its nephrotoxicity.^{2,3} At first, it was thought that the nephrotoxic effect would be reversed promptly with dose reduction. However, with long-term therapy,^{10,11} there is now evidence of permanent renal damage that is clearly dose related. Patients maintained with small daily doses of the drug for five or six years after transplantation of livers have not had any late deterioration of renal function.¹² In renal recipients treated by us with transplantation from late 1979 through 1981, chronic cyclosporine administered in conservative doses has not been accompanied by a heavy graft loss as might be expected with cumulative cyclosporine toxicity. Seventy-seven (83%) of the first 93 primary cadaveric grafts in these pilot trials

survived for at least one year. After this, the rate of subsequent loss was almost identical to that in similar recipients treated in earlier times¹³ with azathioprine and prednisone. By adding other drugs, which by themselves are incapable of allowing long-term graft function, doses of cyclosporine can be commensurately reduced.^{3,6-9}

Monoclonal antilymphocyte globulins, introduced by Cosimi et al,¹⁴ drawing on the hybridoma techniques of Kohler and Milstein,¹⁵ have not yet become commercially available. One such preparation (the so-called OKT3, Orthoclone) is in the last stages of evaluation by the Food and Drug Administration and should be made commercially available this year. The new monoclonal antilymphocyte globulins are advocated for rejection that has not been easily reversed by temporary intensification of steroid therapy. If monoclonal antibody therapy is added to baseline therapy with cyclosporine and steroids, the reversal of rejection, upon completion of the antibody course, may herald a rejection-free future for some patients.¹⁶

More effective immunosuppression has been accompanied by a secondary revolution in organ procurement. A technique now exists for the safe removal of many organs from the same cadaveric donor, without jeopardy to any of these organs.¹⁷ The technique consists of a relatively simple preliminary dissection so that cross clamps can be placed on various parts of the major thoracic or intra-abdominal vessels, allowing core cooling with cold-preservation solutions that are infused into the aorta. What is needed most urgently is a fundamental breakthrough with longer-term preservation techniques that would allow vital organs to be kept for a week or more. Current methods limit preservation of the kidney to not much more than two days; for the heart and liver, the safe time is considered to be six hours or less.

The ability to preserve organs for longer times would have a revolutionary effect on transplantation. A reservoir of stored organs could be developed in each country and used for international sharing with a global impact. In addition, tissue matching might become more practical than it has been. However, donor availability may remain an important limiting factor.¹⁸

The practical role of tissue matching, no matter what the circumstances of preservation, has yet to be completely defined. We now realize that, in renal transplantation, tissue typing at the A and B histocompatibility loci is not a prerequisite for, or even a very discriminating predictor of, success.¹³ Using conventional immunosuppression with azathioprine and pred-

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nisone (with or without old-style polyvalent ALG), matching of the antigens of the A and B loci (four in all) was worth only about 2% points cadaveric kidney graft survival per antigen at one year.^{13,19} Recently, a more dramatic effect of the antigens of the Dr locus was hoped for, but actual experience has not borne out this expectation.

It has been said that the need for tissue matching in kidney transplantation is less with improved immunosuppression (cyclosporine and steroids). Nevertheless, preliminary data from large collections have shown a minor advantage of matching. So far, matching has never been taken into consideration with heart or liver transplantation because of the time limitations of acceptable cold ischemia.

Such improvements as drug combinations that include cyclosporine have not benefited renal recipients whose serum samples contain widely reacting cytotoxic antibodies. These antibodies may render a potential renal recipient nontransplantable. A donor whose tissues do not react with the antibodies of the recipient (negative cross match) can never be found. Although the dread consequence of a positive cross match, namely, hyperacute rejection, is known to be precipitated by an antigen-antibody reaction, efforts to remove the antibodies with plasmapheresis or other techniques have not proved successful so far.

Because the host's immunologic surveillance is weakened by chronic immunosuppression, there is a greatly increased incidence of de novo malignancies, especially lymphomas, in transplant recipients. In recent years, the withdrawal of immunosuppression has resulted in the spontaneous involution of these lesions.²⁰ This immune manipulation in the treatment of cancer seems to have been more firmly established in the transplant population than in any other clinical setting.

With the broad advances of the past five or six years, hepatic and cardiac transplantations have become services, along with renal transplantation, as opposed to experimental procedures. The same has not been possible with pancreas transplantation, in which the one-year graft survival has remained poor, with an unacceptable patient mortality related to the procedure itself.

The romantic newer transplant procedures have spawned large numbers of new programs. By the end of 1985, there were 40 liver transplant programs in the United States and more than 70 teams with pretensions of expertise in cardiac transplantation. Debates have flourished about how to discourage this proliferation of centers. In addition, there has been increasing

interest by government agencies, third-party payers, and private agencies in promoting interconnecting organ-sharing programs. As a start, a highly effective system of voluntary organ sharing has already been set up by the existing programs.

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