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## IMMUNOSUPPRESSION IN ORGAN TRANSPLANTATION

THE search for effective and safe methods of suppressing the immune response has been evolving over four decades. Progress has been marked by many disappointments and a few forward leaps. Clinical organ transplantation has served as the proving ground for many of these advances, beginning in the early 1950s, shortly after a working model of the artificial kidney provided for the short-term maintenance of life in patients with end-stage renal disease. The first attempts to suppress the rejection response, with whole-body irradiation and bone marrow transplantation, were unsuccessful. Since then, there have been two main avenues of approach to the prevention and treatment of graft rejection, one employing drugs and the other antibodies. After the discovery by Schwartz and Dameshek[1] in the 1950s that the antimetabolite 6-mercaptopurine also had immunosuppressive activity, and its preliminary success in prolonging the survival of dog-kidney transplants, Hitchings and Elion[2] synthesized a series of mercaptopurine derivatives, seeking a compound with an improved ratio of immunosuppression to bone marrow toxicity. The fruit of this effort was azathioprine, first used clinically in 1962[3]; this marked the beginning of the modern era of immunosuppression. Although a number of other antimetabolites useful in cancer therapy were subsequently evaluated for their immunosuppressive action, none matched the therapeutic efficacy of azathioprine in preventing transplant rejection.

It was close to two decades before a more powerful drug, cyclosporine, came into widespread use in the early 1980s.[4] This compound, a natural product of a fungus, was identified during a screening program to develop new antifungal agents but was rejected for that purpose because of its "side effects" on the immune system. Cyclosporine is a lipophilic cyclic peptide composed of 11 amino acids. Although the success rates with kidney transplantation had been rising each year before the introduction of cyclospor-


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ine, the new drug produced an immediate increase of 10 to 15 percent in short-term rates of graft survival,[5] and it has been even more successful in permitting the widespread diffusion of heart and liver transplantation. As prophylaxis to prevent rejection, both azathioprine and cyclosporine are generally used in combination with corticosteroids (such as prednisone), which are themselves potent immunosuppressants. Each of these agents has different effects on the immune response, and they potentiate each other in practice. Some protocols use cyclosporine and prednisone without azathioprine. Acute rejection episodes are generally treated with short courses of high-dose methylprednisolone. Unfortunately, the well-known side effects of steroids are a burden and a hazard in transplant recipients who must take these medications indefinitely at some dose level.

After almost another decade, a new immunosuppressive drug, FK 506, has emerged as a result of the continuing screening of natural products of soil fungi.[6] This agent has not yet been evaluated fully in the clinic,[7] but it is already causing excitement because of the characterization of its mode of action in relation to that of cyclosporine. In contrast to the polypeptide structure of cyclosporine, FK 506 has the structure of a macrolide antibiotic (such as erythromycin), yet cyclosporine and FK 506 exert very similar effects on lymphocytes; they prevent the synthesis of interleukin-2 and other lymphokines important in lymphocyte growth and function. Each compound binds to similar but different proteins, both of which are peptidyl-prolyl isomerases, enzymes that promote the folding of their substrates.[8,9] The substrates for the isomerases that bind cyclosporine and FK 506 are as yet unknown but are likely to be part of a common pathway in lymphocyte growth and function. Another drug, rapamycin,[10] is structurally similar to FK 506 and has also been found to have immunosuppressive effects.

The opportunity is now at hand to develop a rational basis for the design and evaluation of drugs with selective immune effects. There are two major problems with the existing treatments. First, toxic effects on vital organs limit the amount of drug that can be administered. For example, azathioprine is a bone marrow suppressant, whereas cyclosporine is nephrotoxic and may also produce hypertension, hyperkalemia, and liver and neurologic impairment.[4] Second, it is difficult to balance the risk of infectious complications from too much immunosuppression against the goal of preventing graft rejection. Simply removing the side effects of these drugs would not necessarily allow them to be used with impunity; moreover, some transplant rejections are resistant to all available treatments, especially in recipients who have been immunized by a previously rejected transplant. The article in this issue of the *Journal* by Moran et al.[11] on the beneficial effects of adding the prostaglandin $E_1$ analogue misoprostol to cyclosporine and prednisone in the prevention of acute renal-graft rejection appears to confirm studies in animals[12] of the immunosuppressive properties of long-acting methylated prostaglandin $E_2$ and should promote more intensive investigation of adjunctive drug therapy with prostaglandins.

Antibodies directed to the lymphoid cells of the immune system, though never used alone, have been important adjuncts to antirejection therapy. Starting in the 1960s, immune globulins resulting from the immunization of horses or rabbits with lymphocytes, thymocytes, or cultured lymphoblasts were administered to transplant recipients, at first intramuscularly and later intravenously, as a means of reversing rejection episodes or as initial therapy for the first few days after transplantation, to prevent rejection.[13] Such antilymphocyte globulins, though generally useful, have been of variable potency and also have the potential disadvantage of containing antibodies directed against a wide range of nonlymphoid tissues, such as platelets, macrophages, and connective-tissue elements. Indeed, thrombocytopenia, fever, skin rash, and serum sickness–like reactions are commonly encountered with such therapy. More precise targeting of treatment to molecules present on specific cells of the immune system is now possible through the use of monoclonal antibodies. The first antibody to be used in the clinic, anti-CD3,[14] now licensed as OKT3, is directed only against T lymphocytes and has been extraordinarily effective in the reversal of rejection. Currently, it is being evaluated for use as induction therapy to prevent rejection.[15] Its precise target is one of the CD3 molecules that compose the antigen-receptor complex of the T cell. The antibody has the disadvantage of first activating all accessible T cells, resulting in sometimes severe febrile and circulatory problems for the first day or two, but it is tolerated well thereafter without further systemic side effects.

Like the other substances used for antirejection therapy, OKT3 is a general immunosuppressant. Since monoclonal antibodies have been made against the cell-surface molecules that define subsets of cells, the possibility of more selective targeting has been under active investigation. For example, monoclonal antibody to the interleukin-2 receptor can bind only to T lymphocytes activated recently, sparing the cells not involved in an immune response during the time of administration. Because such an approach has been shown to prolong transplant survival in animals,[16] trials have begun in humans. The article in this issue by Soulillou et al.[17] on anti–interleukin-2-receptor therapy in renal transplantation shows that such an antibody can be beneficial in preventing rejection. The antibody compared favorably with a standard antithymocyte globulin in its ability to prevent rejection and promote graft survival when it was given in a prophylactic manner after transplantation; it was also much better tolerated. In the case of a fresh transplant, the activation of T lymphocytes would reflect the emerg-

ing immune response to the HLA antigens of the graft, although incipient immunity to active infection might also be impaired. Although the patients in the anti–interleukin-2-receptor group had the same incidence of viral infections as those in the antithymocyte-globulin group, the rate of bacterial infection was reduced. Similar results are being obtained with another anti–interleukin-2-receptor antibody.[18] It is expected that even more selective and effective monoclonal-antibody–based treatments will emerge, with an emphasis on those active during the induction phase. Although treatment may ultimately be drug-based, at present monoclonal antibodies provide the best approach to specific targeting in vivo, either for the temporary inhibition of a receptor or for cell destruction (with a native antibody or toxin conjugate).

One of the major questions remaining in clinical transplantation is whether it will be possible to induce states of antigen-specific unresponsiveness, so that true tolerance is achieved with little or no long-term drug therapy. Although improved short-term success rates do translate into better long-term survival, the exponential rate of graft loss over time in patients with HLA mismatches has not changed over the past two decades.[5] In general, stable, drug-treated graft recipients maintain the ability to react to their donors in the mixed-lymphocyte culture, whereas some have reduced or absent cytotoxic T-cell responses.[19] There are indications that in some transplant recipients, T cells with cytotoxic potential can become anergic to the graft with time,[20] although much remains to be learned about how this comes about and whether deliberate previous exposure to transplant antigens, as with blood transfusions, should be a part of future protocols. Many important details of the regulation of the immune response are still unknown. Ideally, one would like to alter the host's initial contact with the graft to promote a state of donor-specific unresponsiveness. The same goal obviously applies in states of autoimmune disease in which a specific immune response needs to be suppressed, and the best way to effect this would also be through the induction of immune tolerance. Present treatments fall short in this regard.

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## PRISONERS OF TECHNOLOGY

### The Case of Nancy Cruzan

LIFE can now be sustained by medical technology under circumstances that just 15 to 20 years ago would have signified imminent death. This new power permits dramatic recoveries from some previously hopeless calamities. But, as with power in general, there is a dark side to it. Increasingly we find that life is being sustained indefinitely when there is no hope of recovery, simply because no one knows what else to do. Such a life may be filled with suffering, but sometimes it is devoid of anything — of pleasure, sensation, or comprehension.

This is the state of Nancy Cruzan, a 32-year-old woman who, as described elsewhere in this issue,[1] has been in what most agree is a persistent vegetative state since a car accident seven years ago. Although the diagnosis is not unanimous, the prognosis is. Everyone agrees that she will not recover; CT scans show that her cerebral cortex has already atrophied.[2] But she is not dead, and she will probably live in her senseless state for many more years, thanks to sophisticated medical care and tube feeding through a gastrostomy. The costs are immeasurable anguish to her family and $130,000 yearly to the state of Missouri.

Three years ago, when it became apparent to even the most hopeful that Nancy Cruzan would not recov-