

Transplantation

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The three principal struts of transplantation are organ preservation, immunosuppression, and tissue typing. Major pragmatic advances have been made possible by improved static preservation with the University of Wisconsin solution. The safe preservation limits for all organs, but particularly the liver, have been greatly increased since 1987. The most important ingredients of the University of Wisconsin solution are thought to be the impermeants that prevent cell swelling. Two research directions are identifiable in the literature—one, eliminate unneeded constituents of the University of Wisconsin solution, and the other, increase the additives, which already number more than 10.¹

The growth of transplantation during the last decade owes much to cyclosporine. The use of cyclosporine with steroids, to which other agents can be added in more or less elaborate cocktails, made possible the transplantation of cadaveric kidneys, livers, hearts, and other organs with an effectiveness scarcely dreamed of 10 years ago. Yet, the full profile of cyclosporine actions is incomplete.²

Aside from its immunosuppressive qualities, the spectrum of seemingly unrelated cyclosporine activities is bewildering.² Nephrotoxicity and hypertension are the best known and principal dose-limiting side effects. Metabolic, cosmetic, and neurotoxic side effects may also occur. Some symptoms may be so subtle that they are not mentioned unless specific inquiries are made.

The foregoing side effects of cyclosporine and its desired inhibition of the immune system had not been thought to be interrelated by a common mechanism. This has been changed by clinical observations with another immunosuppressive agent called FK 506 (Fujisawa Corporation, Osaka, Japan), which has a totally different structure than cyclosporine. FK 506 is a macrolide obtained from cultures of *Streptomyces tsukubaensis*. Like cyclosporine, it inhibits the activation of T lymphocytes, in part by depressing the production and expression of multiple cytokines of which interleukin 2 and interferon gamma have been the most extensively studied.³ The in vivo immunosuppressive qualities of FK 506 have been studied in mice, rats, dogs, monkeys, baboons, and humans.⁴ To date, there has been only one investigational new drug trial for FK 506, and this has taken place at the University of Pittsburgh. However, multicenter trials are scheduled to begin in the spring of 1990 in Europe and in approximately one dozen American centers. So far, investigational new drug applications have not been developed for indications other than in transplantation.

Extensive clinical trials with FK 506 were begun in February 1989,^{5,6} first, for the rescue of patients who had intractable liver allograft rejection or toxic reactions under immunosuppres-

sion, which included cyclosporine,⁵ and subsequently as primary therapy. By February 1, 1990, 36 kidneys, 151 livers, and 14 hearts, lungs, or heart-lung grafts had been transplanted with an immunosuppression regimen of FK 506 and low-dose steroids. All of the thoracic organ recipients and more than 90% of the liver recipients are alive. The kidney recipients, who represented an unusually complex and difficult collection of cases, have a graft survival rate of 80%, with a patient mortality rate of 3%.⁷ Overall, the low mortality, high graft survival, good graft function rates, and relative nondependence on steroids reflect a large and safe therapeutic window for FK 506.

The side effects of FK 506 tend to affect the same organ systems as cyclosporine, although frequently not to the same extent and sometimes not in the same direction. It may be less nephrotoxic than cyclosporine, usually does not produce hypertension, reduces instead of increases serum cholesterol levels, and has little effect on serum uric acid levels. It does not cause gingival hyperplasia or coarsening of the facial features and, instead of hirsutism, there may be hair loss. The diabetogenic and neurotoxic effects of FK 506 are similar to those of cyclosporine. Because FK 506 usually does not elicit a biochemical red flag such as azotemia to warn of overdosage, minor signs of neurotoxicity such as tremors, tingling of the hands and feet, light sensitivity, insomnia, nightmares, and mood changes have been useful to help guide dosage adjustments (T.E.S., J.J.F., Mark Porter, MD, unpublished data, 1990).

In rats and dogs, FK 506 and cyclosporine have other effects that could have therapeutic significance in humans. Both drugs cause augmentation of the regeneration response after partial hepatectomy,⁸ and they prevent the hepatocyte atrophy and organelle disruption that occur after portacaval shunt (T.E.S., Kendrick A. Porter, MD, Vincenzo Mazzaferro, MD, et al, unpublished data, 1990).

The fact that two such chemically different drugs as FK 506 and cyclosporine appear to modulate the same physiological and immunologic parameters would be difficult to explain were it not for discoveries about their binding sites. The cyclosporine binding site is a cytosolic protein with a molecular weight of 17 000⁸ called "cyclophilin," which possesses peptidyl-prolyl isomerase (PPIase) activity.^{9,10} Peptidyl-prolyl isomerase is an enzyme discovered in mammalian tissues¹¹ that catalyzes the slow *cis-trans* isomerization of proline peptide bonds in oligopeptides and accelerates rate-limiting steps in the folding of several proteins during their synthesis. By virtue of its isomerization of partner molecules, PPIase could modulate various intracellular signal transduction processes, contributing to the manifold physiological effects enumerated previously. Peptidyl-

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prolyl isomerase is widely distributed in many tissues, not just in lymphocytes. For example, cyclophilinlike receptors are in the photoreceptors of *Drosophila*. In mutant *Drosophila* deficient in cyclophilin, rhodopsin production is defective.¹² This observation could establish a link with the neurotoxicity caused by PPIase-inhibiting drugs.

It was thought at first that cyclophilin and PPIase were identical.^{9,10} This hypothesis became untenable when the cytosolic binding site of FK 506 (molecular weight, 11 800) was found to be distinct from cyclophilin, but to also possess PPIase activity.^{13,14} Thus, cyclophilin and the FK 506 binding site seem to be members of an emerging class of novel and ubiquitous cytoplasmic proteins that regulate T-cell activation but also regulate other metabolic processes.

FK 506 probably will have other applications than in transplantation. Dramatic remissions using FK 506 have already been observed in hemolytic-uremic syndrome, steroid-resistant nephrotic syndrome caused by focal segmental glomerulonephritis, psoriasis, and malignant pyoderma gangrenosum (unpublished data, 1989). Because FK 506 augments hepatic repair and regeneration⁷ (T.E.S., Kendrick A. Porter, MD, Vincenzo Mazzaferro, MD, et al, unpublished data, 1990), it may be especially valuable for patients who have chronic liver disease with or without an autoimmune origin.

Other new agents to control rejection also are being tested clinically. Murine monoclonal antibodies (OKT3 is the prototype) can be directed against the whole T-lymphocyte population. Clinical trials in France¹⁵ and the United States¹⁶ are in progress with anti-interleukin 2-receptor antibodies, which have a more highly focused target. These preparations are immunosuppressive, but their inherent immunogenicity and inconvenience of administration may limit their usefulness. Anti-T lymphocytes have also been used as carriers of cytotoxic immunotoxins.¹⁷

Tissue matching is important with intrafamilial transplantation, but controversy continues about the value of HLA matching for cadaveric transplantation. The issue has become one of public policy because tissue matching is used for kidney distribution nationally. Because by law the United Network of Organ Sharing has been required to collect reports on the almost 20 000 cadaveric kidney transplantations performed in the United States since November 1987, an analysis of this material to resolve the dispute is eagerly awaited. At the International Transplantation Society meeting (August 1990), a principal topic for debate will be the justifiability of making tissue matching the basis for kidney distribution.

Recently, several elective partial liver transplantations from live donors have been performed at the University of Chicago, including the much

publicized event in late 1989 of an elective partial liver transplantation from a healthy mother to her daughter born with biliary atresia. The skill and courage of the management teams were tested by significant but not unexpected operative complications in the recipients. However, at last report, all donors and recipients were well. Earlier in 1989, the same procedure was performed in Australia, Brazil, France, and Japan, with variable results. All observers agree that living donor liver transplantation should be attempted only by experienced transplantation teams and at centers with the most sophisticated ancillary resources.

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