

## Closing Remarks

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WE have heard so much data today that an attempt to summarize would be futile. It is doubtful that any drug used in transplantation has been more extensively studied before its first human use than FK 506. One reason for this extraordinary care was concern that the agent might be toxic and could cause arteritis, gastrointestinal complications, diabetes mellitus, or central nervous system toxicity. As it has turned out in the clinical trials, the drug was not only extraordinarily effective in preventing rejection but, in addition, it was relatively free of side effects. The drug probably has slight diabetogenic properties, similar to those of CyA. However, it can be used with such small (or no) doses of steroids that there is a net gain in avoidance of posttransplantation diabetes. By itself, FK 506 has minor league nephrotoxicity, compared with CyA, and probably does not cause hypertension.

FK 506 was used first to reverse rejection in liver recipients who had failed to respond to conventional therapy. The results greatly exceeded our expectations. Livers that develop evidence of chronic rejection have not been salvageable with any past therapeutic regimens. When liver rejection was controlled with FK 506, it was suspected from the outset that more was being achieved than merely switching off the genesis of the disappearing bile duct syndrome in some of these patients. An impressive array of subsequent work has shown that FK 506 can actually contribute to hepatic regeneration and repair. This is the first oral drug, to my knowledge, which has such properties.

Later, an extensive clinical trial was initiated, using FK 506 as primary treatment, first in liver recipients, then in recipients of kidney, heart, lung, heart-lung, and pancreas allografts. Although the follow-ups are still short with these extrahepatic organs, the results have been encouraging, in an experience that now exceeds 60 cases.

More needs to be learned about the pharmacokinetics of FK 506, but enough information has been provided thus far by Vankataramanan (this issue) to allow its effective use. In experimental animals, the extraordinary feat, accomplished by investigators in half a dozen laboratories, of inducing "graft acceptance" after a short course of treat-

ment was highly effective, even when started as late as 4 days after transplantation. The fact that graft acceptance could be induced at such a late time is only the beginning of the story. Mechanisms of graft acceptance, which were examined by Murase and associates (this issue) are not compatible with any of the existing hypotheses of tolerance, including clonal deletion, active enhancement, emergence of suppressor cells, or redistribution of lymphocyte subsets.

The results with FK 506 in experimental animals and in humans have been so extraordinary that a long list could be made of a number of possible achievements which had previously been just beyond our grasp. The prospect of successfully performing intestinal transplant is supported by several papers in this issue. Multivisceral transplantation, which has never previously been successful in animals, has now been reported by Murase. A long series of autoimmune diseases has also been brought up for consideration for FK 506 therapy, including diseases affecting the liver, multiple sclerosis, Crohn's disease, and a variety of skin disorders, to provide an incomplete list.

No one believes that FK 506 will quickly permit successful xenotransplantation across widely divergent species, but any advance which produces such profound control of cell-mediated rejection should be applicable to resolve at least one aspect of the xenograft reaction. What remains to be done is to achieve control of the preformed antibody component of xenograft rejection, ie, the component which causes instant destruction of the transplant by occlusion of its microvasculature.

We hope that the seminal papers on the development of FK 506 which appear in this monograph will provide a stimulus for further advances in experimental and clinical transplantation.

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0041-1345/90 \$3.00 + 0