pressed with FK-506. Transplant Proc 1987;19(suppl 6):98-9.
18. Nalesnik MA, Todo S, Murase N, Toxicology of FK-506 in the Lewis rat. Transplant Proc. 1987;19(suppl 6):89-92.
19. Starzl TE, Marchioro TL, Waddell WR. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 1963; 117:385-95.
20. Sawada S, Suzuki G, Kawase Y, Takaku F. Novel immunosuppressive agent, FK 506 in vitro effects on the cloned T cell activation. J Immunol 1987;139:1797-803.
21. Zeevi A, Duquesnoy R, Eiras G, et al. Immunosuppressive effect of FK-506 on in vitro lymphocyte alloactivation: synergism with cyclosporine. A. Transplant Proc 1987;19(suppl 6):40-4.
22. Zeevi A, Duquesnoy R, Eiras G, Todo S, Makowka L, Starzl TE. In vitro immunosuppressive effects of FR 900506 on human T lymphocyte alloactivation. Surg Res Comm 1987; 1:315-23.
23. Sanghvi A, Warty V, Zeevi A, et al. FK-506 enhances cyclosporine uptake by peripheral blood lymphocytes. Transplant Proc 1987;19(suppl 6):45-9.
24. Starzl TE, Marchioro TL, Porter KA, Iwasaki Y, Cerilli GJ. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation and in human renal homotransplantation. Surg Gynecol Obstet 1967;124:301-18.

DISCUSSION

Dr. Richard Wood (London, England). Although FR 506 is a potentially exciting immunosuppressive agent, it appears to cause hyperglyemia. Cyclosporine and steroids in high doses also cause this problem. Therefore in addition to the synergy in treating rejection that you have observed, is there also synergy in the development of hyperglycemia when FR 506 is used in combination with cyclosporine and steroids?

Dr. Hockerstedt (Helsinki, Finland). Do you have any results on the effect of FK on the liver? I do not mean transaminase changes; I would like to hear some histologic results because other groups have found really adverse side effects on the liver. Why do you continue to use a rather low dose of cyclosporine in the control dogs. In group 9, cyclosporine and prednisone, there really was no difference in survival with the nontreatment group with the exception of one dog, and I am sure that none of us would start to use cyclosporine with these results.

Dr. Todo (closing). Dr. Wood, we know that the Cambridge group claimed that this drug induced hyperglycemia. Actually, only one dog died with hyperglycemia on the twenty-third day of treatment with a single FK drug (2 mg/kg). This dog had pancreatitis as well as mild jaundice, but other than that, we did not see any significant correlations with the dose of FK and hyperglycemia. The glucose levels in the monkeys and baboons are almost stable, 100 mg/dl, throughout the treatment. However, in the rats, treated with an oral dose of 4/mg of FK for 1 month, there was an elevation in glucose level, but this was very minor.

The second question regarding changes in the liver, central local hepacyte swelling occurred in dogs but not in the rats or monkeys.

Dr. Hockerstedt, regarding the continuous low-dose use of cyclosporine, our system was to have a treatment baseline that was not effective to which low doses of FK could be added. We were testing a possible strategy for clinical trials. We know that if we stop cyclosporine, or lower the dose, in patients, we frequently see rejection.

Editors' note: This article contains more material than this Discussion addressed.