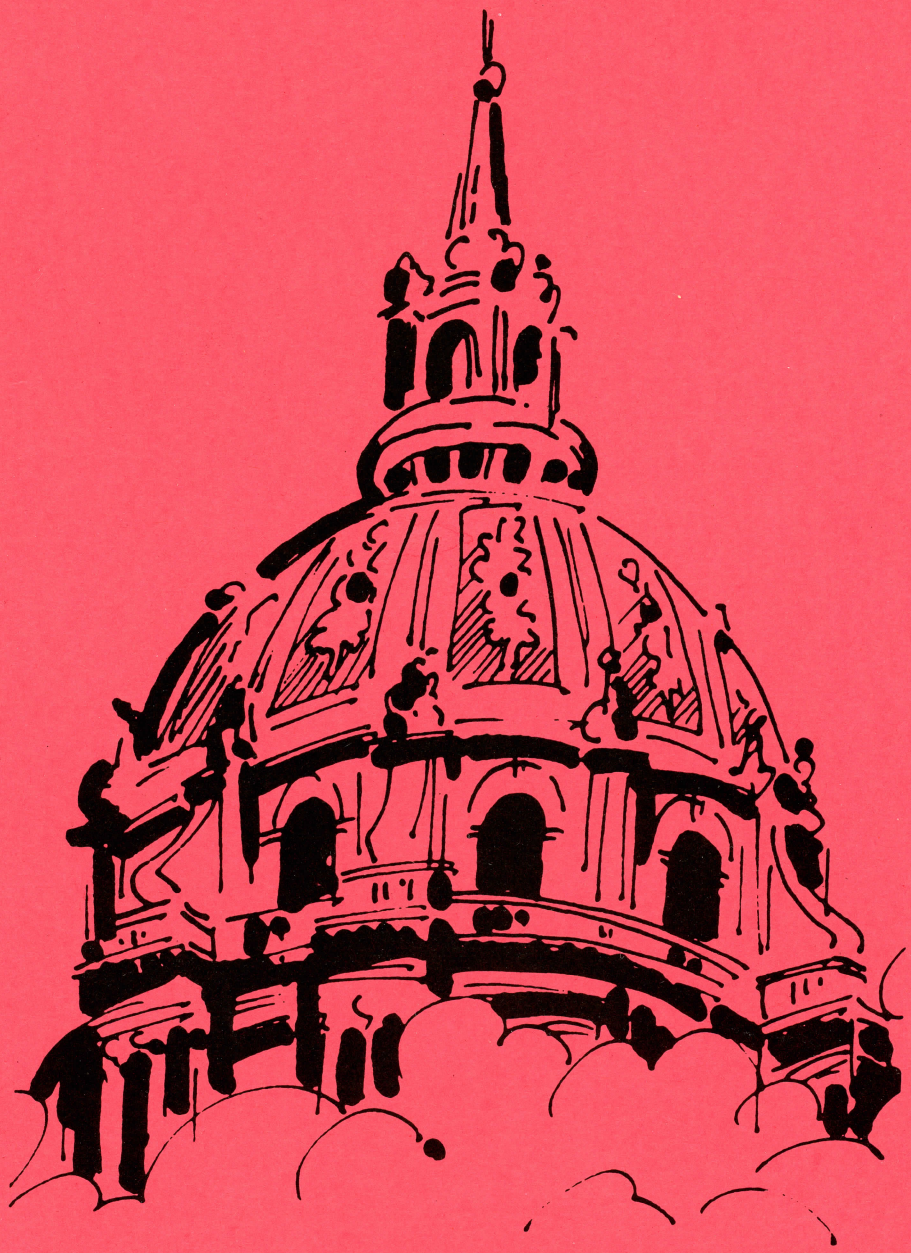
IIIrd International Symposium
on
SMALL BOWEL TRANSPLANTATION



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SERUM CYTOKINES LEVELS AFTER SMALL BOWEL TRANSPLANTATION (SBT) IN PIGS. INFLUENCE OF FK506 TREATMENT.

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Allotrasplantation of the small intestine without immunosuppression invariably results in death of the recipients from intestinal graft rejection. In addition the large lymphoid mass included in the mesentery of the graft predisposes to recipient GVHD. Immunosuppressive treatment has increased graft survival. However acute cellular rejection (ACR) and infections remain two main problems in small intestinal transplantation. Most of the methods for monitoring the onset of ACR are invasive (e.g. serial mucosal biopsies). In the present study serum cytokines levels were determined after SBT in pigs with and without immunosuppression, in attempt to identify early graft rejection.

Five pigs underwent SBT: 2 of them had no immunosuppression (group 1) and 3 received FK506 (0.2 mg/kg/day IM) (group 2). ACR occurred within 4 to 7 days after transplant in both groups. The histology confirmed severe ACR in group 1 and mild to moderate ACR in group 2. At this time, in group 2 FK506 was increased to 0.3÷0.4 mg/kg/die. Pigs without FK506 died for rejection after 12 days after surgery, while in FK506 treated animals death occurred after 26±5 days for emaciation and sepsis. Only one graft of this group showed signs of rejection at autopsy. The following serum cytokines were determined at various time after surgery: IL-1, IL-2, IL-6, IL-7 by EIA methods (Cytokit™, Assay Research Inc.,MD,USA).

After transplantation we observed in group 1 animals progressive increase of serum IL-2, IL-6 and IL-7 levels at the time of occurrence of ACR. The animals died with elevated levels of cytokines. Variation of IL-1 levels was not significant. In pigs of group 2 IL-7 levels increased at the onset of ACR from 5.41 ± 1.94 to 13.07 ± 2.72 ($p=0.01$), IL-6 raised from 4.13 ± 1.66 to 8.46 ± 2.17 ($p=0.05$). while IL-1 and IL-2 remained unchanged. During treatment of rejection with high FK506 doses, both IL-6 and IL-7 decreased to the initial values. In conclusion, both IL-6 and IL-7 are able to induce a T lymphocyte activation and furthermore IL-7 induces a synergistic cytotoxic activity with IL-6. Both IL-6 and IL-7 raised during ACR independently from the histological grade of rejection and were influenced by successful treatment of ACR. Serum levels of these two cytokines may offer a possibility of monitoring ACR and the degree of immune response.

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SERUM DIAMINE OXIDASE HAS NO PROGNOSTIC VALUE IN ACUTE SMALL BOWEL REJECTION IN RATS

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Rejection of intestinal allografts is still a major problem hindering clinical transplantation. A serum marker that could detect rejection at an early stage would be of great help in adjusting immunosuppressive protocols. The enzyme diamine oxidase (DAO) is mainly produced by mature enterocytes and a correlation exists between intestinal and serum DAO activity.

To study the value of DAO as marker of acute rejection, fully allogeneic total orthotopic small bowel transplantation (SBT) was performed in rats using the WAG-to-BN donor host combination (group 2: daily serum DAO determination until rejection, n=9). Syngeneically transplanted WAG rats served as control (group 1: daily serum DAO determination until day 16, n=6). Statistical analysis among the groups on postoperative days was tested using the nonpaired Student-t-test after taking the logarithm of the individual data with $p < 0.05$ considered significant. The prognostic value of DAO for SBT rejection was evaluated using a non-parametric grafical representation of the relationship between rejection and the occurence of DAO level changes.

Animals in group 1 survived indefinitely and animals in group 2 died of rejection between 10 and 18 days. In both group 1 and 2 a fluctuating serum DAO pattern with time was found. Basal serum DAO level was significantly decreased in allogeneic transplanted animals compared to syngeneic controls at day 13, 14 and 16. At that time, however, extensive mucosal sloughing had already taken place. Studying allotransplanted animals individually, no prognostic DAO change, indicating onset of rejection, could be found.

These data indicate that the small bowel transplantation procedure itself is responsible for fluctuating serum DAO levels in the first two weeks postoperatively and that monitoring serum DAO has no value in early detection of acute small bowel rejection. Whether serum DAO value is suppressed by early transplantation-related factors should be investigated in a chronic rejection model following small bowel transplantation.