Recent Results of Small-Bowel Transplantation in the Rat Model

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Since its original description by MONCHIK and RUSSELL (1971), the model of small-bowel transplantation in the rat has proved to be remarkably productive. The availability of inbred strains has allowed the phenomena of rejection and graft-vs-host disease (GvHD) to be studied separately in a controlled fashion that is not possible in large-animal models. Moreover, the advent of cyclosporine therapy has produced a flurry of new investigations employing the rat, as is evident from the contributions to this workshop.

Previous work from this laboratory has focused on the effect of cyclosporine on the immunology and function of small-bowel transplants in the rat (KIRKMAN et al., 1984; 1985). In our experimentation, cyclosporine has proved to be highly effective in the prevention of rejection. When the drug was given at a dose of 15 mg/kg per day for 7 days following transplantation, graft survival exceeded 100 days in the strain combination Lewis x Brown Norway F1 hybrid (LBN) into Lewis and was significantly prolonged in the combination Lewis x Wistar Furth F1 hybrid (LWF) into Lewis. Cyclosporine was less successful in preventing GvHD. When Lewis bowel was transplanted into either LBN or LWF recipients, host survival was prolonged by cyclosporine, but animals frequently succumbed to GvHD when cyclosporine was discontinued.

The histologic and functional correlates of rejection have also been carefully examined in our rat model (MADARA and KIRKMAN 1985). Histologically, the earliest abnormalities in jejunal grafts occurred within 3 days post-transplantation and consisted of focal endothelial cell injury of the microvasculature and focal injury of crypt epithelial cells. Both alterations were associated with the infiltration of large lymphoid cells, and both progressed markedly over the ensuing 6 days. In contrast, the structure of the villus absorptive cells was not markedly altered until the 9th postoperative day. These structural abnormalities were largely paralleled by functional deficits in both passive and active ion transport, as determined in the Ussing chamber. These results have led to the hypothesis that the primary targets for rejection in small-bowel transplantation are the endothelial cells of the microvasculature and the crypt epithelial cells. Damage to the villus epithelium is most likely secondary and related to ischemia produced by microvascular injury and/or decreased epithelial regenerative ability which is secondary to crypt injury. Of importance, the histologic and functional abnormalities caused by rejection were markedly ameliorated by the use of cyclosporine in these short-term experiments.

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Recent laboratory investigations have turned to the longer-term consequences of small-bowel transplantation in the rat. This has required the development of techniques for placing the graft in continuity with the host gastrointestinal tract and has led to a significant increase in technical complications. Initial work has focused on the metabolic consequences of systemic, as opposed to portal, venous drainage. It seems likely that future clinical small-bowel transplants will employ systemic drainage for reasons of simplicity and safety. Nevertheless, the effects of a partial portacaval shunt on the nutrition and metabolism of the host have received little study. Aberrations in serum ammonia and amino acid levels have been observed following creation of an Eck's fistula in rats for studies of hepatic encephalopathy (CUMMINGS et al. 1976; HINDFELDT et al. 1977; HAWKINS et al. 1982). Whether this will be seen following small-bowel transplantation with systemic venous drainage remains unknown. The remainder of this paper will address this question. The data remain preliminary and are submitted in the spirit of a workshop contribution.

Materials and Methods

Animals
Adult male Lewis rats weighing between 150 and 250 g were obtained from Microbiological Associates, Walkersville, Maryland, USA, or from Charles River Laboratories, Kingston, New York, USA. Recipient and donor were always obtained from the same source.

Experimental Groups
Three groups of animals were studied:
1) Group I: \( n = 6 \) unmanipulated controls
2) Group II: \( n = 5 \) recipients of out-of-continuity small-bowel transplants, with both ends of the graft exteriorized as stomas
3) Group III: \( n = 6 \) recipients of in-continuity small-bowel transplants, with near total resection of native jejunum and ileum

Venous drainage in both groups II and III was into the systemic circulation, and all transplants were isografts.

Operative Techniques
The technique for out-of-continuity small-bowel transplantation was modified from MONCHIK and RUSSELL (1971) and has been previously described (KIRKMAN et al. 1984). For in-continuity grafts, the host intestine was resected from proximal jejunum to distal ileum, preserving the ileocecal valve.

Anastomoses between graft and host bowel were performed using a single layer of interrupted 7–0 silk, with the entire procedure performed as a single stage.

Postoperative Studies
All animals were weighed daily. Blood samples were obtained by cardiac puncture under light ether anesthesia. For ammonia levels, 1 ml heparinized blood was