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Effect of Low Molecular Weight Dextran on Gastric Ulceration and Gastric Secretion in Pylorus-Ligated Rats* (32799)

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There is recurrent interest in the possible role of vascular factors in the genesis of peptic ulceration. Low molecular weight dextran (LMWD) has been advised in a wide variety of circulatory disorders in which tissue perfusion may be impaired. In view of its biorheological properties, the present study was designed to ascertain the effects of LMWD on gastric ulceration and acid secretion in rats.

Methods and Materials. A. *Effects on gastric ulceration.* Adult male Sprague-Dawley rats ranging in weight from 180–220 gm were deprived of food for 48 hours and water for 12 hours before surgery. The animals were lightly anesthetized with ether, and pylorus ligation (1) was performed through a midline incision by placing a 4-0 silk ligature around the pyloroduodenal junction, taking care not to occlude any blood vessels. Randomized test rats received 150 mg/100 gm of body weight of intravenous 10% isoosmotic LMWD (Rheomacrodex 40,000, from Pharmacia Laboratories, Piscataway, New Market, New Jersey) and control rats received an equal volume of normal saline. Following recovery from anesthesia the rats were kept under constant laboratory conditions until they were sacrificed after 6, 9, 12, and 16 hours, respectively. Each animal was housed individually in a cage with a raised bottom of wide wire mesh to insure immediate passage of feces from the cage and did not have access to food or water during this time.

At the end of the period the surviving rats were lightly reanesthetized with ether, venous blood samples were taken for hematocrit determination, and rectal temperatures were recorded; the stomachs were removed and each animal was sacrificed by bilateral thoracotomy. The stomachs were opened along the greater curvature and examined with a dissecting binocular microscope with 10× magnification for the presence of ulceration. Rats which were found dead before reoperation were included in the study only if there was definite evidence of perforation, and of the presence of gastric contents in the pleural or peritoneal cavity at autopsy. The severity of ulceration was determined by the methods of Pauls *et al.* (2), in which the grade of ulceration signifies the number of ulcers from grade 1-plus to 4-plus. The effects of LMWD on ulcer activity was evaluated by comparing the Ulcer Index (average plus grade of ulceration in a given group × percent of animals showing ulceration in that group) in the test and control groups.

B. *Effect on gastric secretion.* Effects of LMWD on gastric secretion was studied in identically performed experiments in which the rats were sacrificed after 4 hours, thus avoiding the contamination of secretion by blood when longer periods are used. In all 69 rats, gastric contents were centrifuged and analyzed individually for volume, acid, and pepsin. Titratable acid was determined to pH 7.0 with 0.01 *N* NaOH. Pepsin concentration was determined by the method of

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TABLE I. Incidence of Rumenal Ulceration in Saline- and LMWD-Treated Rats Following Varying Periods of Pylorus Ligation.[a]

Hours after pylorus ligation	Control			LMWD		
	No. of rats	No. with ulceration	% Ulceration	No. of rats	No. with ulceration	% Ulceration
6	22	9	40.9	23	5	21.7
9	25	13	52.0	23	8	34.8
12	20	16	80.0	20	8	40.0
16	21	17	81.0	19	7	26.8

[a] Reduction in incidence of ulceration statistically significant ($p < 0.05$).

Reich *et al.* (3), using casein as substrate; 1 unit was defined as equivalent to the absorbency of 1 μg of tyrosine liberated per hour.

Statistical significance was determined by the Student's *t* test. Incidence of ulceration as well as acid and pepsin outputs were analyzed statistically since these values were determined in each rat, but the Ulcer Index was not subjected to statistical analysis because it does not refer to individual animals but to whole groups.

Results. Effect on gastric ulceration. The LMWD afforded marked protection against the development of rumenal ulceration (Table I). A clearer picture is obtained by considering the Ulcer Index (Fig. 1), which reflects both the incidence and severity of ulceration. A linear relationship was noted between the Ulcer Index and time after pylorus ligation, control rats showing an index of 40 after 6 hours rising to 370 after 16 hours. The LMWD reduced the Ulcer Index after 16 hours from 370 to 30. No difference was found in the hematocrit determination between the two groups.

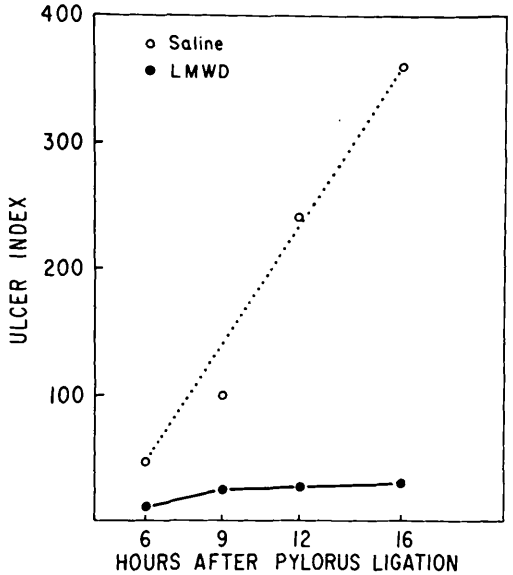

FIG. 1. Ulcer Index in control (saline) and LMWD-treated rats plotted against time after plyorus ligation.

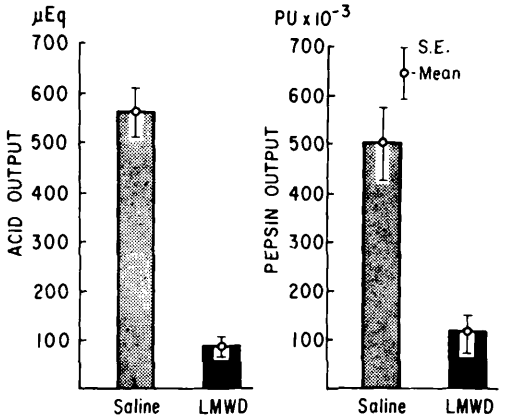

FIG. 2. Effect of LMWD on acid and pepsin secretion (4-hour output) in pylorus ligated rats. Difference between saline and LMWD treated groups statistically significant ($p<0.001$).

Effect on gastric secretion. The effects of LMWD are seen in Fig. 2. Intravenous LMWD reduced the acid output by 85% and pepsin output by 70%. Both the volume and acid concentration were diminished. However, pepsin concentration was unaltered and the decreased output reflected the reduction in volume. The difference between test and control groups were statistically significant ($p<0.001$). No pyrogenic reactions were noted in the LMWD-treated rats.

Discussion. Focal reduction in capillary blood flow leading to local depression of mucosal resistance has been implicated as the final common pathway in the genesis of gastroduodenal ulceration (4,5). Low molecular weight dextran is of established benefit in circulatory disorders that produce tissue hypoxia (6). This effect is attributed to the ability of LMWD to reduce blood "sludging" and thus improve flow in the capillary circulation.

The present study demonstrates that LMWD has a marked protective action against the development of rumenal ulcers in pylorus-ligated rats. Conceivably an improvement in mucosal blood flow might contribute to the reduction in ulceration. However, in this study it is more likely that the effect on ulceration resulted from inhibition of acid and pepsin output in the gastric secretion.

The mechanism of gastric secretory inhibition is somewhat speculative. It has been demonstrated that gastrointestinal excretion plays a major role in the elimination of dextran, accounting for 15% of the intravenously administered dose (7,8). We have incubated LMWD with 0.1 *N* HCl and with gastric juice *in vitro* and *in vivo* and have not found any binding of acid or pepsin. The introduction into the duodenum of various sugars causes inhibition of motility and secretion in transplanted fundic pouches, presumably through the release of enterogastrone (9). However, in preliminary experiments, we have failed to suppress gastric secretion by the intraduodenal instillation of LMWD. The most likely mechanism of action lies in the observation that LMWD inhibits the release of histamine from most cells (10). In this respect it resembles heparin which is also a sulfated polysaccharide, and which has been shown to suppress gastric secretion when administered in pharmacological doses (11).

Elucidation of the mechanism of action clearly requires further study. The inhibitory action must be tested against a wide variety of secretagogues.

Summary. The effects of low molecular weight dextran were studied on gastric ulceration and gastric secretion in pylorus-ligated rats. The LMWD protected rats against the development of gastric ulceration and also reduced acid and pepsin output. Further studies need to be undertaken to elucidate its mechanism of action.

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