Jejunal ulcers produced by indomethacin

While studying the anti-inflammatory effect of indomethacin in rats we frequently observed acute perforating jejunal ulcers leading to generalized peritonitis. The following experiments were made to verify this accidental observation.

Female Sprague-Dawley rats (Holtzman Farms, Madison, Wisconsin, U.S.A.) weighing about 100 g and kept on Purina Laboratory Chow and tap water *ad libitum* received single doses of indomethacin (1, 2, 4 and 8 mg) into the jugular vein. Depending on the dose, 20–90% of the rats died within two to four days. The survivors were killed at different intervals after indomethacin treatment.

After macroscopic inspection specimens of jejuna were fixed in ethanol-formol and embedded in paraffin for staining with haematoxylin-phloxine and with the PAS technique.

On opening the abdominal cavity, generalized peritonitis was observed. A serofibrinous exudate filled the abdomen and many adhesions developed between the intestinal loops. Twenty-four h after treatment numerous circular or elongated ulcers 2 to 4 mm in size became evident in the jejunum. Some of these ulcers were superficial, affecting only the mucosa, others penetrated into the muscularis and destroyed the entire intestinal wall. The most severe lesions were observed between the second and the fourth days. Doses as low as 1 mg indomethacin caused ulceration while the administration of 8 mg led to extensive lesions and accelerated death. No ulcers were found in the stomach, ileum or colon.

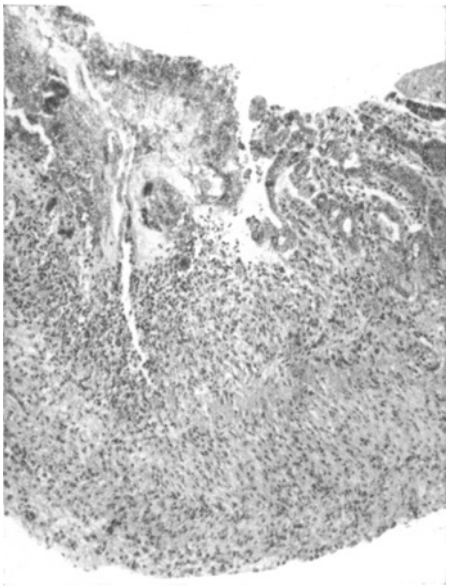

FIG. 1. Acute ulcer in the jejunum four days after the intravenous injection of 4 mg indomethacin. (PAS 75X).

Histologic examination confirmed the macroscopic findings. Marked inflammation was observed in the vicinity of the ulcers extending into the mesentery. The small vessels were dilated and filled with erythrocytes but there were no thrombi or vascular occlusions. Numerous polymorphonuclear leukocytes and fibrin strands could be seen on the serosa and in the mesenteric fat.

Patients treated with indomethacin have developed gastrointestinal symptoms such as nausea, vomiting, dyspepsia, peptic ulcer and gastrointestinal haemorrhage, particularly when large doses were given (Lövgren & Allander, 1964; Ballabio, 1965; Rothermich, 1966). Anderson (1965) found that indomethacin can cause gastric erosion and haemorrhage in starved guinea-pigs. In dogs, Nicoloff (1968) observed that the administration of indomethacin induced antral and gastric ulceration with melena and perforation, as well as jejunal ulcers.

Our investigations show that in rats the jejunum is most susceptible to the ulcerogenic effect of indomethacin. The pathogenesis of jejunal ulcers still needs elucidation and it is felt that this easily reproducible experimental model may facilitate the study of factors influencing jejunal ulcers in rats.

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Effect of subcutaneously administered degraded carrageenan on the production of histamine-induced gastric and duodenal ulceration

We recently reported the pronounced and prolonged inhibitory effect of parenterally administered degraded carrageenan on the acid gastric secretory response of the guinea-pig to histamine (Eagleton, Watt & Marcus, 1968). We have now made a comparison of the protection afforded by parenteral carrageenan against histamine-induced gastric ulceration and histamine-induced duodenal ulceration in the same species.

For the selective production of gastric and duodenal ulcers, histamine acid phosphate was given to fasted adult male albino guinea-pigs, 550–650 g, and the lesions evaluated (Eagleton & Watt, 1965, 1967). Freshly prepared degraded carrageenan (5% aqueous solution) derived from the red seaweed *Eucheuma spinosum* was given as a single subcutaneous injection, 400 mg/kg, to all test animals 12 h before administration of histamine; control animals received no carrageenan. For the production of gastric ulcers, the animals were injected intraperitoneally with 5 mg of histamine (doses refer to the salt) per kg and killed 3 h later, i.e. 15 h after receiving carrageenan. For the production of duodenal ulcers, 8 injections of 0·25 mg histamine/kg were given intramuscularly at $\frac{1}{2}$ h intervals; the animals were killed 4 h after the first injection of histamine, i.e. 16 h after receiving carrageenan.

We also investigated the effect of degraded carrageenan in doses ranging from 195 to 550 mg/kg on the incidence and severity of histamine-induced duodenal ulceration, the carrageenan being injected 12 h before histamine. The volume and total acid concentration (titration with phenolphthalein as indicator) of the gastric juices removed at autopsy were measured.