

## Role of Gastric Acid in Aspirin-Induced Erosive Gastritis<sup>1</sup> (35057)

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Aspirin induces superficial erosive gastritis in man and experimental animals via a poorly understood mechanism. Some studies suggest that aspirin in contact with the gastric mucosa may alter the permeability of the mucosal barrier to H<sup>+</sup> (1). Mucosal damage would result from the back diffusion of H<sup>+</sup>. However, aspirin need not come into contact with the mucosal surface to produce injury since typical erosions are readily produced in rats by parenterally administered aspirin (2). Moreover, aspirin given parenterally has been shown to alter gastric mucus production (2) in a way which in turn could alter mucosal permeability. The purpose of the studies forming the basis of this report was to define the role of gastric acid in the development of gastric erosions produced by the parenteral administration of aspirin to rats. If cellular injury resulted from back-diffusion of acid across a gastric mucosa rendered more permeable by circulating aspirin, gastric erosions would not occur if the stomach's capacity to secrete acid were lowered during the period of aspirin administration. Gastric irradiation was selected as the method of reducing gastric acid secretion (3). Our data will show that achlorhydric rats do not develop gastric erosions after receiving large doses of aspirin subcutaneously.

**Methods.** Under general anesthesia, 24 albino rats were subjected to gastric irradiation consisting of 1750 rads delivered to the eviscerated stomach over 11.5 min with appropriate shielding of the rest of the animal (3).

Sham procedures, during which the stomach was exposed and manipulated in a fash-

ion similar to that of the experimental group, were performed on weight paired controls.

Three weeks later, 9 pairs of animals underwent pyloric ligation after 48 hr of fasting. Four hr after the completion of the operation, the animals were killed and their gastric contents were analyzed for volume and HCl concentration. The latter was measured by titration to pH 7.0. Results were expressed as 4-hr output of HCl.

The remaining 15 pairs of animals received 600 mg/kg of aspirin in 4 divided subcutaneous doses over 2 successive days. Four hr after the last dose, the animals were killed and their stomachs were inspected under a dissecting microscope. The amount of bleeding and the number and extent of ulcers were estimated.

**Results.** The irradiated animals had an average weight of 211 g while that of the control animals was 307 g. The coats of the irradiated animals were not as sleek and their wounds not as well healed as those in the control group.

Gastric acid output was significantly different in the 2 groups of rats. The average 4-hr output of HCl in the control group was 1.09 meq, while that of the irradiated group was only 0.10 meq.

There were also significant differences be-

TABLE I. Degree of Aspirin-Induced Bleeding.

Amount of blood	No. of animals	
	Irradiated	Control
0	9	1
Trace	4	1
1+	1	2
2+	1	6
3+	0	1
4+	0	4

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TABLE II. Incidence of Aspirin-Induced Gastric Erosions.

No. of ulcers	No. of animals	
	Irradiated	Control
0	11	1
1-5	4	5
6-10	0	3
11-15	0	3
15-20	0	2
>20	0	1

tween the irradiated and the control groups with respect to the effects of aspirin on the gastric mucosa. Table I summarizes the amounts of intragastric blood observed. The number of observed ulcers are summarized in Table II.

The gastric erosions produced by parenteral aspirin occurred only in the glandular mucosa and were more numerous at the junction of the antrum and the corpus (Fig. 1). Of the four animals in the irradiated group that

developed gastric erosions, two had a single erosion less than 1 mm<sup>2</sup> in surface. Of the remaining two animals, one had a 5-mm<sup>2</sup> area of mild intramucosal bleeding, while the other had patchy areas of intramucosal hemorrhage throughout the glandular mucosa.

Histologically, the glandular mucosa of the control animals contained scattered areas of hemorrhagic necrosis with infiltration of the necrotic area with leukocytes. The lesions never extended deeper than the muscularis mucosae (Fig. 2). The glandular mucosa of the irradiated stomachs showed focal replacement by granulation tissue infiltrated by capillaries and round cells. Remaining areas of recognizable mucosa were thin and showed cystic dilatation of the glands. Although the superficial mucosal cells were still present in these areas, parietal and chief cells were not recognizable (Fig. 3).

*Discussion.* Our data show that the gastric erosions produced consistently in rats by the parenteral administration of large doses of



FIG. 1a. Stomach of irradiated rat given aspirin; glandular mucosa is thin and free of erosions. (b) Stomach of sham-irradiated rat given aspirin shows typical aspirin erosions.

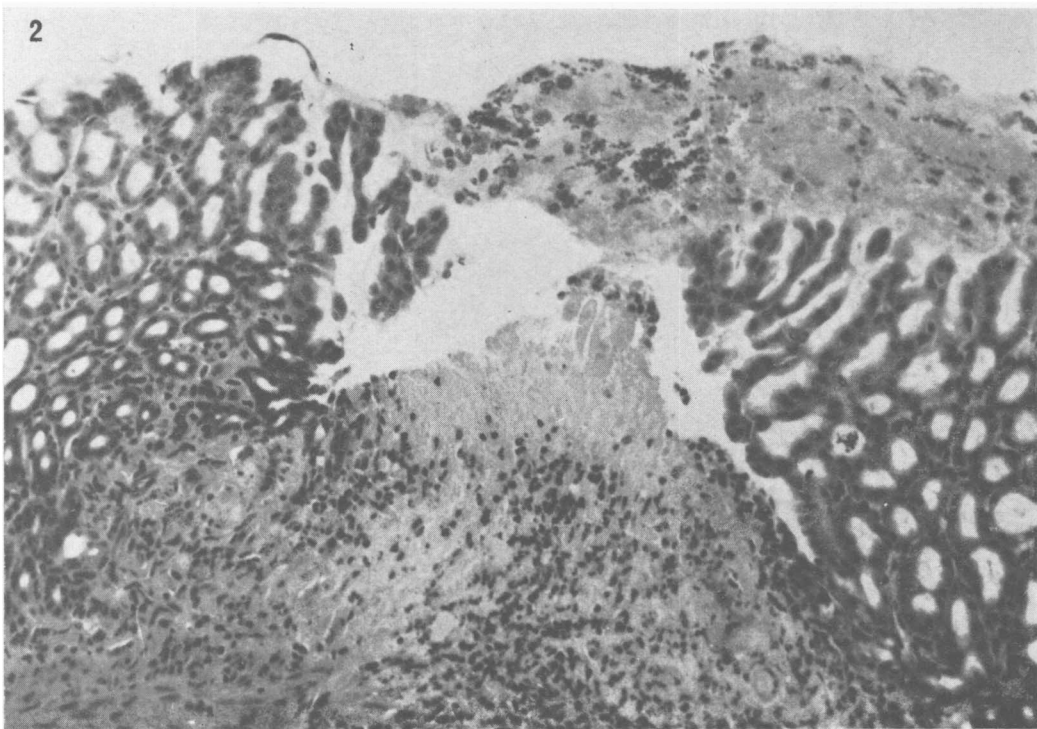


FIG. 2. Sham-irradiated rat given aspirin; typical aspirin erosion in glandular mucosa; H & E,  $\times 100$ .

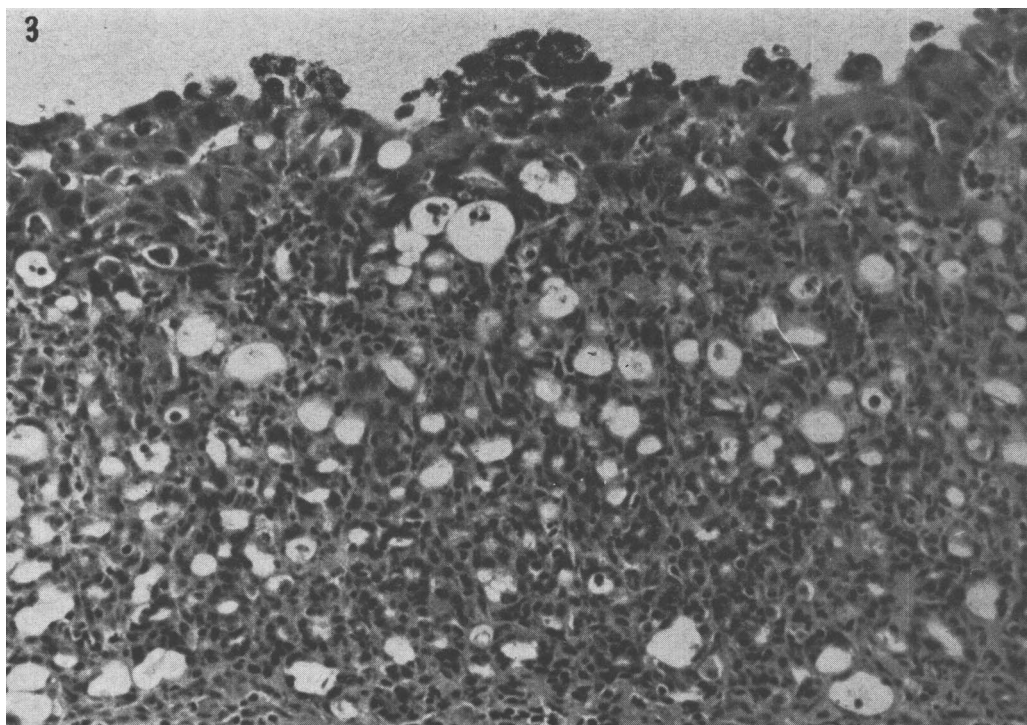


FIG. 3. Irradiated rat given aspirin; cystic dilation of gastric glands; H & E,  $\times 100$ .

aspirin do not occur when the rats have been rendered achlorhydric by gastric irradiation. These observations suggest that the gastric mucosal necrosis attending the parenteral administration of aspirin to rats does not reflect some metabolic action of circulating aspirin *per se* on the gastric epithelium. Furthermore, the data support the thesis that gastric HCl plays an important role in the phenomenon of gastric mucosal injury by aspirin perhaps by back-diffusion of  $H^+$  across a mucosal membrane rendered more permeable by aspirin. Obviously, they do not prove this view since gastric irradiation destroys not only parietal cells but other cellular elements, some of which, such as the mast cells, may play a role in this phenomenon.

Our data are in general agreement with those of Davenport (4) on the role of HCl in gastric mucosal injury produced by *direct* exposure of the gastric mucosa to aspirin. He found that the irrigation of canine Heidenhain pouches with either 100 mM HCl or 20 mM aspirin did not cause mucosal bleeding.

Significant bleeding occurred when the pouches were irrigated with 20 mM aspirin in 100 mM HCl.

These experimental data may also clarify an intriguing clinical problem. We have found that many patients with acute hemorrhagic gastritis have a preexisting chronic gastritis. In some of these patients, aspirin ingestion preceded the onset of bleeding (5). For obvious reasons, it would be worthwhile knowing whether a chronically inflamed and atrophic gastric mucosal membrane is more or less susceptible than a normal gastric mucosa to the injurious effects of aspirin. *A priori*, one would expect a chronically inflamed and atrophic gastric mucosa to be more readily damaged by aspirin. However, our data suggest that the atrophic gastric mucosa, at least insofar as this experimental model is concerned, is *less* rather than more susceptible to injury by parenterally administered aspirin.

*Summary.* The purpose of this study was to determine whether preexisting atrophic

gastritis and high intragastric pH render the gastric mucosa more or less susceptible to the ulcerogenic effects of *parenteral* aspirin. Radiation-induced gastric atrophy was used to produce achlorhydria in rats. Properly shielded rats received 1750 rads to the eviscerated stomach. Paired controls were subjected to a sham procedure. By comparison with the paired controls, all the irradiated rats became achlorhydric. When challenged with aspirin given parenterally (600 mg/kg/day in 4 divided doses over 2 consecutive days), the average number of gastric erosions in the sham irradiated control animals was 10, while the average number of erosions in the irradi-

ated animals was 0.25. The data suggest that gastric HCl plays an important role in the phenomenon of gastric mucosal injury by parenterally administered aspirin.

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