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Histologic Study of Gastric Lesions in Food-Restricted Rats (38012)

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Hemorrhagic or "stress" ulcers are seen with increased frequency in acutely ill or severely injured patients treated in intensive care units (1, 2). The pathogenesis of this condition has not been clarified, and, increasingly, animal models are being used to study the circumstances leading to development of similar gastric lesions under experimental conditions.

In most animal models, immobilization (3, 4), exposure to gravitational stress (5), or forced exercise (6) are being used to produce gastric ulcers. We have recently described an additional animal model in which food-restricted rats are allowed to run in activity cages. If animals of suitable size are used, they develop gastric lesions within a few days, and most of them die within a few weeks (7, 8).

The present communication describes the histologic changes in rat stomachs associated with the development of gastric

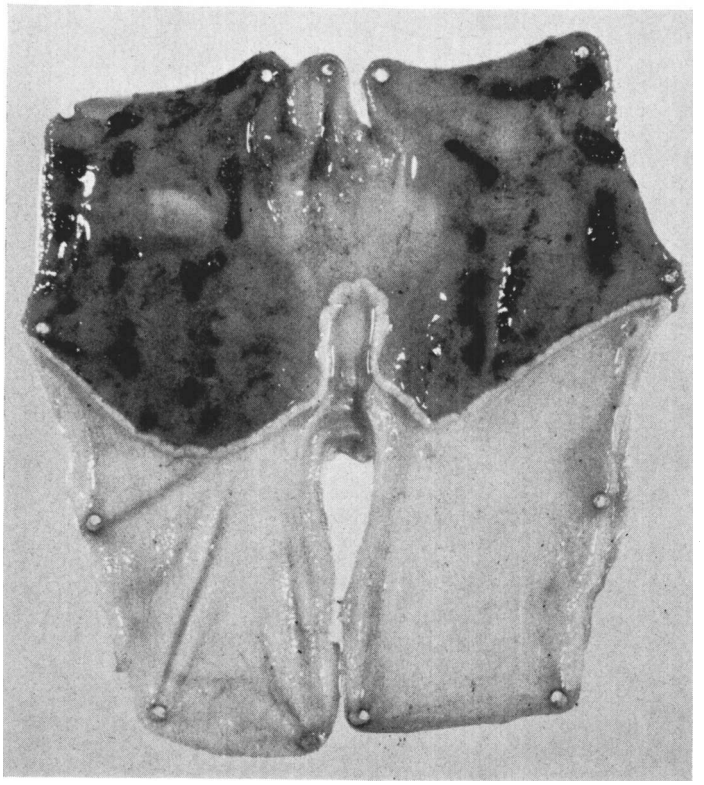

FIG. 1. Macroscopic appearance of gastric lesions in food-restricted rats.

lesions using the last procedure. These lesions resemble, to a large extent, the changes seen in the human counterpart of the "stress" ulceration (1).

Materials and Methods. Twelve male rats of the Sprague–Dawley strain (Sprague–Dawley Co., Inc., Madison, WI) weighing about 150 g each were used in the study. They were placed individually in laboratory cages with adjacent activity wheels (Model No. LC-34, Wahmann Manufacturing Co., Baltimore, MD) (10 animals) and were offered food (Purina Laboratory Chow, Ralston Purina Co., St. Louis, MO) for 1 hr a day only (9:00–10:00 AM). Drinking water was available without any restriction. During the duration of the experiment, the animals were kept in an air-conditioned

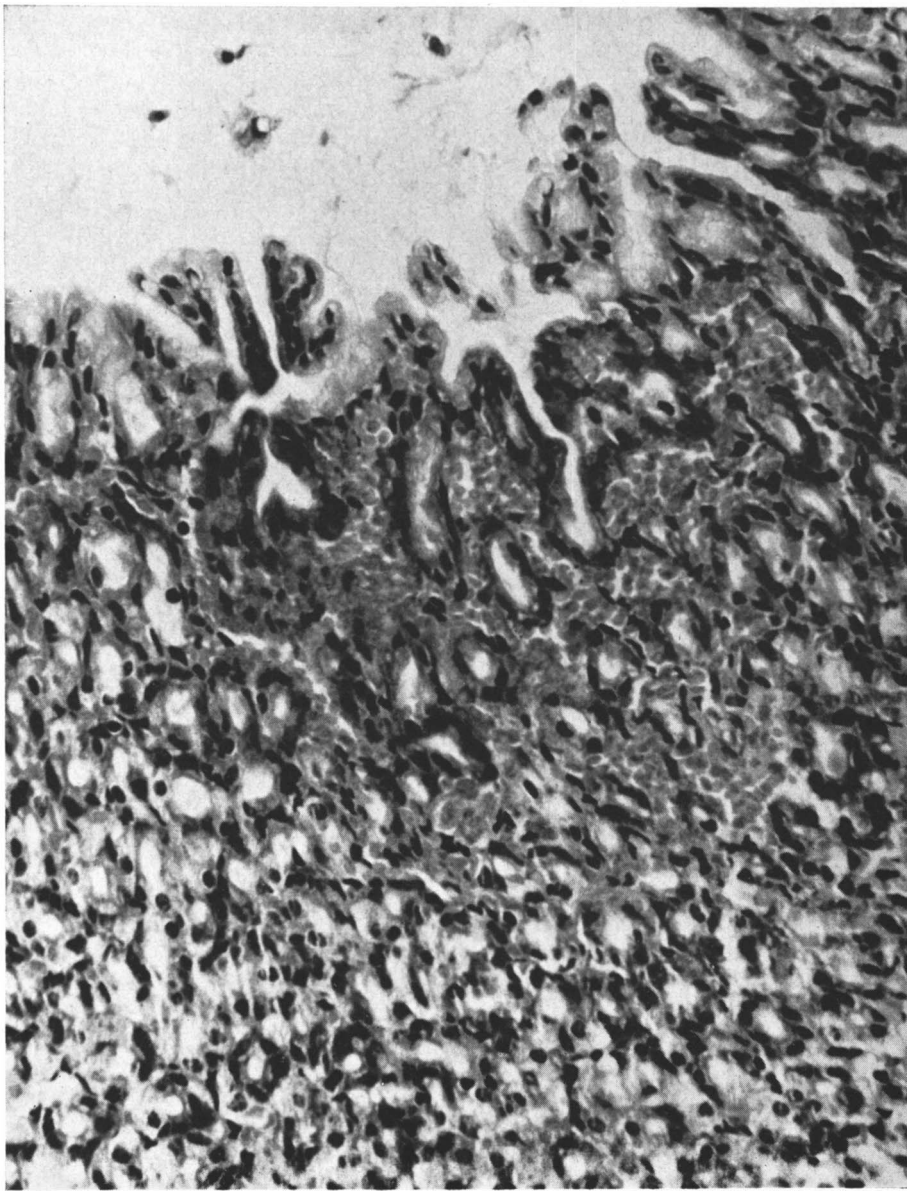

FIG. 2. The initial phase of gastric ulcer development, characterized by submucosal hemorrhage.

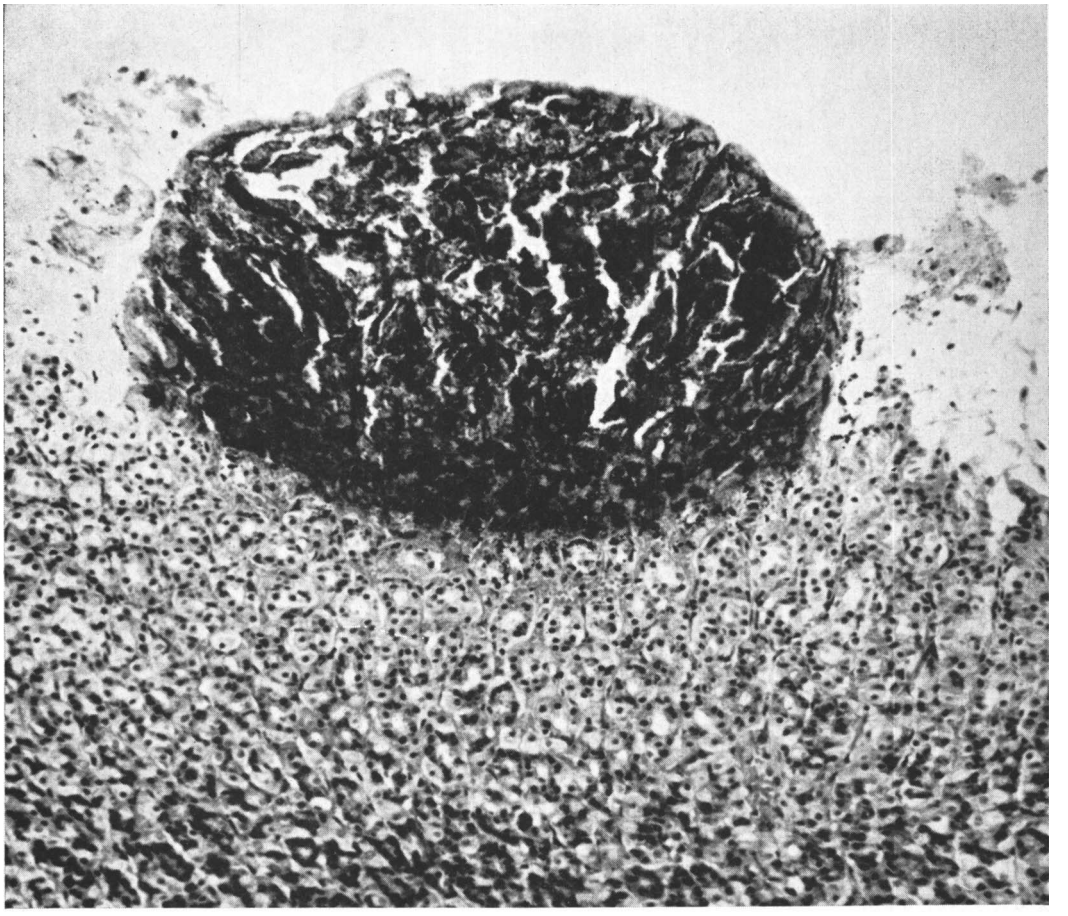

FIG. 3. Progression of gastric lesion to the "mushroom" stage. Note the membrane layer on the surface of the lesion.

animal room with a 12-hr light/dawn cycle. Six additional rats were kept under similar laboratory conditions; however, their access to food was not limited.

Since our previous data have shown that there is considerable individual variation in the length of time needed to develop the gastric ulceration, the animals were sacrificed after six days of experiment. Their stomachs were then dissected, stretched flat on paraffin beds for gross inspection, and preserved in buffered formaldehyde. For histologic examination, the sections were stained with a haematoxylin–eosin combination.

Results. Gross inspection of the stomachs revealed presence of gastric hemorrhage of various degree and extent (Fig. 1) in 8 of the 10 surviving animals in the food-restricted group. Two other animals from this group and all six rats of the control group were without any macroscopic evidence of gastric damage. The animals with the most extensive lesions had fresh and digested blood in the intestinal tract. The gastric lesions ranged from pinpoint hemorrhagic petechiae to oblong, red to black erosions oriented parallel to the long axis of the stomach. The majority of the lesions were found in the body of the stomach with occasional erosions in the antrum; the fundic section was free of any ulceration.

Microscopic examination of the lesions showed gradual changes in the intensity and extent of gastric damage. The first observable indication of gastric lesions was a

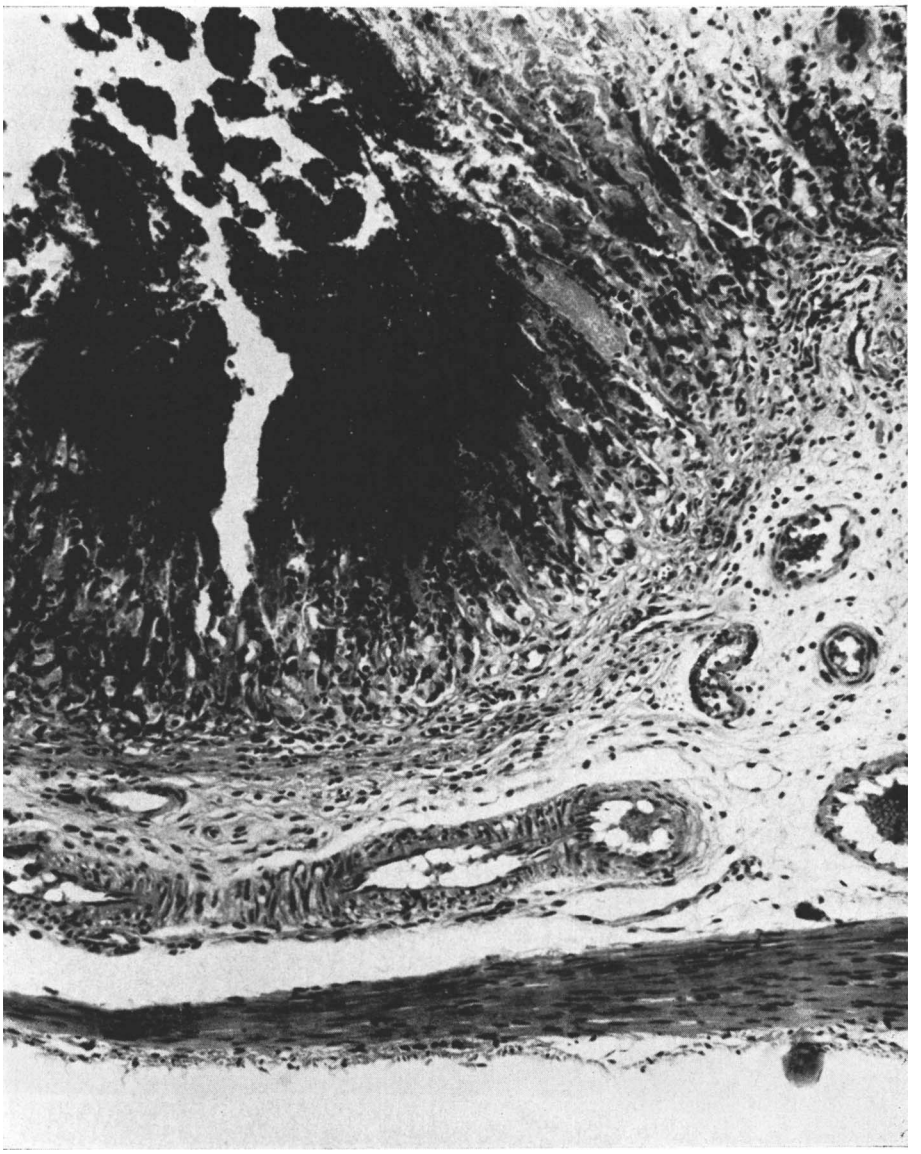

FIG. 4. The breakdown of the "mushroom" lesion and formation of an erosion.

development of small foci of capillary congestion. The capillaries were dilated or even disrupted, with erythrocytes filling the interstitial spaces. This type of lesion appeared first in the mucosal layer in close proximity to the gastric surface (Fig. 2). In other lesions, these foci of capillary congestion were increased in size and interstitial hemorrhage became quite obvious. Frequently, hemorrhagic lesions protruded over the mucosal surface in the form of a "ball" or "mushroom" while still enclosed by the basement membrane of the gastric mucosa (Fig. 3). Still other lesions showed loss of the enclosing basement membrane, necrosis, and disintegration of the epithelial cells resulting in the formation of mucosal erosion (Fig. 4). In some lesions, the erosion and necrosis extended throughout the whole mucosal layer into the submucosa (Fig. 5). Polymorphonuclear leukocytes were then seen at the periphery delineating the lesions.

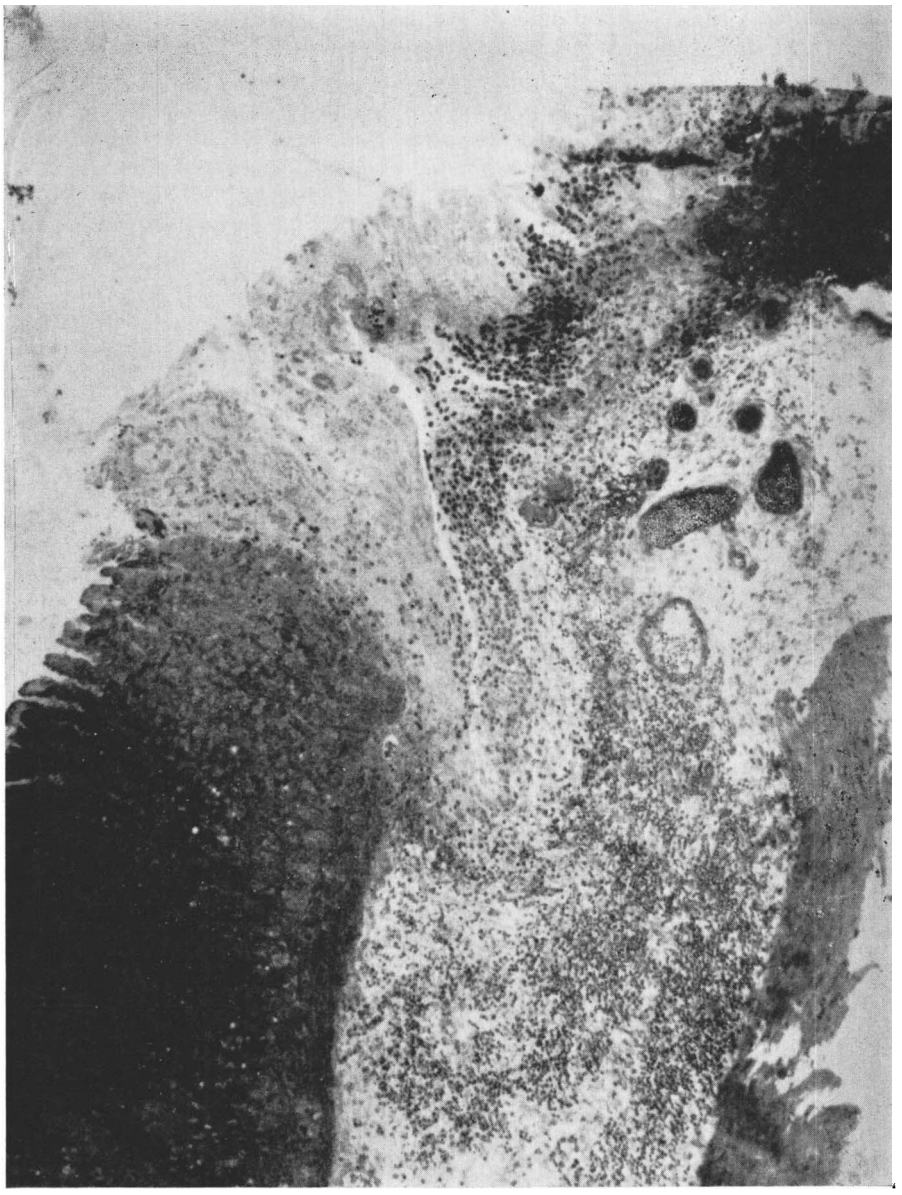

FIG. 5. Penetration of the gastric erosion into the submucosal area.

No thrombi of any type were seen in the vessels of the gastric mucosa or areas associated with the lesions. Histologic examination of the stomachs from the control animals failed to show any of the above-described changes.

Discussion. As in our previous studies (7, 8), the simultaneous restriction of food and increased running activity led to production of gastric lesions in the experimental animals. The lesions seemed to be initiated by a localized capillary congestion developing close to the mucosal surface below the basement membrane and "venting" toward the lumen. Pooling of blood led to a slight rise of accumulated material beneath the basement membrane, giving the appearance of pinpoint hemorrhage. The break of the basement membrane was probably followed by deepening and widening of the erosion and

gave the appearance of a larger confluent lesion. This process is similar to that described in gastric lesions of critically injured or septic patients (1) or in stress ulcers following war wounds (2). One exception was the absence of fibrin in any of the lesions observed in our animals. It has been suggested, however, that the thrombi may occur in later stages of the "reparative" phase of ulceration (2). Most of the lesions in our animals were of an acute nature and did not show any clear indication of the tissue-damage repair.

The etiology of the initial local capillary congestion is not clear at this time. Our findings indicate that it may occur without noticeable changes to the mucosal surface epithelium. Whether the capillary congestion reflects a reaction to an injured deep-seated gland or represents the effect of a vascular spasm remains to be determined. The absence of any fibrin or platelet thrombi indicates that, in this model at least, a thrombotic occlusion of the capillary did not play a role in the pathogenesis of the gastric lesions.

The described sequence of events leading to development of full-blown gastric erosions resembling the human lesions (1, 2) indicate that this animal model can be used to study various aspects of genesis, treatment, and prevention of "stress" ulcers.

Summary. Rats limited to food intake of 1 hr a day and allowed to run in an activity wheel developed gastric lesions which, on histologic examination, resembled human stress ulcers. The lesions in the animals started as small mucosal hemorrhages and developed progressively to form ulcers in the gastric mucosa. Some of the lesions penetrated to the submucosal layers. No thrombi were observed in the mucosal vessels.

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