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Rôle of Pepsin in Experimental Production of Gastric Ulcer in the Rat.*

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(Introduced by B. Kramer.)

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The rôle of gastric juice in the etiology of gastric and duodenal ulcer has been stressed. The hydrochloric acid has received the major portion of attention.[1] This investigation attempts to evaluate the relative importance of pepsin in the experimental production of gastric ulcer in the albino rat.

Buchner, Siebert and Malloy[2] reported that subcutaneous injections of histamine into fasting rats produced ulcers of the prostomach. These authors, as well as Burkle-de la Camp[3] contended that the resultant increase of both hydrochloric acid and pepsin were responsible for the observed ulcers.

It occurred to us that a more direct approach to this problem could be made with controlled feeding experiments, employing mixtures of pepsin and hydrochloric acid and hydrochloric acid alone. In such manner, we felt that the relative importance of these factors could be evaluated.

A total of 58 rats of the original Wistar strain, averaging in age 4 months, were fed the Steenbock-Bills[4] stock diet. Fresh lettuce or sliced carrots were added on feeding days. Fluids were supplied by means of stoppered flasks, with glass tube outlets, attached to the cages. The rats were then able to partake of these solutions ad lib.

The first group (1) received a 20% (by weight) mixture of granular pepsin (1:10,000 Parke, Davis and Co.*) in 0.3% solution of hydrochloric acid. The second group (2) received a 0.3% solution of hydrochloric acid alone. These solutions were freshly prepared every other day. One-half of each group (A) were fasted for 2 days and fed on the 3rd day; the control half of each

*Parke, Davis and Co. kindly supplied the pepsin used in our experiments.

1 Dragstedt, L. R., *Surg., Gyn., and Obst.*, 1936, **62**, 118.

2 Buchner, Siebert and Malloy, *Beitrage zur path. anat. and alleg. Path.*, 1928, **81**, 391.

3 Burkle-de la Camp, H., *Deutsche Z. f. Chirurgie*, 1929, **220**, 31.

4 Bills, C. E., Honeywell, E. M., Wirick, A. M., and Nussmeier, M., *J. Biol. Chem.*, 1931, **90**, 619.

group (B) had access to food at all times. The third group (3) received a 20% (by weight) mixture of inactivated pepsin (by heat) in 0.3% solution of hydrochloric acid, being fasted for 2 days and fed on the 3rd day.

In group 1A, 19 of the 20 rats, or an incidence of 95%, showed multiple ulcer-like lesions in the prostomach. In group 1B, one rat had 5 and another had only one lesion in the prostomach. The remaining 8 showed no gross changes. In group 2A only 3 animals developed gastric lesions. The other 10 showed no gross changes. In group 2B, out of 10 animals none showed any gross gastric lesions. In group 3, 2 of 10 rats (20%) developed gastric lesions.

The lesions have raised margins and umbilicated centers. They measure approximately 0.5 to 5 mm. in greatest diameter. Microscopically, the lesions simulate a localized erosive or ulcerative gastritis. These lesions are in no sense comparable to peptic ulcers in man since they occur in the proventriculus which is lined with squamous epithelium.

These experiments appear to establish that pepsin is a more important factor than HCL in the production of gastric lesions in the rat. With alternating fasting periods, 19 of 20 animals (95%) had multiple ulcer-like lesions in the pepsin group, while with 0.3% hydrochloric acid alone only 3 of 18 (16%) developed similar gross lesions. With continuous access to food, only 2 of the 10 animals had gastric lesions in the pepsin group and none in the acid group. Inactivated pepsin and 0.3% hydrochloric acid with fasting periods of 48 hours in our controls produced lesions in 20% of our animals. This almost corresponds to the incidence in group 2A (hydrochloric acid alone). The spontaneous occurrence of similar lesions in the rat is rare. In a series of 1144 rats examined by Fibiger[6] only 11 spontaneous prostomach lesions were found. Pappenheimer and Larimore[5] also reported that these rarely occurred in rats on complete diets. We found no gastric lesions in 65 control animals on various laboratory diets and fasting periods.

Conclusions. 1. Pepsin in combination with hydrochloric acid is far more effective than hydrochloric acid alone in the experimental production of ulcer-like gastric lesions in the albino rat. 2. Fasting is an important factor in the experimental production of these ulcer-like lesions.

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5 Pappenheimer, A. M., and Larimore, L. D., *J. Exp. Med.*, 1924, **40**, 719.

6 Fibiger, J., quoted by Burkle-de la Camp, H., *Deutsche Z. f. Chirurgie*, 1929, **220**, 31.