8751 P

Neoplastic Hyperplasia of Gastric Mucosa in Rats.*

GEORGE R. SHARPLESS. (Introduced by F. W. Hartman.)
From the Department of Laboratories, Henry Ford Hospital, Detroit.

This is a report of the production and prevention of morphological changes in the fore-stomach of rats by means of the diet.

Pappenheimer and Larimore[1] described lesions in the fore-stomachs of rats which appeared as round or oval discs with a small central ulcerated depression. The cause of the lesion was not found, but excess base or acid or Vitamin A deficiency were found not to be the etiological agents. Findlay[2] described changes in the fore-stomach associated with Vitamin B deficiency. Fujimaki has published a number of reports on the production of similar morphological changes in the fore-stomachs of rats by feeding different purified diets. His first hypothesis[3, 4] was that the condition was caused by Vitamin A deficiency, but later[5, 6] found that butterfat and/or cod liver oil caused a more marked change. The conclusion was drawn[6] that any of a number of fatty acids might play a partial etiological rôle.

The basal diet used to produce the lesion described here is as follows: Casein (vitamin free) 4.0%; dried brewer's yeast 5.0%; salts McCollum No. 185, 4.0%; butterfat, 5.0%; carbohydrate (starch, sugar, or dextrin), 82.0%; viosterol (15 drops per kilo of food).

Rats 28 to 35 days old, weighing 60 to 110 gm. were used. The lesion develops within 3 months, and all of the animals on the above diet which have been examined to date (40) have been affected.

The macroscopic appearance of the lesion varies from a few small elevated round or oval discs to long ridges of thickened epithelium with small papillomatous projections. There is a depression in the center of ridges and discs which may show ulceration. The normal fore-stomach is thin and elastic, but in animals with a severe

* Presented before American Society of Experimental Pathology, Washington, D. C., March 26, 1936.

1 Pappenheimer, Alwin M., and Larimore, Louise D., *J. Exp. Med.*, 1924, **40**, 719.

2 Findlay, G. M., *J. Path. and Bact.*, 1928, **31**, 353.

3 Fujimaki, Yoshitomo, *J. Cancer Res.*, 1926, **10**, 469.

4 Fujimaki, Yoshitomo, *Gann*, 1927, **21**, 8.

5 Fujimaki, Yoshitomo, *Trans. Jap. Path. Soc.*, 1928, **18**, 548.

6 Fujimaki, Yoshitomo, *Trans. Jap. Path. Soc.*, 1931, **21**, 708.

lesion the epithelium is so greatly thickened that its elasticity has been lost.

Older lesions may show from 2 to 8 epithelial cysts which vary in size up to 6 mm. in diameter. The most frequent site of occurrence is near the ridge separating the fore-stomach from the glandular portion, but it may occur in any one or all parts of the fore-stomach.

Microscopically, the lesion is characterized by a greatly thickened squamous epithelium which may show papilloma formation with keratinization at the surface. The papillae are markedly hypertrophied and may show active proliferation, numerous mitotic figures, and epithelial cells with hyperchromatic nuclei. In some cases the epithelial papillae show active proliferation with invasion of the submucosa. Ulceration of the epithelium may occur and epithelial cysts walled off by squamous epithelium and filled with keratin may be present.

Twenty-five rats fed the basal diet with 12.0% casein instead of 4.0% had normal stomachs.

Six rats, from 2 litters, fed the basal diet with 0.2% cystine and 6 fed the basal diet with 0.05% methionine did not develop the lesion, whereas littermate controls fed the basal diet alone invariably showed the characteristic changes. Cysteine hydrochloride and glutathione have also been tried but have not prevented the development of the lesion.

The rats nearly always have some hair in their stomach contents, which may act as an irritant and thus be a factor contributing to the production of the lesion. However, there is as much hair in the stomachs of those that do not develop the lesion as in those that do; thus it cannot be the primary etiological factor.

These rats are not in a chronic state of Vitamin A deficiency; their livers show abundant Vitamin A by the antimony-trichloride test, and supplementing the diet with carotine has not prevented the condition. Pappenheimer and Fujimaki have also found that Vitamin A deficiency is not a factor in the development of the lesion.

Metastases have not been observed in any of these rats.

These observations indicate that neoplastic hyperplasia of the gastric mucosa of rats may be produced by feeding a diet low in casein and prevented by supplementing the diet with cystine or methionine. These changes are apparently unrelated to Vitamin A deficiency.