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## Profound Morphological Changes Following Ulceration in the Prostomach of Rats.

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(Introduced by A. J. Carlson.)

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After finding that ulcers could be produced in the prostomach of rats by protein restriction or starvation (Hoelzel and DaCosta[1]) our attention was directed toward determining whether such ulcers might become malignant. Marked overgrowths were seen early in ulcerated areas, but, as the work of Bullock and Rohdenburg[2] indicated, this is not a malignant change. Simple overgrowths were particularly prominent in the prostomach of rats in which ulceration was produced with diets high in fat and low in protein. This corresponds to the results obtained by Fujimaki and his coworkers,[3] except that these workers believed that they were dealing with cancerous changes due to disturbances in nutrition and independent of ulceration.

The first indication that the changes were like Fibiger's[4] came when a young rat died after 58 days on a diet of white bread. The prostomach showed numerous small nodular prominences on the outer surface. On the inner surface there was some ulceration but with only moderate overgrowth. Experiments were undertaken to produce similar or greater gross changes in other rats. Distinct single or multiple nodules were produced in the prostomach of 31 rats and somewhat vague nodules in 9 others. Considering only those rats with distinct nodules, only 2 occurred among about 200 rats on low protein diets for less than 40 days. Eight appeared among 79 rats on similar diets for 40 to 230 days, with or without starvation of less than 15 days. No distinct nodules were seen in any of 10 rats that died after single periods of starvation of from 15 to 20 consecutive days, but 3 out of 4 rats that died after starving from 26 to 29 days showed nodules. The other 18 cases appeared among 38 rats starved from 2 to 12 times, 5 days or more each time, for periods totaling from 23 to 102 days, and generally with ade-

[1] Hoelzel and DaCosta, PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 382.

[2] Bullock and Rohdenburg, *J. Cancer Res.*, 1918, **3**, 227.

[3] Fujimaki, Okabe, Kimura, Wada, and Hiratsuka, *Trans. Jap. Path. Soc.*, 1928, **18**, 548.

[4] Fibiger, *Z. f. Krebsforsch.*, 1920, **17**, 1.

quate diets in between starvation periods. Seven rats here included had been sacrificed after having been kept long enough on adequate diets, following periods of starvation, to heal all or nearly all ulcers. The object was to determine what effect this would have on any nodules that might be present. In one of the 7 rats, no nodules were evident and the animal may never have had any. In another rat, one nodule was evident on the outer surface of the prostomach and about a dozen were distinct only on the inner surface. In this rat, one large ulcer had not entirely healed. In the other 5 rats, all ulcers had healed, no nodules showed on the outer surface and only from one to 3 nodules were evident on the inner surface of the prostomach in each rat. These results indicate that most, if not all, nodules would eventually disappear with an adequate diet but that they disappear much more slowly than prostomach ulcers.

Histological examination proved that some of the largest nodules were only epithelial cyst-like structures which were generally located at the ridge between the prostomach and main stomach—precisely where Fibiger found cysts. Other nodules were cornified globular masses more or less completely surrounded by epithelium. In most cases a continuity with the normal epithelial layer of the prostomach could be demonstrated. In some rats, small epithelial masses appeared to be separated but this was evidently an artefact due to cutting through atypical downgrowths. In no case was the muscular wall of the prostomach penetrated or invaded, as in Fibiger's rats. On the whole, our results may be explainable on the basis of the views expressed by Bullock and Rhodenburg. They regarded lesions like those produced by Fibiger as probable consequences of simple mechanical and/or chemical irritation. In our work the irritant was the acid gastric juice which primarily produced the ulcers. In the results obtained by Fibiger, Bullock and Rhodenburg, and Fujimaki and his coworkers, the acid gastric juice may also have been the main factor since they all employed diets low in protein or instituted procedures that would interfere with a normal food intake. Whether true malignancy can be produced by a more prolonged application of simple principles such as we employed still remains an open question.