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Production of Gastric and Duodenal Ulcers in the Cat by Intramuscular Implantation of Histamine.*

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The finding of Code and Varco[1] that prolonged stimulation of gastric secretion could be obtained by the injection of a histamine beeswax mixture into dogs offered a means of testing whether endogenous gastric secretion could produce ulcers of the stomach or duodenum. Cats were chosen for this investigation, because it had been found in a recent study in this laboratory that these animals developed erosions and ulcerations of the stomach and duodenum quite readily when 0.4% hydrochloric acid was instilled daily into the stomach through a fistula (Walpole). It seemed possible that a profitable comparison might be made between ulcer production in response to endogenous and exogenous acid.

Experimental Procedure. The problem was approached by first studying the effects of single injections of the histamine beeswax mixture on gastric secretion and then observing the effects produced by chronic histamine administration. The effect of the histamine beeswax mixture upon gastric secretion was studied in 3 cats with a standard type of gastrostomy.

Controls. Control observations were made with 2 of these animals some days prior to the injections of histamine. The continuous secretion of the fasting stomach was collected every 8 hours for 24 hours. Several days later each cat was given an intramuscular injection of plain beeswax mixture equivalent in amount to that in a dose of the histamine beeswax mixture and the continuous gastric secretion was collected every 8 hours for 24 hours. In addition, in 3 control cats beeswax alone was implanted daily intramuscularly over periods varying from 8 to 23 days. In each instance, the cat gained weight and its general health appeared

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1 Code, C. F., and Varco, R. L., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 475.

satisfactory. One of these cats was killed and subjected to a careful necropsy. There was no ulcer. The other cats continued in good health. During the period of this study, 13 cats kept in the laboratory for other purposes have been subjected to necropsy. No ulcers were found. The cat has been used periodically as an experimental animal in the surgical laboratory over a period of years. No spontaneous ulcers have been observed.

Method. The acidity of the gastric juice was determined by colorimetric titration. In both groups the quantity of secretion obtained and the maximum free acidity produced were considerably lower than that following stimulation with histamine in beeswax. The maximum free acidity of the gastric juice following administration of plain beeswax was 48 clinical units, and of 6 samples collected 3 had no free acid. The maximum free acidity attained by the fasting stomachs was 66 clinical units, and of 6 samples collected 3 contained no free acid. The experiments indicate that plain beeswax in the dose given had no effect upon gastric secretion.

As a routine, the dose of histamine used in the beeswax mixture was 20 mg of the free base. This was injected in divided portions into the muscles of the back. In the cats with gastric fistulae, following administration of this dose, either fractional samples were collected or the entire continuous secretion was taken at hourly intervals for 24 hours. Food was withheld for 24 hours preceding injection. As in the dog (Code and Varco) there was a constant copious secretion of gastric juice. After a short lag during the first hour, the free acid rose to values of more than 100 clinical units but usually fell later to a somewhat lower range. In only 2 samples of 108 collected was free acid absent.

To determine the effect of this prolonged abundant flow of gastric juice with high free acidity upon the stomach and duodenum, 7 healthy cats weighing 4 to 8 lb were given each a daily dose of 20 mg of histamine in beeswax injected intramuscularly. The animals were fed each morning and the injections made several hours later. Adequate fluids were supplied by subcutaneous administration of normal saline solution. The animals were sacrificed when they appeared obviously ill, or refused food on 2 successive days, or after blood was noted in several specimens of vomitus.

Histamine in beeswax frequently produced no obvious reaction, but occasionally the injection was followed immediately by a typical chain of symptoms. This consisted of restlessness, increased respirations, and vomiting associated often with salivation and passage of a loose stool. The occurrence of these symptoms seemed to

depend more upon the batch of histamine mixture used than upon the individual animals. Recently, with increased experience in preparation of the material, reactions have been less frequent. In all animals, however, vomiting occurred some time during the course of injections and when not associated with the immediate reaction took place several hours after the injection. The vomitus usually contained free acid.

These 7 cats receiving the histamine beeswax mixture were sacrificed at periods ranging from 3 to 25 days after beginning the injections, the total amount of histamine given ranging from 60 to 480 mg. At necropsy there were erosions or acute ulcers of the stomach or duodenum, or both, in all animals. Two cats had lesions of the duodenum only, 2 had lesions of the stomach only, and 3 had lesions of both stomach and duodenum. In 3 animals there were perforated ulcers, two in the duodenum and one in the stomach. Gastric lesions were limited to the antrum. It seemed obvious that the animals had been sacrificed at various stages of ulcer formation.

Comment. Histamine in beeswax prepared according to the method of Code stimulated a sustained copious flow of gastric juice containing free acid when injected intramuscularly into cats. Repeated injections of histamine in saline solution have been reported as failing to produce ulceration in the gastro-intestinal tract in the dog[2] and also in the cat.[3] Repeated single daily doses of histamine in beeswax in this study were effective in the cat in producing erosions and all stages of ulceration including acute perforation. In one dog tested, ulceration occurred in the duodenum.† These findings suggest the importance of the gradual liberation of histamine from beeswax in maintaining a constant and fairly uniform stimulation of gastric secretion, as opposed to the intermittent stimulation afforded by periodic injections of histamine in watery solution.

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[2] Orndorff, J. R., Bergh, George S., and Ivy, A. C., *Surg. Gynec. Obstet.*, 1935, **61**, 162.

[3] Heinlein, H., and Kastrup, H., *Z. f. d. ges. exp. Med.*, 1938, **102**, 517.

† Since this paper was written intramuscular implantation of histamine has been done in an additional cat and in another dog. Both animals were killed and autopsied when it was apparent that they were ill. The cat had a large ulcer in the fundus 12 days after the administration of histamine was begun. The dog had a small ulcer .5 cm in diameter in the first portion of the duodenum 4 days after histamine administration was begun.