

16413

Effect of Age on Histamine-Induced Ulcer in Dogs.*

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The observation was made in the course of other studies that rather frequently obviously senile dogs given histamine-in-beeswax injections develop severe peptic ulcers rapidly.

Method. Forty-seven dewormed healthy mongrel dogs were divided on the basis of their age into 3 groups. All dogs were subjected to histamine-in-beeswax injection after the method of Code and Varco.¹ Except where noted otherwise, all animals received a daily intramuscular injection of 30 mg of histamine-base-in-wax in the evening. At the time of the injection food pans were removed until the following morning. Unless the dogs died they were sacrificed by intravenous sodium pentothal 12 hours after the last histamine injection.

Group I. Senile dogs: consisted of 14 animals 10 years old or older ranging in weight from 17 to 66 lbs.

Group II. Mature dogs: consisted of 13 animals of comparable size from 1½ to 5 years of age.

Group III. Pups: consisted of 20 animals from 3 to 8 months of age and ranging in weight from 8 to 22 lbs.

All animals were fed a stock diet of vitamin enriched dog biscuit kibbles supplemented by daily fresh horse meat and milk. In addition the animals in Group I were fed the above diet plus a daily supplement of vitamins[‡] for varying periods up to 6 weeks before histamine stimulation was begun in order to assay the effects of improved nutrition.

In determining the ages of animals, we obtained where possible the actual ages from the original owners. In addition no dogs were used unless one of us (C.W.L.) familiar with the veterinary literature concerning canine ageing and two experienced animal caretakers unanimously agreed on a dog's approximate age, which was then recorded before the experiment began. The changes associated with canine ageing from birth to senile decay with particular emphasis on the teeth have been described in detail by Kirk,² by Sisson,³ by Garbutt,⁴ and by Ellenberger and Baum.⁵

All dogs had a blood sample drawn initially for a hemoglobin and hematocrit determination. Also at least once while on histamine-in-wax stimulation each dog had a fasting sample aspirated from the stomach to determine the free and total acid levels.

Results. In Group I, consisting of 14 senile dogs given a daily intramuscular injection of 30 mg of histamine base in beeswax for 5 consecutive days or less, 9 dogs showed typical gastric or duodenal ulcers. Also within this period of 5 days, 4 of these 9 animals with ulcer died of a perforation. Four additional dogs in this group showed multiple gastroduodenal erosions. Only 1 animal in this age group had a negative gastrointestinal tract at the time of sacrifice.

In Group II consisting of 13 dogs of mature age given the same dose of histamine in beeswax intramuscularly for 5 days and then sacrificed, 2 animals showed a duodenal ulcer and 1 showed a single duodenal erosion. The other 10 dogs had negative gastrointestinal tracts.

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¹ Code, C. F., and Varco, R. L., *Proc. Soc. Exp. Biol. and Med.*, 1940, **44**, 475.

[‡] Vit. A, 10,000 units, 100 mg ascorbic acid, Vit. D, 1,000 units, 4 g brewer's yeast, daily to each dog.

² Kirk, H., *The Veterinary Rec.*, 1945, **57**, 212.

³ Sisson, S., *The Anatomy of the Domestic Animals*, W. B. Saunders Co. 1914.

⁴ Garbutt, R. J., *Diseases and Surgery of the Dog*, Orange Judd Publishing Co., Inc., 1938, New York, N. Y.

⁵ Ellenberger, W., and Baum, H., *Anatomie des Hundes*, 1891, Paul Parey, Berlin.

TABLE I.
Ulcer Production in Relation to Dog Age.
(A daily intramuscular histamine-in-beeswax injection for 5 days.)

Age range (yrs)	Dose histamine base—mg/day	No. of dogs	No. ulcer and/or erosion	%
Over 10	30	14	13*	93
1½ to 5	30	13	3	23
Less 1	30	10	1	10
Less 1	15	10	1	10

* 4 dogs died of perforated ulcer.

When daily intramuscular injections of 30 mg of histamine-base-in-beeswax are given to normal healthy dogs of medium age, 40 days (or an average of 23 days) are necessary to produce ulcer with regularity.⁶

Group III consists of 20 pups of which 10 were given 30 mg of histamine-base-in-wax daily as in the above groups and 10 were given 15 mg of the histamine base. Although the body weights of these pups averaged ½ to ⅓ of the weights of the mature and senile dogs, only 2 pups out of the 20 developed an ulcer. The other 18 had negative gastrointestinal tracts at sacrifice. These results are summarized in Table I.

Because of the strong evidence suggesting a vascular etiology for peptic ulcers occurring for the first time in old patients, we made a careful search in these animals for arteriosclerosis but found none grossly or microscopically. We did, however, find microscopic evidence of degenerative changes in practically all dogs in Group I from whom satisfactory sections were obtained. The spleen showed the most consistent changes with senile atrophy manifested by a decrease to virtual disappearance of the lymphoid follicles and a relative increase in prominence and quantity of the trabeculae due to shrinkage in the size of the spleen. The other organ showing the most consistent changes was the liver which showed varying changes from severe chronic passive congestion with central hepatic atrophy (Dog. No. 86) to severe fatty infiltration (Dog No. 2). The severity of the liver changes did not appear to be correlated with the severity of the peptic ulceration in our

series of dogs but was correlated with the time the dogs were fed stock diet before histamine was started. As would be expected the senile dogs showed a relative anorexia, eating much less than the younger animals in proportion to size. All animals exhibit anorexia coincidental with development of an ulcer on histamine stimulation.

The fresh stomach weights of all sacrificed animals were recorded at autopsy and when this weight was plotted against the dogs' body weight on a graph the animals again divide themselves into the same 3 groups as on the basis of the age with pups having the heaviest stomach weights in proportion to body weight and the senile dogs the lightest with the weights of the mature dogs' stomachs lying between. We take this finding as corroboration of the correctness of our criteria for judging age.

Only 1 dog showed a borderline anemia in Group I (10.3 g with a hematocrit of 34). This animal was fed a supplemented diet for 6 weeks before histamine injections were started but died after the fifth injection with a perforated duodenal ulcer.

Discussion. It is of interest that in examining the stomachs and duodenums of over 900 healthy dogs, Ivy⁷ found only one animal with a spontaneous ulcer. This stomach, he states, was taken from an "old emaciated dog." We have no direct proof that some of our senile dogs did not have an ulcer before we gave them histamine except to say that even in old dogs in our own experience spontaneous ulcer has not been observed.

It is likewise of interest to note that the pups showed a greater resistance to ulcer formation in spite of the fact that on the basis

⁶ Hay, L. J., Vareo, R. L., Code, C. F., and Wangenstein, O. H., *Surg., Gyn., and Obst.*, 1942, **75**, 170.

⁷ Ivy, A. C., *Arch. Int. Med.*, 1920, **25**, 6.

of weight they were given a considerably larger dose of histamine.

Similar gradations of susceptibility in relation to age have been reported for other conditions such as anoxia (Glass⁸ *et al.*, Chang⁹) for cardiac sub-endothelial hemorrhages (Visscher¹⁰ *et al.*), for myocardial lesions from digitalis (Barnes¹¹ *et al.*) and for certain drugs (Bastedo).¹² Moreover, there is evidence¹³ that with advancing years the autonomic nervous mechanisms for the control of homeostasis become less efficient resulting in a vagus preponderance in old age.

The senile dogs in this series were 10 years old or older, which age, according to veterinarians² is equivalent to a human age of 70 years. The occurrence of peptic ulcers for the first time in humans in this age is not unusual. Klingenstein¹⁴ observed that over one-half of the patients over 50 with proved gastroduodenal ulcer had the first onset of symptoms past the age of 50. Likewise

Meyer and Saphir¹⁵ have pointed out that old people are likely to develop acute ulcers and succumb to hemorrhage and perforation even with very low acid levels especially following major surgery, febrile disease, or cardiac disease. These clinical observations would suggest that in the genesis of ulcers, particularly in the aged, factors that have to do with mucosal resistance to digestion are at least as important as acid-pepsin levels. Much the same seems to hold true for these dogs inasmuch as the fasting gastric acidities of aspirated juice while on histamine-in-beeswax stimulation were the same in Groups I, II, and III. (Range 60-100° free acid for all groups).

The present study is of practical importance for those investigators studying the ulcer problem experimentally for it indicates that in using the histamine-in-beeswax technic, or more than likely any other ulcer-producing method, one should compare only dogs of the same approximate age.

Conclusion. There is a gradation on the basis of age in susceptibility to histamine-induced ulcer in the upper gastrointestinal tract of dogs. The oldest dogs exhibit the greatest incidence of ulcers and the pups from 3 to 8 months show the greatest resistance with the dogs of mature age intermediate in their susceptibility to ulcer formation.

⁸ Glass, H. G., Snyder, F. F., and Webster, E., *Am. J., Physiol.*, 1944, **140**, 609.

⁹ Chang, T. T., *Luftfahrtmedizin*, 1937-38, **2**, 239.

¹⁰ Visscher, M. B., and Henschel, A., *Am. Heart J.*, 1945, **30**, 592.

¹¹ Dearing, W. H., Barnes, A. R., and Essex, H. E., *Am. Heart J.*, 1943, **25**, 648.

¹² Bastedo, W. A., *Materia Medica, Pharmacology and Therapeutics*, 4th Edition, 1937, W. B. Saunders Co., Philadelphia.

¹³ White, J. C., and Smithwick, R. H., *The Autonomic Nervous System*, 1945, p. 68, The Macmillan Co., New York.

¹⁴ Klingenstein, P., *J. Mt. Sinai Hosp.*, New York, 1940-41, **7**, 432.

¹⁵ Meyer, J., and Saphir, O., *Am. J. Dig. Dis.*, 1943, **10**, 28.

16414

Aminoaciduria in Progressive Muscular Dystrophy.*

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In view of the wasting of muscle which is characteristic of progressive muscular dystrophy, it seemed probable that there might be an increased urinary excretion of minor

nitrogenous products in addition to creatine, *e.g.*, free amino acids. On studying the urine from patients suffering from progressive muscular dystrophy we found that there was a generalized aminoaciduria characterized by

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