quencies (Fig. 1a,b) depending on the number of sensory impulses reaching the cord from the periphery. They can develop tensions of 10 to 15% of a maximal twitch response. Nerve section abolishes them (Fig. 1c). Mammals have not yet been studied.

Summary. A separate small-nerve motor system to frog skeletal muscles is described. It is active reflexly and may be related to muscle tone. It evokes local potentials and local shortening at the region around the nerve-muscle junctions, in sharp contrast to the propagated twitches and muscle impulses which can be elicited, by the usual motor nerves in the same muscle fibres. Small fibre activity alone may set up appreciable muscle tension.

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15478

Benadryl* Fails to Protect Against the Histamine-Provoked Ulcer.†

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It has been shown that synthetic benzhydryl alkamine ethers are capable of preventing fatal asthma induced in guinea pigs by administration of histamine either intravenously or by inhalation of atomized aqueous solution.[1] These drugs also have been demonstrated to be effective in alleviating anaphylactic shock in guinea pigs[2] and dogs.[3] Lowe and his associates also found that the activity of the synthetic benzhydryl alkamine ethers equaled or exceeded that of the 2 Fourneau histamine antagonists, thymoxyethyldiethyl amine (929F) and N-phenyl-N-ethyl-N'-diethylenediamine (1571F).[2] The latter drugs (929F) and (1571F) have been shown to produce no alteration of gastric response to histamine in Heidenhain pouches in dogs.[4,5]

Of the various synthetic benzhydryl alkamine ethers, β-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) was found to be the most potent histamine antagonist in alleviating anaphylactic shock and histamine-induced asthma in guinea pigs.

The effect of benadryl on the action of histamine as judged by blood pressure changes has been studied.[6] It was found that benadryl given intravenously in the amounts of 3 mg per kg body weight abolishes the fall in blood pressure in dogs produced by 0.001 to 0.002 mg per kg body weight of histamine. In that study, the amount of histamine "antagonized" by given doses of benadryl was quantitated and the mechanism of this "antagonism" was stated to be owing to the adsorption of benadryl onto the site of action of histamine, a circumstance which Wells and his associates believes disturbs the histamine equilibrium such that a given amount of his-

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2 Loew, E. R., and Kaiser, M. E., PROC. SOC. EXP. BIOL. AND MED., 1945, **58**, 235.

3 Wells, J. A., Morris, H. C., and Dragstedt, C. A., PROC. SOC. EXP. BIOL. AND MED., 1946, **61**, 104.

4 Burchell, H. D., and Varco, R. L., *J. Pharm. and Exp. Therap.*, 1942, **75**, 1.

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tamine has much less opportunity to reach and combine with its site of action.

The effect of benadryl on gastric secretion stimulated by histamine in dogs with Heidenhain pouches has been reported to show a reduction of approximately 40% in gastric secretion in 3 of the 4 dogs studied (8 out of 12 experiments).[7]

It is the purpose of this study to determine whether benadryl is effective in altering the gastric secretory response to histamine, or in protecting against the histamine-provoked ulcer in dogs.

Methods and Experiments. Seventeen dogs were used in 2 series of experiments.

Series I: In the first series 2 Pavlov (innervated) and 2 Heidenhain (denervated) pouch dogs weighing 15 to 30 kg were used. The animals were fasted 18 hours previous to each experiment. Samples of gastric secretion were obtained every 30 minutes for 3 hours after histamine stimulation and studied for volume, free hydrochloric acid, and total acid.

Six sets of observations were made:

(1) Study of the gastric response to 0.5 mg aqueous histamine administered subcutaneously for standardization of the experiments. (12 experiments).

(2) Study of the gastric response to the same dose of histamine subcutaneously, the animals having received benadryl orally in doses of 5 to 10 mg per kg body weight 30 minutes previously. (12 experiments).

(3) Study of the gastric response to the same dose of histamine subcutaneously, the animals having received benadryl subcutaneously in aqueous solution in doses of 10 to 30 mg per kg body weight 20 minutes previously. (24 experiments).

(4) Study of the gastric response to benadryl alone in doses of 5 to 10 mg per kg body weight administered orally and subcutaneously. (8 experiments).

(5) Study of gastric response to histamine-in-beeswax mixture alone (30 mg base) as prepared after the method of Code and Varco[8] administered intramuscularly. (4 experiments). In this way, gastric response over a 24-hour period was studied.

(6) Study of the gastric response to the simultaneous injections of histamine-in-beeswax (30 mg base intramuscularly) and benadryl-in-beeswax mixture (100 mg intramuscularly) prepared in the same manner. (4 experiments).

Series II: Thirteen healthy intact dogs weighing 10 to 25 kg were used.

Seven dogs were given daily intramuscular injections of histamine-in-beeswax (30 mg base) and benadryl-in-beeswax (100 mg) simultaneously several hours after feeding. As controls, 4 dogs were given daily intramuscular injections of histamine-in-beeswax alone (30 mg) and 2 dogs were given daily intramuscular injections of benadryl-in-beeswax alone (100 mg). Animals surviving 40 days were sacrificed at that time; others died or were sacrificed when signs of impending death were present.

Results. Series I: The results of the studies on gastric secretion can be summarized by stating that in 40 experiments benadryl had no demonstrable effect on the secretory response to histamine. There was no evidence of decrease in volume or acidity of the secretion with benadryl premedication. Some of the data indicated that there was a slight increase in quantity and acidity with slight prolongation of the gastric secretion in response to histamine after benadryl administration.

Series II: (Table I). Results of simultaneous daily injections of histamine-in-beeswax and benadryl-in-beeswax show that all (7) dogs developed gastric and/or duodenal ulceration. The 4 dogs receiving histamine-in-beeswax alone developed ulceration. Of the 2 dogs receiving benadryl-in-beeswax alone, one died after 19 daily injections demonstrating early gastric erosions and petechial bleeding points; the other, sacrificed at 40 days, showed no demonstrable pathology.

The 7 animals receiving both drugs were noted to become more debilitated as evidenced by greater weight loss, anorexia and listlessness than those receiving histamine alone. This occurrence also is reflected in

[7] Loew, E. R., MacMillan, R., and Kaiser, M. E., *J. Pharm. and Exp. Therap.*, 1946, **86**, 229.

[8] Code, C. F., and Varco, R. L., *Am. J. Physiol.*, 1942, **137**, 225.

TABLE I.
Results of Daily Injections of a Mixture of Benadryl-in-beeswax and Histamine-in-beeswax.

Dog No.	Wt in kg	Daily dose of benadryl, mg	Daily dose of histamine base, mg	No. of inj.	Results
1	25	100	30	14	Duodenal erosions
2	20	100	30	5	Three duodenal ulcers, one perforated
3	19	100	30	40	Duodenal ulcer
4	16	100	30	40	" "
5	13	100	30	40	" "
6	10	100	30	29	" " Hemorrhagic gastritis
7	13	100	30	40	Duodenal ulcers
Controls					
8	24	0	30	40	Gastric ulcer Duodenal ulcer
9	23	0	30	40	Gastric ulcer Duodenal ulcer
10	25	0	30	40	" "
11	13	0	30	40	" "
12	20	100	0	19	Gastric erosions Petechial bleeding points
13	15	100	0	40	Negative

the circumstance that only 4 of the 7 dogs survived 40 days, while all 4 receiving only histamine survived 40 days. The 2 receiving benadryl alone survived 19 and 40 days. One dog receiving both drugs died after 5 daily injections of perforated duodenal ulcers with peritonitis. One was sacrificed because of impending death after 14 daily injections of both drugs and showed duodenal erosions, and one sacrificed after 29 daily injections showed duodenal ulcers and hemorrhagic gastritis.

Discussion. Evidence of untoward reactions to benadryl were observed in occasional instances consisting of vomiting when given orally in doses of 10 or more mg per kg of body weight; therefore, we were unable to evaluate the effect of larger doses by this route.

Administration by the subcutaneous route was used to study the effect of larger dosages of benadryl. These dosages were as great and greater than those calculated to be capable of "antagonizing" 0.5 mg of histamine as judged by blood pressure response.

The fact that some of the data (approximately 40%) showed increased volume and acidity where benadryl premedication was given over the response to histamine stimulation alone is not of great significance because the increase was not great. In this respect, benadryl, when given alone, produced neither an increase nor a decrease in the level of gastric secretion in fasting pouch dogs.

The results found in this study, together with the failure of a consistent decrease in gastric secretion as reported by others[7] indicate that benadryl is not a specific antagonist of histamine, but counteracts *some* of the effects of histamine by virtue of its own pharmacological action.

Conclusions. 1. Benadryl fails to alter the gastric secretory response to histamine stimulation in pouch dogs. 2. Benadryl (given in 100 mg doses in beeswax mixture intramuscularly) fails to protect against the histamine-provoked ulcer in dogs.