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Gastric Secretion in Dogs Treated with Histamine Antagonist, Thymoxyethyldiethylamine.

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The phenol ether, thymoxyethyldiethylamine (929F), has been designated a sympathicolytic drug since it diminishes or reverses the action of adrenalin.^{1, 2} This drug has been reported to antagonize the stimulating action of histamine upon isolated uterine and ileal muscle of the guinea pig.³⁻⁶ Furthermore, pre-treatment with 929F prevents severe bronchospasm and death in guinea pigs resulting from histamine liberated during anaphylactic shock or from the intravenous injection of several minimal lethal doses of histamine.^{3-5, 7-9}

These facts suggest that 929F may antagonize the powerful stimulating action of histamine upon the gastric glands which secrete hydrochloric acid. If such an antagonism were demonstrated, 929F could be used to elucidate the question as to whether histamine plays any rôle in the secretory response of the stomach to food. Experiments have therefore been made to determine the effect of 929F upon the gastric secretion induced by injecting histamine.

Methods. At operation, 3 dogs weighing 7 to 10 kg were provided with Heidenhain pouches. After recovery from the operation the dogs were trained to stand quietly to facilitate the collection of gastric juice from the pouches. All dogs were maintained on a diet of canned meat and were fasted 15 to 24 hours before experimental periods.

The volume and acid content of the gastric juice collected during a 2-hour period following the subcutaneous administration of 0.5

1 Levy, J., and Ditz, E., *Compt. rend. Soc. biol.*, 1933, **114**, 971.

2 Bovet, D., and Maderni, P., *Ibid.*, 1933, **114**, 980.

3 Staub, M., *Ann. Inst. Pasteur*, 1939, **63**, 400.

4 Staub, M., *Ibid.*, 1939, **63**, 485.

5 Rosenthal, S. R., and Brown, M. L., *J. Immunol.*, 1940, **38**, 259.

6 McVicar, G. A., and McHenry, E. W., *Canadian Med. Assn. J.* (Proc. Canadian Physiol. Soc.), 1941, **44**, 80.

7 Bovet, D., and Staub, M., *Compt. rend. Soc. biol.*, 1937, **124**, 547.

8 Staub, M., and Bovet, D., *Ibid.*, 1937, **125**, 818.

9 Minard, D., and Rosenthal, S. R., *Proc. Soc. Exp. Biol. and Med.*, 1940, **44**, 237.

mg of histamine diphosphate constituted the control data. After a rest period of 1.5 to 2 hours, a subcutaneous injection of 10 mg of 929F* per kg of body weight was made. Thirty minutes later, the same amount of histamine as that used in the control period was administered subcutaneously. Each sample of gastric juice collected during control and experimental periods was titrated *in toto* for free and total acid with the use of Töpfer's reagent and phenolphthalein, respectively, as indicators.

The total volume of gastric juice and total quantity of free and total hydrochloric acid secreted following histamine injections in dogs treated with 929F were compared with the output obtained from animals earlier the same day when histamine alone was administered. Variations in gastric secretion during experimental periods are expressed as percentage increase or decrease from the control values. This so-called "double histamine test" is an established method of determining the influence of various factors on gastric secretion. We have also made control experiments to determine whether the gastric secretion following the second histamine injection, when the animals were not pre-treated with 929F, was comparable with the secretion obtained following the first histamine injection made earlier the same day.

Results. Following an injection of histamine the secretory response during 10 experiments on 3 dogs treated with 929F was found to be not less, *but more* than the secretory output in the same number of control experiments (Table I). The augmentation of free hydrochloric acid after treatment with 929F amounted to an increase of 73.9% over the average control value. Values for total acid were higher than, but paralleled, the values for free hydrochloric acid. The average total volume of gastric juice secreted by the animals treated with 929F represented an increase of 56% over the control value. Since the increase in volume is less than the increase in the quantity of free and total hydrochloric acid it is apparent that the concentration of hydrochloric acid in the gastric juice secreted after treatment with 929F was also increased. In dogs treated with 929F, hypersecretion and hyperacidity were consistent findings in each of the 10 experiments, although the degree was variable (free acid, 29 to 180%).

The adequacy of the control data was verified by employing the double histamine test 9 times on the 3 dogs without injecting 929F previous to the second histamine administration. The average total

* A 5.0% solution of 2-isopropyl-5-methylphenoxyethyldiethylamine hydrochloride (M.P. 130-131°C).

TABLE I.
Augmentation of Gastric Secretion After Pre-treatment with 929F.*

Time in min.	Volume (cc)		Total acid (mg HCl)		Free acid (mg HCl)	
	Histamine Control	929F + Histamine	Histamine Control	929F + Histamine	Histamine Control	929F + Histamine
15	1.7	3.9	5.93	13.01	4.18	11.88
30	6.1	8.5	22.16	33.99	20.15	30.29
45	4.2	5.9	15.15	25.34	14.27	24.40
60	1.2	2.1	3.97	8.46	3.44	8.01
75	.8	1.2	1.90	4.10	1.85	3.73
90	.6	.9	1.04	2.67	.85	2.17
105	.5	.8	1.28	1.52	.62	.94
120	.1	.2	.07	.33	.04	.09
Total output	15.1	23.5	51.40	89.80	46.40	81.40
Variation from controls (%)	+ 56.0		+74.7		+73.9	

*Averages of data from 10 experiments on 3 dogs.

TABLE II.
Gastric Secretion Following Double-Histamine Injections.*

Time in min.	Volume (cc)		Total acid (mg HCl)		Free acid (mg HCl)	
	1st Histamine	2nd Histamine	1st Histamine	2nd Histamine	1st Histamine	2nd Histamine
15	1.4	2.0	5.46	5.28	2.91	4.84
30	5.6	5.5	19.49	19.68	17.13	19.56
45	3.5	2.8	12.76	10.52	12.25	9.28
60	1.4	1.2	4.56	4.38	4.49	3.58
75	.9	.6	1.84	1.89	1.68	1.61
90	.7	.4	1.57	1.13	1.30	.88
105	.5	.3	.98	.48	1.32	.30
120	.4	—	.87	—	—	—
Total output	14.40	12.8	47.53	43.40	41.08	40.65
% variation of 2nd from 1st	—11.1		—8.68		—1.04	

*Averages of data from 9 experiments on 3 dogs.

output of free hydrochloric acid after the second injection of histamine was 1.04% less than the amount secreted during the test conducted several hours earlier. Only slight differences in total acid and volume were evident. One is, therefore, justified in comparing the output of acid by dogs pre-treated with 929F and injected with histamine with that following a previous injection of histamine the same day. Furthermore, when the average quantity of free or total hydrochloric acid secreted by the dogs after 929F injections was compared with the control output following the second histamine stimulus on other days the increase was approximately 100%.

Thymoxyethyldiethylamine cannot be regarded as a gastric secretory stimulant, for when no histamine was injected the subcutaneous

administration of 929F (10 mg per kg) did not stimulate the production of gastric juice. The doses of 929F administered produced no untoward reactions. Larger doses were not employed in any of the experiments dealing with gastric secretion since subcutaneous injections of 20 mg per kg induce retching, vomiting, and defecation in unanesthetized dogs.

Discussion. The ability of 929F to antagonize the stimulating action of histamine on the smooth muscle of bronchioles, uterus, and ileum³⁻⁹ suggested that the drug might inhibit gastric secretion following stimulation of the gastric glands with histamine. Under the conditions of our experiments 929F *failed to inhibit* gastric secretion induced by injecting histamine. Other investigators have used 40 mg of 929F per kg of body weight to protect guinea pigs against lethal doses of histamine (0.5 mg per kg) injected intravenously. Since our animals received a total of only 0.045 mg to 0.07 mg of histamine diphosphate per kg of body weight, subcutaneously, pre-treatment with a smaller dose of 929F should have sufficed to demonstrate the histamine antagonism if it existed in relation to the gastric glands.

The data constitute additional evidence that 929F does not destroy significant amounts of histamine.^{5, 6} Furthermore, our results suggest that the mechanism whereby histamine induced contraction of smooth muscle fibers may differ from the mechanism involved in stimulation of gastric glands.

The experimental findings also indicate that 929F, instead of inhibiting gastric secretion induced by histamine administration, *augments* the volume as well as the concentration and total output of hydrochloric acid. This unanticipated augmentation of gastric secretion remains unexplained and is of unknown significance. When no histamine was injected, the subcutaneous administration of 929F failed to induce gastric secretion. The augmenting action of 929F on gastric secretion induced by histamine cannot be due, therefore, to the additive effects of 2 gastric secretory stimulants.

Summary. Studies on gastric secretion in dogs provided with Heidenhain pouches definitely indicated that 929F, given subcutaneously, did not induce gastric secretion. However, following an injection of histamine in animals thus treated, the gastric secretion was markedly increased in volume and acidity over that which was obtained during control periods when only the histamine stimulus was employed.

These findings indicate that 929F, in the doses employed, neither destroys histamine nor antagonizes the action of histamine as a gastric secretory stimulant.