With other strains the inhibition of hemagglutination by NRS could be raised to titers similar to those attained by EW if a temperature of 61°C was used for the inactivation of the virus preparations. This is shown in Table III for the PR8, Weiss, Oti and Lee strains. NRS in dilutions of 640-1280 inhibited hemagglutination by heated virus, and thus came close to the values obtained with EW. In the case of the swine influenza strain it was impossible to raise its susceptibility toward NRS as a temperature of 56°C was ineffective and a temperature of 58°C destroyed the hemagglutinating ability of this strain.

Discussion. The observation that an influenza strain may be highly susceptible to one inhibitor and only slightly susceptible to another and the fact that heating will alter the susceptibility of a strain to one inhibitor without changing measurably its susceptibility toward the other is considered evidence for a qualitative difference in the inhibitors involved. If this conclusion is discussed in terms of the enzymatic theory it would have to be assumed that the effect of virus on the two inhibitors is caused by two different enzymatic factors which can exist independently and which can be differentiated by their resistance to heat. The virus factor active against egg white inhibitor is generally more heat labile than the factor against rabbit serum. It is completely or partially destroyed in all strains by a temperature of 56°C whereas, a higher temperature is necessary to inactivate the factor acting against rabbit serum. The independence of the two factors is most clearly demonstrated in the case of the swine influenza strain in which heating to 56°C destroys completely the activity against egg white without measurably altering its activity against serum inhibitor. It is possible that the assumption of still other enzymatic factors for other inhibitors might become necessary, if the enzymatic theory is to be accepted. It seems probable that just as the antigenic composition of strains differs so also will their capacity to react with different chemical substrates be found to vary.

Summary. The hemagglutinating activity of some strains of influenza virus is more susceptible to egg white inhibitor while that of others is more susceptible to inhibition by rabbit serum. Heating to 56°C makes all strains susceptible to inhibition by egg white. When tested with 4 different strains a higher temperature was required to make them as susceptible to inhibition by normal rabbit serum. It is concluded from these results that the inhibitors are not identical. The results are discussed in terms of the enzymatic theory according to which two different enzymatic factors in the virus active against rabbit serum and egg white would have to be assumed.

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17118. Effect of Tagathen* on Histamine-Induced Gastric Lesions in Guinea Pigs.

J. C. VAN METER AND J. J. OLESON. (Introduced by Guy W. Clark.)

From Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

The use of synthetic antihistaminics to prevent or diminish the incidence or severity of histamine-induced ulcers in animals has been reported in less than a half dozen papers. Most of these were concerned with the failure of benadryl* (B-dimethylaminoethylbenzhydryl ether HCl) to prevent experimental ulcer formation.[1-4] In all of these reports the "histamine in beeswax" method of Wangensteen and coworkers[5] was used. In addition

* Brand of antihistaminic drug.

1 Crane, J. T., Lindsay, S., and Dailey, M. E., *Am. J. Dig. Diseases*, 1947, **14**, 56.

2 Friesen, S. R., Baronofsky, I. D., and Wangensteen, O. H., PROC. SOC. EXP. BIOL. AND MED., 1946, **63**, 23.

in a recent paper, the pyloric ligation method of Shay and coworkers[6] was used to evaluate the anti-ulcer effect of thephorin* (2-methyl-9-phenyl-2,3,4,9 tetrahydro-1-pyridindene).[7]

In our initial attempts to establish an assay for the investigation of the influence of diet on histamine-induced ulcer, we tried the histamine in beeswax method. In our hands it frequently resulted in the death of a considerable number of animals due to bronchial spasm. To prevent this the animals were pretreated with tagathen* (N,N-dimethyl-N'-(2-pyridyl)-N'-(5-chloro-2-thenyl) - ethylenediamine citrate) or with epinephrine. Under these conditions we were able to produce only an occasional gastric lesion in a large number of animals. After numerous trials it was found that gastric lesions could be consistently produced by the intramuscular injection of 0.6 mg histamine diphosphate in an aqueous solution twice daily. The number of deaths due to bronchial spasm was practically nil. This led to the study of the influence of diet and various drugs on histamine-induced ulcer in guinea pigs.

Method. Hartley strain guinea pigs weighing 200-350 g were divided into groups containing equal numbers of each sex and average weight. Animals were placed in individual cages and fed the appropriate diet for 5-7 days. At the end of this period the drug supplement was administered twice daily, morning and afternoon, one hour before the intramuscular injection of 0.6 mg histamine diphosphate in distilled water. Food was removed from cages before the first histamine injection and returned 2-3 hours after the second injection. This treatment was continued for 4½ days and all surviving animals were killed and autopsied. Animals succumbing before the end of the test were autopsied as soon as possible after death. Animals were examined for the presence or absence of gastric hemorrhages, erosions and/or perforation.

The synthetic diet used in this work has the following composition expressed in grams: Cerelose 500, Alcohol extracted casein 220, Cellulose 150, Gelatin 60, Salt mixture 50, Corn oil 20, Vitamin A 19,720 I.U., Vitamin D 2,360 I.U., Vitamin E 0.025, Vitamin K .0005, Riboflavin 0.005, Inositol 0.05, Thiamine HCl 0.003, Pyridoxine HCl 0.005, Calcium pantothenate 0.02, Nicotinamide 0.01, p-aminobenzoic acid 0.01, Choline Cl 1.0, Biotin 0.0001, Folic Acid 0.001.

The animals were given 20 mg ascorbic acid orally 3 times per week. This diet was also fed with kale *ad libitum.*

Results. The results are presented in Table I. A high incidence of histamine-induced lesions were obtained on both the basal diet, and the basal plus kale *ad libitum.* On the former the percentage was 92%; on the latter 98%. The omission or addition of extra ascorbic acid to the synthetic diet did not appreciably influence the effect of the histamine.

Since our earlier work indicated that tagathen administration interfered with the production of ulcers by the histamine in beeswax technic, it was decided to investigate the effect of this antihistaminic drug thoroughly. The data in Table I rather clearly demonstrate that the compound if given in sufficient dosage, will prevent a high percentage of the animals from developing gastric lesions. This is attested by the fact that out of 92 guinea pigs receiving 4 or more milligrams of this antihistaminic drug per dose, only 36 exhibited gastric lesions. A considerable number of those affected showed only minimal damage as compared to their controls. At higher dosages than 4 mg the percent incidence is further reduced. This, we believe to be remarkable in view of the previously reported inability of this type of anti-

[3] Harkins, H. N., Hooker, D. H., Alford, T. C., Callander, J., Elliott, S. R., Kearns, W., Mitchner, J., and Cooley, D. A., *Bull. Johns Hopkins Hospital,* 1947, **81**, 79.

[4] Vallery-Radot, P., Halpern, B. N., and Martin, J., *Presse Med.*, 1947, **55**, 185.

[5] Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H., *Surg., Gynec. and Obst.*, 1942, **75**, 170.

[6] Shay, H., Komarov, S. A., Fels, S. S., Merenze, D., Gruenstein, M., and Siplet, H., *Gastroenterology,* 1945, **5**, 43.

[7] Lehmann, G., and Stefko, P. L., *J. Lab. and Clin. Med.*, 1949, **34**, 372.

TABLE I.
Influence of Tagathen on Production of Histamine-Induced Ulcers in Guinea Pigs.

Treatment*	No. animals	Animals showing gastric pathology	
		No.	%
Kale†	11	0	0
Kale† + histamine‡	45	44	98
Histamine‡	25	23	92
No Vit. C + histamine‡	7	5	71
20 mg Vit. C + histamine‡	6	5	83
4 " tagathen§	6	0	0
4 " " + histamine‡	6	0	0
6 " " " "	6	1	17
0.1 " " " " + kale†	6	6	100
0.5 " " " " " "	6	6	100
1 " " " " " "	18	10	56
2 " " " " " "	12	7	58
4 " " " " " "	50	24	48
6 " " " " " "	19	9	47
8 " " " " " "	6	1	17
12 " " " " " "	5	1	20

* All groups received basal diet as given except as noted.
† Kale—fed *ad libitum*.
‡ Histamine diphosphate (0.6 mg) in distilled water injected i.m./pig 2×/day.
§ Tagathen in distilled water orally/pig 2×/day.

histaminic to prevent histamine-induced ulcers. It would appear that such a reduction in ulcer production in so large a group of animals clearly demonstrates the potent anti-ulcer properties of this compound.

In addition to the above reported experiments we have made preliminary investigations on the influence of desiccated thyroid, thiouracil, dried liver cake, 15-unit liver extract, insulin, thyroxine, tannic acid, 2,4-dinitrophenol and casein digests on the incidence of histamine-provoked gastric lesions.[8] None of these was found to have any marked preventive or provocative activity.

Summary. Conditions have been established for the production of gastric lesions in guinea pigs by injection of aqueous histamine without considerable loss of animals due to fatal bronchial spasm.

Tagathen causes a very pronounced reduction in the incidence of gastric lesions produced by this method.

In view of the favorable results obtained, it would seem that a study of the mechanism involved in the anti-ulcer effect produced by antihistaminic compounds of this type, should be made.

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[8] Van Meter, J. C., unpublished data.

17119 P. Blood Flow and Oxygen Consumption of the Brain in Coarctation of the Aorta.*

JOSEPH H. HAFKENSCHIEL, JR., CHARLES W. CRUMPTON,† AND JOHN H. MOYER.
(Introduced by Carl F. Schmidt.)‡
From the E. B. Robinette Foundation, Medical Clinic, Hospital and the Laboratory of Pharmacology, University of Pennsylvania, Philadelphia.

Recent developments making possible measurements of the blood flow to the brain[1,2] and myocardium[3] in man[4] enable the clinical in-

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† Dr. Crumpton is National Health Institute Fellow.