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Effect of Aminophyllin, Histaminase,* and Nicotinic Acid on Histamine-Poisoned Puppy Bronchioles.†

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To the large number of drugs recommended for the relief of bronchial asthma, there have been added in the past few years two new ones; aminophyllin (theophylline with ethylene diamine) and histaminase (torantil.) Although marked clinical relief has followed the intravenous injection of aminophyllin in patients with acute bronchial asthma¹⁻³ little experimental work has been done in regard to the mechanism of action of the drug. During the course of this investigation Young and Gilbert⁴ stated that aminophyllin greatly lessens the constricting action of histamine in the smaller bronchi and bronchioles of rabbit lung sections.

Histaminase, while less well established than aminophyllin in the treatment of bronchial asthma, is thought to inactivate any histamine implicated in acute attacks of asthma.

Nicotinic acid has been observed to benefit a few patients at John Sealy Hospital during status asthmaticus⁵ and was therefore included in this study.

Method. Bronchioles were prepared for microscopic observation by the method of Sollmann and Gilbert.⁶ Puppies were killed by the injection of air into the left ventricle. The lungs were removed and injected intratracheally with a warm solution of 10% gelatin in Ringer's solution. They were then placed in iced Ringer's solution for several hours to harden. Thin sections of lung were made free-hand with a razor, and mounted on a ring of cork in a Petri dish containing 50 cc of Ringer's solution. The dish was placed on the warm stage of a microscope, and the solution was kept at a temperature of 38°C. The size of the bronchiolar lumen was recorded by use of a camera lucida.

* Histaminase was generously supplied by the Winthrop Company.

† A preliminary report of this work was published in *Bull. John Sealy Hospital and University of Texas Medical School*, 1940, **2**, 55.

¹ Herrmann, G. R., and Aynsworth, M. B., *J. Lab. and Clin. Med.*, 1937, **23**, 135.

² Efron, *J. Allergy*, 1936, **7**, 249.

³ Brown, G. T., *J. Allergy*, 1938, **10**, 64.

⁴ Young, R. H., and Gilbert, R. P., *J. Am. Med. Assn.*, 1940, **114**, 522.

⁵ Creel, W. F., personal communication.

⁶ Sollmann, T., and Gilbert, A. J., *J. Pharm. and Exp. Therap.*, 1937, **61**, 272.

The addition of 3 mg of histamine acid phosphate usually resulted in complete closure of the bronchiolar lumen. The preparation was observed for about 10 minutes in order to rule out spontaneous relaxation, and then the test drug was added. Nicotinic acid was used in the form of sodium nicotinate, since acid *per se* has a dilator action.⁶

Results. Typical results with aminophyllin, histaminase, and sodium nicotinate are recorded in Table I.

TABLE I.

Puppy No.	Area of normal Bronchiolar lumen, mm ²	Area after histamine	"Dilator" drug applied	Area after "dilator" drug	% of normal area
2	.474	.000	Aminophyllin 1:2000	.336	75
3	.270	.000	," 1:1000	.270	100
2	.456	*	," 1:1000	.558	122
5	.048	.000	Histaminase 4 units	.012	25
4	.216	.000	," 4 units	.000	0
4	.072	.000	Sod. nicotinate 1:1400	.000	0
5	.021	.000	," 1:2100	.000	0

*Histamine not applied.

Aminophyllin 1:2000 to 1:1000 caused marked dilatation of histamine-poisoned puppy bronchioles in all 6 experiments in which it was tried. With normal bronchioles it caused moderate dilatation in 2, and had no effect in one experiment.

Histaminase caused slight dilatation of histamine-poisoned bronchioles in 3 experiments and had no effect in 2 experiments. This slight action after a few minutes was not unexpected, since one unit of histaminase is assayed to neutralize 1 mg of histamine dihydrochloride only after 24 hours' incubation at 37.5°C. Histamine was inactivated by histaminase when the pH was maintained at 7.4 by phosphate buffer during 24 hours' incubation at 37.5°C. Only by fulfilling these rigid conditions was it possible to obtain inactivation.

Nicotinic acid as sodium nicotinate 1:4200 to 1:1400 caused slight dilatation of histamine-poisoned bronchioles in two experiments and had no effect in 8 experiments.

Conclusions. Aminophyllin is an effective dilator of histamine-poisoned puppy bronchiolar sections. Histaminase and nicotinic acid had little or no effect in the concentrations used.