of animal, the mode of administration, etc., Pyribenzamine may appear to be one or 20 times as active, and Benadryl may appear to be one-half or equally as active as Neohetramine. The significance of these comparisons is not clear because laboratory methods of testing are as yet unrelated to clinical effectiveness.

In a clinical comparison of 2 antihistaminic drugs, Loveless[6] recently reported that Benadryl was better suited to the treatment of Ménières syndrome and intrinsic allergic asthma while Pyribenzamine was more effective in the treatment of non-seasonal extrinsic asthma. It may be inferred from this report that different drugs will be required in the treatment of different forms of hypersensitivity. Since laboratory methods of testing do not give a reliable index of the clinical value of the antihistaminic drugs, it would appear that final evaluation of these drugs can be established only in human subjects, and then only with reference to the treatment of specific allergic states.

Summary. As judged by the intraperitoneal toxicity in mice, Neohetramine is about one-half as toxic as other antihistaminic agents. Weanling rats, receiving as much as 200 mg of Neohetramine per kg body weight per day over a period of 3 months, grew at a normal rate, exhibited no abnormalities in blood morphology and developed no organ pathology. Neohetramine showed marked activity against the bronchiolar and capillary actions of histamine. Quantitative estimates of the amount of histamine antagonized by Neohetramine varied with the method of testing. Neohetramine conferred protection against anaphylactic shock in guinea pigs actively sensitized to horse serum. The implications of these findings are discussed.

[6] Loveless, M. H., *Am. J. Med.*, 1947, **3**, 296.

16140 P

Pharmacological Characteristics of Neohetramine, a New Antihistaminic Drug. II.

N. B. DREYER AND DONALD HARWOOD. (Introduced by John V. Scudi.)
From the Department of Pharmacology, University of Vermont, Burlington, Vt.

Several compounds which have anti-histaminic properties have been described recently.[1,2] Stress has been laid mainly on their ability to counteract histamine activity and certain allergic phenomena. Many of these compounds possess other properties as shown by their action on smooth muscle and glandular activity.[3,4] Neoantergan[3] is stated to have local anesthetic and quinidine-like properties. Benadryl[4] has some atropine-like activity. Pyribenzamine[5] and 01013[6] enhance epinephrine responses. Described below are some effects of a new anti-histamine compound, Neohetramine.

Its anti-histamine activity was tested on the isolated ileum of guinea pig; isolated uteri of guinea pig, cat, and rat; blood pressure of cats and dogs; the intestine of the cat *in situ*, and blood vessels of the rabbit ear perfused at room temperature. Flow of saliva from submaxillary gland and blood pressure of the cat and dog served to test the effects of Neohetramine on the autonomic nervous system. All excised organs were suspended in

[1] Feinberg, S. M., *J. A. M. A.*, 1946, **132**, 703.

[2] Winters, C. A., *J. Pharmacol. and Exp. Therap.*, 1946, **87**, 256.

[3] Dews, P. B., and Graham, J. D. P., *British J. Pharmacol.*, 1946, **1**, 278.

[4] Dreyer, N. B., and Denton, C., *Fed. Proc. Am. Soc. Exp. Biology*, 1947, **6**, 324.

[5] Yonkman, F. F., *et al.*, *J. Pharmacol. and Exp. Therap.*, 1946, **87**, 256.

[6] Lee, H. M., *et al.*, *ibid.*, 1947, **90**, 83.

oxygenated Ringer fluid kept at 36-37°C. and movements were recorded by the usual lever arrangement writing on smoked kymograph paper. Blood pressure was measured with a mercury manometer.

On the guinea pig ileum and uterus, and uterus of the cat where histamine caused contraction, Neohetramine was capable of abolishing the action of histamine. The amount of histamine causing a submaximal contraction varied from one experiment to another but was kept constant for any particular experiment. Histamine, as base, 0.03 to 0.3 μg per ml gave good contractions of guinea pig ileum. The amount of Neohetramine required to abolish such a contraction was determined and the ratio of Neohetramine to histamine base was calculated. For the cat uterus the ratio was .7:1; for guinea pig uterus, 1.4:1 and for guinea pig ileum, 2.7:1. Neohetramine showed greatest activity on the cat uterus, somewhat less on the guinea pig uterus, and least on the guinea pig ileum.

Neohetramine was less effective in counteracting the action of histamine on the blood pressure of the cat and dog. The fall in blood pressure caused by 1 to 2 μg of histamine was easily offset by 2.5 mg per kg of Neohetramine. However, the vaso-depression caused by larger amounts of histamine, (5-7 μg per kg) was reduced but could not be completely nullified by 8 to 10 mg per kg of Neohetramine. Neohetramine, like Pyribenzamine, was not capable of altering the inhibitory action of histamine on the rat uterus. The inhibition was as marked after Neohetramine as before, even when the ratio of Neohetramine to histamine was as high as 50 to 1. The vaso-constriction of the perfused rabbit ear caused by histamine could be completely counteracted by Neohetramine in a ratio of 1:1.

In atropinized cats and dogs under urethane, or chloralose and urethane anesthesia, Neohetramine (1-5 mg per kg) caused the following changes: an immediate drop in blood pressure without change in heart rate, followed by recovery in a few minutes. This was attributed to cardio-depressant action resulting from a high concentration of Neohetramine in coronary blood. As the drug became generally distributed in the body, the final concentration was insufficient to continue this cardio-depressant action. Large amounts of Neohetramine (8-10 mg per kg) produced a temporary hypotension. Straub heart preparations showed that Neohetramine diminished systolic contraction. As the concentration of Neohetramine in the perfusion fluid was increased, the depression of systole became greater. This was due to direct action on the cardiac muscle and was abolished on washing. Cardiometric measurements on the dog heart showed a diminished systolic and an increased diastolic volume after injection of Neohetramine. On the perfused rabbit ear, Neohetramine caused only slight transient dilatation.

Neohetramine showed little or no effect on sympathetic responses, following injection of epinephrine or sympathetic nerve stimulation. Potentiation of injected epinephrine as described for other anti-histaminics by Yonkman[5] and Lee[6] could not be demonstrated. This lack of potentiation to epinephrine was confirmed on the cat blood pressure and the isolated rabbit uterus. On the parasympathetic nervous system, Neohetramine exerted some atropine-like action on the chorda tympani, but even large doses (8 mg per kg) failed to abolish chorda secretion. Atropine on the other hand (.1 mg per kg) effectively abolished all chorda tympani activity. Vagal inhibition of the heart produced by weak faradization in the anesthetized cat could be eliminated by Neohetramine, but an increase in the strength of faradization tended to restore some vagal inhibition. However, Neohetramine did not lessen the vagal effects on the intestine. In several instances Neohetramine seemed to potentiate vagal contractions of the intestine.

Total and free acidities of gastric juice obtained by rhythmic stimulation of the left vagus were unaltered by Neohetramine, 1-5 mg per kg.

Summary. The above observations indicate that Neohetramine possesses well-marked anti-histaminic properties. In addition it has slight atropine-like actions; it does not alter epinephrine or sympathetic nerve responses.