

uric acid. It seems, therefore, that the reticulo-endothelial system is not the seat of uric acid destruction in the dog.

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Histamine and Acetyl Choline Contraction-Ratio in the Surviving Intestinal Strip.

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Knowledge of the significance of histamine in biological processes would be materially increased if assays of higher specificity and sensitivity were available. In the absence of such tests it is necessary to look for an increased number of reactions both chemical as well as biological, indicative of histamine. Such reactions might aid by their variety rather than by their specificity.

Experiments with various smooth muscle contractants, forms of shock, etc., now in progress in this laboratory made it advisable to compare the reactivity of chicken and mouse intestine to histamine and acetyl choline. This ratio is well known to be 2:1 in the guinea pig.¹ This figure agrees on the average with our own observations. However, we have not infrequently dealt with individual variations such as guinea pig intestinal strips with a histamine-acetyl choline ratio of 5:1 or 1:1. It should be remembered that the iliac end of the guinea pig intestine is generally conceded to be more reactive than the duodenal.

The action of histamine and acetyl choline upon the mouse and chicken intestine does not appear to have been studied previously. The reactivity of the mouse uterus to histamine has been shown to vary with the concentration.^{2, 3, 4} Low concentrations (1:1,170,000) stimulate contraction, while high ones (1:1,250) inhibit. Generally speaking, the use of intestinal strips in preference to other smooth muscle seems advantageous in some instances, because a number of strips of the same intestine can be used and checks can be run conveniently.

¹ Guggenheim, M., *Die Biogenen Amine*, Springer, Berlin, 1924, 103, 219.

² Cow, D., *J. Pharm. Exp. Therap.*, 1920, **14**, 275.

³ Abel, J. J., and Macht, D. I., *J. Pharm. Exp. Therap.*, 1920, **14**, 279.

⁴ Adler, L., *Arch. f. Exp. Path. u. Pharm.*, 1918, **83**, 248.

In the present determinations the Schultz-Dale technique was used. The bases were added to the isolated intestinal strip suspended in 25 cc. oxygenated Tyrode's kept at 38-40°C. Dilutions neutralized to phenolphthalein were made in Tyrode's solution so that 1 cc. contained a unit amount of histamine di-hydrochloride* or acetyl choline hydrobromide.† Absence of hydrolysis of the acetyl choline was insured.

In the mouse, chicken, and guinea pig, mixtures of histamine and acetyl choline had an effect equal to the sum of the 2 separate effects, without gross augmentation or retardation.

Sixty-six intestinal strips from 26 white mice showed that the response to acetyl choline was rather regular regardless of sex or weight. Added to the 25 cc. bath, 0.001 mg. of acetyl choline (1-26,000,000 dilution) always caused a decided contraction unless the strip had been weakened by previous tests with other substances. A response to 0.0001 mg. was not infrequent, and in a few instances 0.000,01 mg. caused a contraction. (See Figs. 1, 2.)

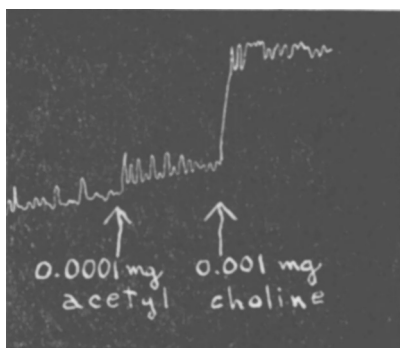


FIG. 1. Mouse Intestine.

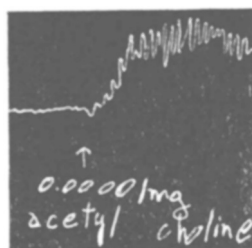


FIG. 2. Mouse Intestine.

The reaction of mouse intestine to histamine was varied. In all amounts less than 50 mg. the histamine usually had no effect. In such an event acetyl choline was added to show reactivity. Sometimes there was a slight alteration of rhythm or a slight relaxation. In 40 strips tested with amounts of histamine varying from 0.0001 to 50 mg., slight contractions were infrequently caused by 0.1 mg., 1 mg., 5.0 mg., and invariably (in each single test on each of 3 mice) by 50 mg. (Fig. 3.) It was concluded that histamine, at least in low concentrations, acted so unreliably that it could not safely be made use of in establishing a ratio.

* Hoffmann LaRoche, c. p.

† Eastman, c. p.

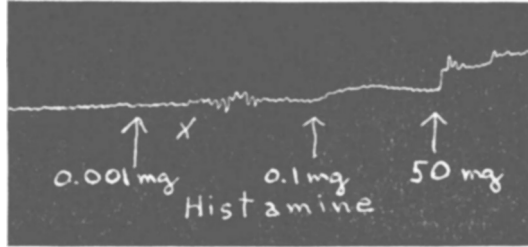


FIG. 3. Mouse Intestine.

Examination of the intestines of 5 chickens one to 3 months old showed that 0.1 mg. histamine or 0.001 mg. acetyl choline certainly caused a contraction, 0.05 mg. histamine often did so, and 0.01 mg. histamine or 0.0001 mg. acetyl choline was sometimes sufficient. (Figs. 4, 5.) This established a ratio of 100:1, which held up very

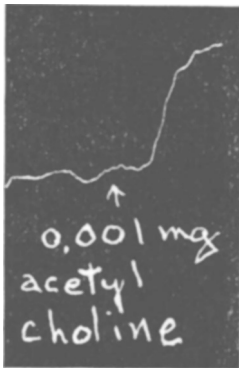


FIG. 4. Chicken Intestine.

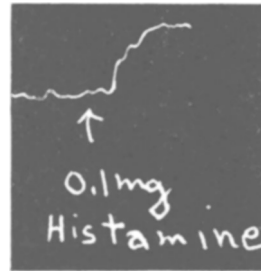


FIG. 5. Chicken Intestine.

well in 4 chickens. However, one of the 5 chickens, obviously ill, had a ratio of 10:1 (0.1 mg. to 0.01 or 0.5 to 0.05).

Naturally, the accuracy of the ratios described is limited by the nature of the dilutions employed, which were multiples of 10. Since individual variations of the ratio are to be found in the test animals described above, such ratios should be regarded as only of suggestive value in assaying the bases as stated in the first paragraph.