The identification of the contractor substance is aided by the use of thymoxyethyldiethylamine. This drug is specific in counteracting the effect of histamine on the guinea pig ileum.[7] It has no comparable effect upon contractions produced by KCl, $NaHCO_3$, acetylcholine, or the contraction produced in rare instances by adrenaline. Acetylcholine produces no contraction of an atropinized muscle. The slight changes in pH of the blood following nerve stimulation were not sufficient to affect the activity of the muscle strip and most sera were diluted with a buffer solution. On the other hand, the contractor substance obtained in the blood from the rabbit's ear following nerve stimulation was heat stable, active in an atropinized bath, but inactive after addition of thymoxyethyldiethylamine. In these respects it is "histamine-like". The source of this substance in the rabbit's ear has not been determined.

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Thymoxyethyldiethylamine Antagonism to Circulatory Effects of Histamine in Anesthetized and Nonanesthetized Dogs.

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Although thymoxyethyldiethylamine (Thym.) has been found to antagonize histamine (Hi) effects on isolated smooth muscle[1-4] and to exert a protective action in guinea pigs against anaphylactic and Hi shock,[2, 3, 5] little work has been done regarding its action in carnivorous animals in which the circulatory effects of Hi are most striking. We have undertaken to investigate Thym. antagonism to the hypotension and hemoconcentration resulting from Hi administration in anesthetized and nonanesthetized dogs, and to observe the effects of Thym. alone.

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7 Rosenthal, S. R., and Minard, D., *J. Exp. Med.*, 1939, **70**, 415.

1 Bovet, D., and Staub, A. M., *C. R. Soc. Biol.*, 1937, **124**, 547.

2 Staub, A., and Bovet, D., *C. R. Soc. Biol.*, 1937, **125**, 818.

3 Staub, A. M., *Ann. Inst. Pasteur*, 1939, **63**, 400, 485.

4 Rosenthal, S. R., and Minard, D., *J. Exp. Med.*, 1939, **70**, 415.

5 Rosenthal, S. R., and Brown, M. L., *J. Immunol.*, in press.

In the first series of experiments, dogs under light amytal anesthesia (60 mg/kg intraperitoneally) were used. Mercury manometer recording of carotid pressure, tracheal cannulation with pneumometer recording of respiration, and cannulation of the femoral vein for injection completed the preparation.

Four dogs served to establish the effects of small (1-10 γ) and large (.25-1.0 mg/kg) doses of Hi injected intravenously. Accompanying the blood pressure fall after large Hi doses, signs of severe respiratory obstruction were observed and taken to indicate bronchial constriction.

In 10 dogs prepared as above, depressor effects of 1-10 γ doses of Hi were studied before and after subcutaneous administration of 40 mg/kg Thym. After Thym. the depressor effects of these Hi doses were markedly decreased. Acetylcholine responses were affected but slightly, thus indicating a specificity of Thym. action similar to that observed on isolated smooth muscle.[4]

TABLE I.
Depressor Responses to Hi and Acetylcholine Before and After Thym.

	Before Thym.	After Thym.
Hi 4 γ	39 mm Hg	10 mm Hg
Ac 2 γ	40	30

After large Hi doses, the drug had no apparent effect either on the degree of blood pressure fall or recovery rate; however, indications of bronchial constriction were no longer evident.

In the second series of experiments, using nonanesthetized dogs, arterial pressure readings from the femoral artery exposed under local anesthesia were obtained with a needle and anaeroid manometer, a spinal fluid trap being interposed. Blood samples were drawn and injections were made into the femoral vein. Hemoglobin concentrations were determined by the Sanford-Sheard photelometer.[6]

The effects of subcutaneous administration of 40 mg/kg Thym. on pulse rate, blood pressure, and hemoconcentration were observed in 5 animals. The pulse and blood pressure uniformly showed a rise in 5-10 minutes after injection, reached a peak in 30-45 minutes, and gradually declined to normal. The hemoglobin level usually showed a transitory rise of less than 10%.

The effects of Hi (1 mg/kg intravenously) were studied in 16 experiments on 9 dogs with and without previous Thym. administration. The results, summarized in Table II, indicate a significant

[6] Sanford, A. H., Sheard, C., and Osterberg, A. E., *Am. J. Clin. Path.*, 1933, **3**, 405.

TABLE II.
Hemoconcentration After Hi in Nonanesthetized Dogs With and Without Thym. Treatment.

	Maximum hemoconc., avg (% of initial level)		Recovery time, avg (To 10% of initial level)	
No. of expts.	Histamine	Thym. + Histamine	Histamine	Thym. + Histamine
9	26.5		> 110 min	
7		11.8		30 min

reduction in both the degree and duration of hemoconcentration following histamine in animals receiving Thym. On the other hand, the blood pressure effects of Hi (1 mg/kg) were not appreciably altered by Thym. treatment.

Discussion. Staub[3] failed to observe a decrease in the depressor response to Hi in chloralosed dogs after intravenous Thym. injection, probably because the Hi doses used (.02 mg/kg) were beyond the effective range of Thym. However, we can confirm in dogs this author's observations in guinea pigs on Thym. antagonism to bronchoconstrictor effects of Hi.

Insufficient experimental work precludes any postulation regarding the mechanism of Thym. antagonism to the depressor effects of small Hi doses. However, it seems unlikely that Hi vasodilatation is involved; more probably Thym. action is limited to abolishing venoconstrictor effects of Hi.

Whether the marked hemoconcentration observed in nonanesthetized dogs after Hi represents solely a loss of plasma volume or whether an influx of red cells from a reservoir such as the spleen is an important factor has not been investigated. Hence, it is premature to suggest that Thym. may reduce loss of plasma volume in histamine shock.

Summary. Thymoxyethyldiethylamine administered subcutaneously to (a) anesthetized and (b) nonanesthetized dogs reduces or abolishes the depressor effects of small histamine (Hi) doses and prevents the bronchial constrictor action of large Hi doses in (a) and reduces the hemoconcentration following large Hi doses in (b), but in neither (a) nor (b) are the depressor effects of large Hi doses appreciably altered.