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Rôle of Thyroid in Cyclopropane-Adrenalin Tachycardia.*

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Cyclopropane greatly enhances the activity of adrenalin on the automatic tissues of the dog's heart. A dose of .01 mg of adrenalin per kilogram intravenously causes only escape phenomena in the unanesthetized animal, while under deep cyclopropane anesthesia this same dose results in multifocal ventricular tachycardia.[1] Decerebration and crossed circulation experiments indicate that the cardiac response to the direct adrenalin stimulation is dependent upon the functional integrity of a brain center above the pons, the heart having been sensitized by cyclopropane acting directly upon it.

Since the thyroid gland appears to sensitize the whole or part of the sympathetic nervous system,[2] the influence of the thyroid on cyclopropane-adrenalin tachycardia has been investigated.

Methods. Sixteen dogs were anesthetized with cyclopropane without premedication, intubated to insure an open airway, and connected through a soda-lime carbon dioxide absorber to a 100 liter rubber bag containing a 30 to 32% mixture of cyclopropane in oxygen. This concentration of the anesthetic mixture produces deep surgical anesthesia with at least partial intercostal paralysis in dogs. The animals were allowed to equilibrate on this constant mixture for 30 minutes. The test dose of .01 mg of adrenalin per kilogram in 5 cc of normal saline was then injected into the left radial vein at a constant rate over a 50-second period. The duration of the resulting ventricular tachycardia was determined by observation of the beam of the electrocardiograph and by electrocardiograms (lead II) taken over a 5-minute period beginning with the injection.

Eleven of the animals were then thyroidectomized, care being taken to preserve the superior pair of parathyroid glands. Twenty-six days later the test dose of adrenalin was again injected under cyclopropane anesthesia and the duration of ventricular tachycardia noted.

To determine the effects of thyroid feeding, 9 of the 11 thyroidecto-

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1 Allen, C. R., Stutzman, J. W., and Meek, W. J., *Anesthesiology*, 1940, **1**, 158.

2 Wolf, W., *Endocrinology in Modern Practice*, 2nd ed., W. B. Saunders, 1939.

mized dogs and the 5 intact dogs were given desiccated thyroid glands (Parke, Davis) for 12 days. The dose for 12 of the animals was 400 mg per kilogram per day and for the other 2, 200 mg per kilogram per day for the first 7 days and then 400 mg per kilogram per day for the remaining 5 days. On the thirteenth day the duration of ventricular tachycardia was again determined for all 14 animals.

As a measure of the degree of hypo- and hyperthyroidism, oxygen consumption values were determined on 6 of the dogs by the method of Kunde.[3]

Results. The response to the injection of adrenalin during cyclopropane anesthesia before and after thyroidectomy is shown in Table I. In 5 of 11 animals cyclopropane-adrenalin tachycardia was entirely abolished after removal of the thyroids, and in the remaining 6 the duration of the arrhythmia was reduced from an average of 56 to 30 seconds.

That the removal of the thyroid was the essential factor in this reduction was shown by feeding 9 of the dogs desiccated thyroid. Cyclopropane-adrenalin tachycardia reappeared in 3 of the animals and in the others increased in duration.

Following operation there was little residual thyroid tissue, as can be seen from the average decrease in oxygen consumption of 33% for the dogs tested. These results and those obtained by substitution therapy are summarized in Table II.

TABLE I.
Effect of Thyroidectomy and Subsequent Thyroid Feeding on Duration of Cyclopropane-Adrenalin Tachycardia in Dogs.

	Duration of ventricular tachycardia		
Dog No.	Intact control sec	Thyroidectomized sec	Thyroid feeding (after thyroidectomy) sec
1	46	20	85
2	35	0	83
3	67	50	76
4	40	25	97
5	45	0	64
6	55	0	88
7	68	30	110
8	52	28	62
9	64	26	82
10	51	0	
11	48	0	
Avg	52	16	83

Note. The dose of thyroid for dogs 1 to 7 was 400 mg/kg/day for 12 days and for dogs 8 and 9 200 mg/kg/day for the first 7 days and then 400 mg/kg/day for the remaining 5 days.

[3] Kunde, M. M., and Steinhaus, A., *Am. J. Physiol.*, 1926, **78**, 127.

TABLE II.
Effect of Thyroidectomy and Subsequent Thyroid Feeding on Oxygen Consumption in Dogs.

		Thyroidectomized		Thyroid feeding (after thyroidectomy)		
Dog No.	Control cc O_2/M^2/min.	cc O_2/M^2/min.	% deviation from control	cc O_2/M^2/min.	% deviation from control	% deviation from hypothyroid level
1	129	63	—51	171	+33	+171
2	115	72	—37	197	+71	+174
3	106	79	—25	158	+53	+100
4	156	103	—34	235	+51	+128
5	139	102	—27	236	+70	+131
6	108	83	—23	186	+72	+124
Avg	125 cc/M^2/min.	84 cc/M^2/min.	—33%	197 cc/M^2/min.	+58%	+135%

Note. The dose of thyroid was 400 mg/kg/day for 12 days.

Surface area calculated by the formula of Meehs (S.A. = $\sqrt[3]{\text{weight}^2} \times 0.112$).

The effect of thyroid feeding in 5 normal dogs was next determined. The dose was 400 mg per kilogram daily for 12 days. When the animals were anesthetized with cyclopropane and the test dose of adrenalin injected on the thirteenth day, one died of ventricular fibrillation. The average duration of ventricular tachycardia for the remaining 4 dogs was 61 seconds, compared to an average of 40 seconds in the same animals before thyroid feeding. Loeb, Bassett, and Friedman[4] reported that regressive changes in the thyroid glands of guinea pigs followed the administration of thyroid substance. It is then possible that in the present work the feeding of thyroid tissue to intact dogs diminished their own thyroid activity, and therefore the total thyroid effect was actually diminished.

Discussion. Garrelon and Pascalis[5] believe that adrenalin-chloroform syncope was induced by adrenalin stimulation of the vagus. This resulted in the elimination of a thyroid hormone which was the sensitizing agent. The heart being suddenly sensitized to chloroform, the resulting fibrillation was really a chloroform syncope. The evidence for a primary production of increased tonus in the vagus by adrenalin is not particularly convincing.

Our experiments show that the heart becomes more sensitive to adrenalin and cyclopropane as the thyroid activity is increased. Cyclopropane-adrenalin tachycardia may occur, however, in thyroidectomized animals which show a marked decrease in their basal metabolism, so the thyroid is not absolutely necessary for the reaction. However, it does modify the response.

[4] Loeb, L., Bassett, R. B., and Friedman, H., PROC. SOC. EXP. BIOL. AND MED., 1930, **28**, 209.

[5] Garrelon, L., and Pascalis, G., *Press. Medicale,* 1930, **1**, 649.

A more plausible explanation for the increase in cyclopropane-adrenalin tachycardia in the hyperthyroid state and the decrease in the hypothyroid state seems to be that the thyroid hormone sensitizes the heart to adrenalin. A cardiac accelerator response to adrenalin greater than the control has been demonstrated when cats,[6] rabbits,[7] and terrapins[8] are in the hyperthyroid state. Thyrotoxic rabbit and dog hearts were reported as more susceptible to irregularities than normal controls.[9] An increased cardiovascular reaction to adrenalin is the basis for a clinical test for hyperthyroidism.[10]

Aumann and Youmans[11] recently demonstrated that the thyroid hormone sensitizes the excitatory adrenergic but not the inhibitory adrenergic neuro-effector division of the autonomic nervous system. The present work on cyclopropane-adrenalin tachycardia also seems to indicate that the thyroid sensitizes the excitatory adrenergic neuro-effector system.

Summary. Following thyroidectomy the duration of cyclopropane-adrenalin tachycardia was decreased in the dog. In the hyperthyroid state the period of tachycardia was longer than in the control.

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Excretion of Estrogen in Bile.

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There is considerable evidence that the liver plays an important part in the metabolism of estrogens. This evidence may be summarized as follows: (a) incubation of liver slices with estrogens *in vitro* results in marked diminution in estrogenic activity;[1-7] (b) ex-

6 Sawyer, M. E., and Brown, M. G., *Am. J. Physiol.*, 1935, **110**, 620.

7 McDonald, C. H., Shepeard, W. L., Gree, M. F., and DeGroat, A. F., *Am. J. Physiol.*, 1935, **112**, 227.

8 Lewis, J. K., and McEachern, D., *Bull. Johns Hopkins Hosp.*, 1931, **48**, 228.

9 Rosenblum, H., Hahn, R. G., and Levine, S. A., *Arch. Int. Med.*, 1933, **51**, 279.

10 Goetsch, E., *Penn. Med. J.*, 1920, **23**, 431.

11 Aumann, K. W., and Youmans, W. B., *Am. J. Physiol.*, 1940, **131**, 394.

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