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# Further Observations on the Effects of Thyroid Hormone Preparations on Cholesterolemia and Atherogenesis in Cholesterol-Fed Cockerels

By J. STAMLER, M.D., R. PICK, M.D., AND L. N. KATZ, M.D.

*With the assistance of Mrs. D. Century and Mr. P. Johnson*

Administration of large doses of thyroid hormone preparations (desiccated thyroid powder, thyroxine, triiodothyronine, diiodotyrosine) to cholesterol-fed chicks was associated with decreased rate of weight gain and partial inhibition of hypercholesterolemia. Consistent, definitive inhibition of aorta and coronary atherogenesis was not observed, despite partial suppression of hypercholesterolemia. Potassium iodide and thyroid-stimulating hormone of the anterior pituitary were essentially without effect.

**P**REVIOUS studies from this department indicated that thyroid hormone administration was partially effective in preventing hypercholesterolemia and atherogenesis in cholesterol-fed chicks.<sup>1-4</sup> It was also shown that hypothyroidism counteracted the ability of estrogens to prevent coronary atherosclerosis in cholesterol-fed cockerels.<sup>5-7</sup> The experiments described in the present report were undertaken to explore further the parameters of the effects of thyroid hormone. They included analyses of the influences of potassium iodide, thyroxine, diiodotyrosine, triiodothyronine, desiccated whole thyroid, and thyroid-stimulating hormone of the anterior pituitary (TSH).

## METHODS

Six series of chronic experiments were accomplished in cockerels, varying in duration from 3 to 9 weeks. All studies were carried out on Hy-line cockerels reared in a battery brooder in the laboratory from 1 day of age. The birds subsisted on a commercial chick starter mash until onset of the experiments. Each experimental group was made up of 9 to 18 birds. The nutritional, bio-

chemical and pathologic procedures were in conformity with the established technic of atherosclerosis research of the department.<sup>4</sup> In general, the experiments involved studying the influences of hormone administration in cockerels placed on a diet supplemented with cholesterol, with or without cottonseed oil. The detailed experimental designs, procedures, diets and hormonal regimens are presented in the tables with the findings.

## RESULTS

The findings in the first 3 series of experiments, studying the effects of oral feeding of desiccated thyroid powder and parenteral administration of TSH, are presented in table 1. Additional observations on the effects of thyroid powder are also contained in tables 2 and 3, so that a total of 6 such experiments was carried out. TSH was without consistent effect on any of the parameters measured, including hypercholesterolemia and atherogenesis in the aorta and coronary arteries. This negative result was obtained with dosages as high as 25.0 mg./bird/day (S21).

Incorporation of desiccated thyroid powder at the 0.5 to 1.0 per cent level in cholesterol-fat-supplemented mash tended to result in an increase in feed intake, although this was not a consistent finding (tables 1 to 3). Thyroid-induced decrease in rate of weight gain and partial inhibition of diet-induced hypercholesterolemia were almost invariable observations. Findings on atherogenesis in these thyroid-fed cockerels were much less definitive. In some experiments no effects of thyroid ad-

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ministration on aorta lesions were observed; in others slight, questionably significant decreases in incidence and/or grade were noted; in still others there seemed to be an actual hormone-induced intensification of aorta atherogenesis. Similarly, antiatherogenic effects of thyroid on the coronary vessels were observed in some experiments, but not others (tables 1 to 3). These variable effects of thyroid on atherogenesis could not be correlated with presence or absence of cottonseed oil in the cholesterol-supplemented mash (table 2), duration of the experiment, age of the cockerels, or season of the year (tables 1 to 3).

In series 29, the effects of potassium iodide

in the drinking water were analyzed. In conformity with previous observations of potassium iodide in cholesterol-fed cockerels,<sup>1</sup> this salt had no significant effect, tending to intensify, rather than lessen, hypercholesterolemia and atherogenesis.

In this experiment, the effects of various thyroid preparations were also studied (table 3). The dosages of each preparation used were such that the content of organic iodine received by each group of chicks was different. Thus, the desiccated thyroid group received 2.3 mg./bird/day of organic iodine; the thyroxine group, 3.9; the diiodotyrosine group, 2.1; the triiodothyronine group, 0.9.

TABLE 1.—*Effects of Desiccated Thyroid and TSH on Plasma Cholesterol Levels and Atherogenesis in Cockerels on High-Cholesterol, High-Fat Diets*

Series, date, age, duration	Group	Survival to end of experiment (%)	Feed intake (Gm./chick/day)	Terminal weight (Gm.)	Plasma total cholesterol (mg. %)	Gross thoracic aorta atherogenesis incidence <sup>†</sup> and grade <sup>#</sup>		Microscopic coronary atherogenesis incidence <sup>†</sup> and extent <sup>‡</sup>	
S9 4/51-7/51 7-17 weeks 10 weeks	1 C-O**	92	133±12†	1712± 89	574± 62§	100%	2.2±0.3	—	—
	1 C-O	88	116± 6	1460± 53	283± 36	86%	1.9±0.3	—	—
	Thyroid†† TSH*	72	102± 6	1669± 72	445± 27	100%	2.1±0.2	—	—
S19 9/52-11/52 12-19 weeks 7 weeks	1 C-O	100	109± 7	1950	577± 41	100%	1.8±0.2	90%	24%± 4
	1 C-O	67	137±11	1549	374± 27	88%	1.8±0.4	38%	27%±15
	Thyroid†† TSH*	75	115± 6	1679	791±153	100%	1.8±0.2	100%	19%± 7
S21 10/52-1/53 12-16 weeks 3+ weeks	1 C-O	100	—	2188±278	517± 42	100%	1.6±0.2	70%	17%± 3
	1 C-O	89	—	2189±360	358± 21	100%	0.9±0.2	64%	18%± 5
	Thyroid†† TSH*	70	—	2368±393	755±127	86%	1.2±0.2	86%	25%± 9

\*TSH was given as a single daily injection at dosage levels of 0.5-10.0 mg., 5.0-25.0 mg. and 25.0 mg. in S9, S19 and S21 respectively.

\*\*1 C-O is chick starter mash + 1% cholesterol + 5% cottonseed oil.

†Standard error of the mean.

††In S9, S19, and S21 the desiccated thyroid powder was mixed in the mash at the 0.5%, 1.0% and 1.0% level respectively.

§In S9, S19 and S21, the cholesterol values are means of multiple bleedings at 1, 2, 4, 6 and 9 weeks on experiment; at 2 and 7 weeks; and at 1 and 3 weeks respectively.

† Incidence is the percent of birds with lesions.

#Grade is the mean grade for birds with lesions, i.e. exclusive of birds graded 0; the grading is on an arbitrary scale 0-4 (4).

‡Extent is evaluated based on a microscopic examination of 2 standard Sudan-stained heart sections on each bird; all arteries and arterioles in each section are counted, and the per cent demonstrating atherosclerotic plaques calculated. The values are the per cent of vessels with lesions in birds with lesions.

TABLE 2.—*Effects of Desiccated Thyroid on Plasma Lipids and Atherogenesis in Cockerels on High-Cholesterol Diets With and Without Supplementary Cottonseed Oil\**

Series, date, age, duration	Group	Survival to end of experiment (%)	Feed intake (Gms./chick/day)	Terminal weight (Gms.)	Plasma total cholesterol (mg. %)	C/P ratio	Gross thoracic aorta atherogenesis incidence and grade		Microscopic coronary atherogenesis incidence and extent	
S23 3/53-5/53 8-19 weeks 11 weeks	1-2 C  1-2 C Thyroid	90  100	174±12  174±12	1875  1381	151±9† 148±8** 136±4† 238±14**	—  —	11%  50%	0.5±0.0  0.9±0.4	56%  78%	12%±3  13%±4
S37 1/55-3/55 14-19 weeks 5 weeks	2 C 2 C 2 C-O 2 C-O Thyroid	100 67 100 100	170±12 181±30 160±7 130±11	1426 1377 1376 1230	288±25‡ 157±8‡ 450±62‡ 261±28‡	1.03±0.08 1.07±0.05 1.18±0.12 1.22±0.07	40% 17% 50% 60%	0.9±0.3 0.5±0.0 0.4±0.2 0.8±0.2	90% 100% 100% 90%	16%±3 10%±4 13%±2 15%±3

\*Thyroid dosage: S23, 1%; S37, ½% for the first week, 1% thereafter.

†Mean of 2 bleedings during first 5 weeks of experiment on diet of 1% cholesterol (1C).

\*\*Mean of 3 bleedings during last 6 weeks of experiment on diet of 2% cholesterol (2C).

‡Mean of 2 bleedings at experimental weeks 2 and 5.

TABLE 3.—*Effects of Various Thyroid Preparations on Plasma Lipids and Atherogenesis in Cockerels on High-Cholesterol, High-Fat Diets. S29, 11/53-12/53, 5 Weeks*

Group	Survival to end of experiment (%)	Feed intake (Gm./chick/day)	Terminal weight (Gms.)	Plasma total cholesterol* (mg. %)	C/P ratio‡	Gross thoracic aorta atherogenesis incidence and grade		Microscopic coronary atherogenesis incidence and extent	
1 C-O	100	107±12	1683±69	284±56	1.31±0.19	90%	1.0±0.2	100%	15%±2
1 C-O Thyroid‡	90#	119±16	1303±33	287±27	1.58±0.15	67%	0.8±0.2	33%	10%±1
1 C-O Thyroxine‡	60†	144±29	—	191±11	—	83%	0.5±0.1	83%	12%±5
1 C-O Diiodotyrosine‡	100	107±11	1218±50	248±15	1.01±0.09	70%	0.8±0.3	100%	10%±2
1 C-O Triiodothyronine‡	90	110±10	1348±63	337±35	1.36±0.07	89%	0.8±0.2	100%	10%±2
1 C-O KI‡	90	110±15	1484±40	529±38	1.35±0.09	100%	1.6±0.2	100%	22%±5

\*Data from 2 bleedings at 2 and 5 weeks on experiment, except for thyroxine group, which was bled at 2 weeks only.

†Six additional birds died 1 day before termination of the experiment.

‡Data from final bleeding only.

‡‡Dosages: desiccated thyroid powder, 1.0% orally in the mash or 1,190 mg./bird/day, or 2.3 mg. organic iodine daily; thyroxine, 6 mg./chick/day or 3.9 mg. organic iodine daily; diiodotyrosine, 3.5 cc. of a special preparation (RESH) parenterally, containing 2.1 mg. organic iodine daily; triiodothyronine, 1.5 mg. daily, or 0.9 mg. organic iodine; KI, 100 mg./200 cc. drinking water.

#Three additional birds died 1 day before termination of the experiment.

In the 2 groups on highest dosage (desiccated thyroid and thyroxine), several birds died spontaneously 1 day prior to termination of the experiment. All hormone-treated groups exhibited decreased rate of weight gain. All except the triiodothyronine-treated birds (on lowest dosage of organic iodine) had partial inhibition of hypercholesterolemia (table 3). No group manifested significant suppression of atherogenesis.

#### DISCUSSION

The most impressive aspect of these experiments is the virtual absence of a consistent effect of thyroid hormone preparations on atherogenesis. This lack of a clearcut anti-atherogenic influence was noted, despite moderate, partial inhibition of hypercholesterolemia by thyroid hormones. This dissociation of findings with respect to hypercholesterolemia and atherogenesis forcefully poses the problem of the reasons for the apparent lack of thyroid antiatherogenesis.

The data of the present experiments do not serve to clarify this problem. However, certain suggestions may be entertained, particularly in relation to findings cited in the older literature. Thus, the dosages of thyroid hormones were large in these experiments. It is an old observation that thyroid hormones in large doses are capable of producing vascular damage (arteriosclerosis, not atherosclerosis) in animals on their usual diets (without an atherogenic supplement of cholesterol and fat).<sup>4, 8, 9</sup> It is also known from previous work that large doses of thyroid hormones may produce arterial injury and intensified atherogenesis in rabbits on high-fat, high-cholesterol diets.<sup>10</sup>

Based on these observations, it may be suggested that the findings with large doses of thyroid hormones in the present experiments may represent the end result of 2 opposing processes—thyroid-induced partial inhibition of hypercholesterolemia, tending to suppress atherogenesis, and thyroid-induced vascular damage, tending to intensify atherogenesis in animals with the prerequisite nutritional-metabolic derangement. In actuality, the in-

terrelationships are probably even more complex.

#### SUMMARY

1. Administration of large doses of thyroid hormone preparations (desiccated thyroid powder, thyroxine, triiodothyronine, diiodotyrosine) to cholesterol-fed chicks was associated with decreased rate of weight gain and partial inhibition of hypercholesterolemia.

2. Consistent, definitive inhibition of aorta and coronary atherogenesis was not observed, despite partial suppression of hypercholesterolemia.

3. Potassium iodide and thyroid-stimulating hormone of the anterior pituitary were essentially without effect.

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#### SUMMARIO IN INTERLINGUA

1. Le administration de grande doses de preparatos de hormon thyroide—pulvere de thyroide desiccate, thyroxina, tri-iodothyronina, di-iodotyrosina—a gallettos tractate con cholesterol dietari esseva associate con relevation del ganio de peso e un inhibition partial del hypercholesterolemia.

2. Non esseva observate un inhibition uniforme e definitive de atherogenesis aortic e coronari, in despecto del partial suppression de hypercholesterolemia.

3. Ioduro de kalium e hormon thyroido-stimulatori de pituitario anterior esseva essentialmente sin effecto.

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