

EFFECT OF THYROID EXTRACT AND METHYLTHIOURACIL  
ON SPONTANEOUS CARCINOGENESIS AND DNA SYNTHESIS  
IN THE MAMMARY GLAND OF C<sup>3</sup>H MICE

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The effect of thyroid extract and methylthiouracil on carcinogenesis and DNA synthesis was studied in the mammary glands of C<sup>3</sup>H mice. In a dose of 0.1 mg daily thyroid extract had no significant effect on DNA synthesis in the mammary gland but halved the incidence of a deno-carcinoma in the mice. Thyroid extract in a dose of 8 mg daily appreciably increased the level of DNA synthesis in the mammary gland but had no effect on the incidence of adenocar-cinoma in the mice. Methylthiouracil lowered the level of DNA synthesis and the incidence of adenocarcinoma by two-thirds. The possible mechanisms of action of thyroid and methyl-thiouracil on DNA synthesis and on malignant transformation in the mammary gland are dis-cussed.

Clinical data on the effect of thyroid preparations on carcinoma of the breast in women are just as contradictory [9, 10] as experimental data on the effect of methylthiouracil on proliferative processes and on malignant transformation in the mammary gland [17, 18].

It was accordingly decided to study the effect of thyroid extract and methylthiouracil on malignant transformation and on DNA synthesis in the epithelial cells of the mammary glands of C<sup>3</sup>H mice.

EXPERIMENTAL METHOD

Nulliparous C<sup>3</sup>H mice initially weighing 23-24 g were divided into four groups. The animals of groups 1 and 2 were given thyroid extract in doses of 0.1 and 8 mg respectively daily with the diet. The animals of group 3 received methylthiouracil in a dose of 10 mg daily. The mice of group 4 were the control. The ex-periment lasted 9 months. The percentage of animals with adenocarcinomas of the mammary gland and the level of DNA synthesis in the mammary glands were determined in mice of the experimental and control groups.

The 16 mice, four from each group, in which the level of DNA synthesis was determined received an intraperitoneal injection of thymidine-H<sup>3</sup>, with specific activity 8.6 mCi, in a dose of 0.7  $\mu$ Ci/g body weight, 1-3 h before sacrifice. The mammary glands were fixed in Carnoy's fluid, and after ordinary histological and autoradiographic treatment the number of labeled nuclei per thousand cells in the epithelium of the ducts and in the terminal portions of the gland was counted.

EXPERIMENTAL RESULTS

The results are given in Table 1.

Thyroid extract in a daily dose of 0.1 mg had no significant effect on DNA synthesis in the mammary gland, while at the same time the incidence of carcinoma in this situation was halved in the animals of this

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TABLE 1. Effect of Thyroid Extract and Methylthiouracil on Yield of Spontaneous Tumors and Level of DNA Synthesis in the Mammary Gland of C<sup>3</sup>H mice

Substance given and dose	No. of mice		No. of mice with tumors				percent of control		
	total	No. surv. until appear. of 1st tumor	abs	%	Level of DNA synthesis	P	No. of mice	index of labeled nuclei	P
Thyroid extract -0,1 mg	38	37	11	30	50	0,01	4	0,8	0,5
Thyroid extract -8 mg	38	20	12	60	100	—	4	2,0	0,001
Methylthiouracil, 10 mg	38	27	5	19	31	0,001	4	0,2	0,001
Control	68	51	31	61	100	—	4	0,6	—

group; death of the animals from causes unconnected with mammary gland carcinoma was least in this group. Thyroid extract in a dose of 8 mg daily, i.e., a dose known to be toxic, considerably increased the intensity of DNA synthesis in the mammary gland, but the incidence of carcinoma of this gland remained unchanged; mortality among the animals from other causes in this group was highest. Methylthiouracil, in a daily dose of 10 mg, lowered the incidence of adenocarcinoma by two-thirds and lowered the level of DNA synthesis in the mammary gland by an equal degree.

The inhibitory effect of small doses of thyroid on tumor formation may be connected with the following mechanisms: 1) the compound stimulates luteinizing function [3] and simultaneously lowers the follicle-stimulating activity of the pituitary [4], thus leading to a decrease in estrogen production; 2) by intensifying hormone metabolism in the body, it prevents the accumulation of sex hormones and their cumulative action; 3) in small doses it increases the number of acidophils, which are known to produce prolactin [6], in the anterior lobe of the pituitary [16], it promotes differentiation of the glandular epithelium of the mammary gland, and thereby inhibits processes of carcinogenesis [1]; 4) small doses of thyroid extract, by intensifying the immunological reactivity of the animal, may prevent the appearance of atypical tumor cells. Large doses of thyroid, stimulating DNA synthesis in the mammary gland but ineffective in inhibiting malignant transformation, reduce the number of acidophils in the anterior lobe of the pituitary [16] and inhibit the immunological reactivity of the body. The possibility likewise cannot be ruled out that the strongly luteinized ovary is the source of a large quantity of progesterone, which stimulates carcinoma of the mammary gland [11].

The decrease in incidence of adenocarcinoma and the inhibition of DNA synthesis in the mammary gland by two-thirds in mice receiving methylthiouracil are in agreement with data in the literature [16] and are attributed to lowering of the gonadotropic activity of the pituitary [5].

Hence, unlike in rats reacting to hypothyroidism by an increase in the number of gonadotropic basophils [2, 8] and by hyperplasia in the mammary gland [9], in mice the directly opposite reaction is observed. Species differences in the reaction of the reproductive organs to hypothyroidism has also been observed in birds [15]. Nevertheless, species-specificity in the reaction of the reproductive organs to hypothyroidism is not absolute. Furth [7], for instance, observed hyperplasia in the reproductive organs of mice in which a hypothyroid state had been induced by administration of radioactive iodine. In experiments with rats, results have also been obtained to show that hypothyroidism may be accompanied by a decrease in gonadotropic activity [14].

In women a state of hypothyroidism is more often accompanied by hyperplasia in the organs of the reproductive system and by menorrhagia [12]. In some cases, however, hypothyroidism may be accompanied by atrophic changes in the reproductive organs and by amenorrhea.

The mechanism of this varied response of the reproductive organs to hypothyroidism has not yet been explained and requires further study.

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