EFFECT OF HYPOTHYROIDISM ON DEVELOPMENT OF MAMMARY GLAND TUMORS IN RATS

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A state of hypothyroidism induced in rats by means of 6-methylthiouracil is accompanied by the formation of tumors in the mammary gland and other organs. It is postulated that tumors of the mammary gland and other organs are associated with the hyperestrogenization of hypothyroid rats.

Although considerable attention has recently been paid to the role of thyroid function in the genesis of carcinoma of the mammary gland, the problem still remains unsolved. Clinical and, in particular, experimental data so far published are extremely contradictory.

On the one hand, it has been found that hypothyroidism stimulates proliferative processes in the mammary gland [9, 20, 25] and may be responsible for the high incidence of mammary gland carcinoma in rats [18], while on the other, prolonged administration of methylthiouracil has been shown to induce atrophic changes in the organs of the reproductive system and to inhibit spontaneous carcinogenesis in mice of line C3H, highly susceptible to cancer [12, 27].

Biological tests of the pituitary glands of hypothyroid animals likewise have not yielded consistent results. Besides data indicating that the pituitary glands of thyroidectomized animals possess increased gonadotropic activity [10, 13], there are other reports that thyroidectomy depresses the gonadotropic activity of the pituitary [24, 26].

The object of the present investigation was to study the effect of prolonged continuous, and intermittent administration of methylthiouracil on the formation of mammary gland tumors in rats, and to examine the effect of thyroidectomy on the number of basophil cells, which are responsible for the secretion of follicle-stimulating hormone (FSH), in the adenohypophysis.

EXPERIMENTAL METHOD

Altogether 133 noninbred female rats, initially weighing 120 g, were used in the experiments. This species of animal was chosen because, according to data in the literature, benign and, in particular, malignant neoplasms of the mammary gland are observed in them in fewer than 1% of cases [11, 19]. The total number of rats was divided into three groups. The animals of group 1 received 6-methylthiouracil with the food in a dose of 10 mg daily for two years, while the rats of group 2 received methylthiouracil during the same period and in the same dose, but with intervals (30 days of feeding with the compound, 30 days of rest). The rats of group 3 acted as the control.

Throughout the experiment, animals with tumors of the mammary gland were sacrificed when their condition worsened. The mammary glands, thyroid, and other organs in which tumors were found macroscopically were subjected to histological investigation.

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TABLE 1. Effect of Methylthiouracil on Tumor Formation in Mammary Gland and Other Organs of Rats

Group of animals	Number of rats in group	Number of rats with tumors	Number of mammary gland tumors	Time before appearance of first mammary gland tumor (days)
1	42	17	9	527
2	41	7	6	598
3	50	1	—	—

TABLE 2. Number (in %) of Different Types of Cells in Adenohypophysis of Female Rats under Normal Conditions and after Thyroidectomy

Animals	Zone of adeno-hypophysis	Acidophil cells	Basophil cells	Chromophobe cells
Control	Peripheral	34.95 ± 1.00	7.0 ± 0.20	58.05 ± 1.70
Thyroidectomized	"	17.28 ± 1.57	8.75 ± 0.61	73.97 ± 1.37

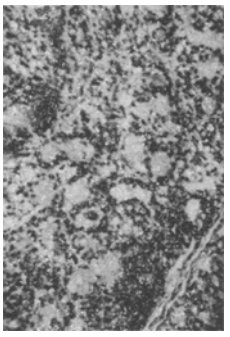

Fig. 1

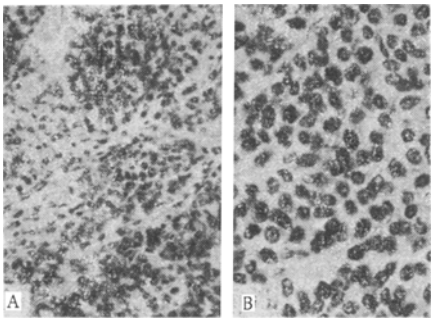

Fig. 2

Fig. 1. Diffuse hyperplasia of mammary gland (63×).

Fig. 2. Adenocarcinoma of mammary (A) and thyroid (B) gland: A) 140×; B) 280×.

In an additional experiment, in order to study the mechanism of the influence of hypothyroidism on the mammary gland, the total number of gonadotropic cells in the anterior lobe of the pituitary was counted in nine female rats weighing 250 g on the eighth day after thyroidectomy, using the method described previously [7]; six female rats of the same weight were used as controls.

EXPERIMENTAL RESULTS

The results shown in Table 1 demonstrate that methylthiouracil, when administered daily, induced tumors in various organs in 17 of the 42 rats. Tumors of the thyroid and pituitary glands are not included in this number, because the ability of methylthiouracil to induce tumors of the thyroid [4, 8] and thyrotropic tumors of the pituitary is well known [16-22]. After intermittent administration of thiouracil, tumors were found in only seven of the 41 rats. Of the nine rats of group 1 in which mammary gland tumors were found, eight had an adenocarcinoma of the gland and one had diffuse hyperplasia of the gland (Figs. 1, 2A). In five rats of group 2 carcinoma of the mammary gland was found, and in one rat a cyst filled with milk debris. Besides tumors of the mammary gland, three rats of group 1 had carcinoma of the lung, two rats had tumors of the liver (sarcoma and hepatoma), two rats had luteogranulosa-cell tumors of the ovaries, and one rat had an adenocarcinoma of the thyroid (Fig. 2B) together with carcinoma of the parathyroid gland.

In group 2, besides neoplasms of the mammary gland, a sarcoma of the liver was discovered (in one rat). In the control group, one rat developed an ovarian tumor of mixed type.

Results showing the effect of thyroidectomy on the relative percentages of different types of cells in the adenohypophysis are given in Table 2. They show that the number of basophils in the peripheral zone, where cells responsible for the secretion of FSH [7, 23] are mainly situated, was higher than in the control

($P = 0.02$). After thyroidectomy, the number of acidophils in all zones of the adenohypophysis also fell sharply, in agreement with data in the literature [2, 6].

The results of these experiments indicating an increase in the number of basophils (responsible for the secretion of FSH) in the hypothyroid rats thus suggest that hyperplasia and carcinoma of the mammary gland in the experimental rats were the result of hyperestrogenization of the animal. It must also be remembered that depression of estrogen metabolism in hypothyroidism and depression of the inactivating function of the liver may have a favorable effect on the cumulation of estrogens during hypothyroidism.

Tumors of nonendocrine organs discovered in these experiments, and which were also obtained by other workers in analogous experiments [1, 3, 4, 17], are evidently also due to hyperestrogenization of the hypothyroid rats. The ability of estrogens, when administered for long periods, to induce tumors in the kidneys, liver, and other organs is well known [15, 21]. Evidence against the view that methylthiouracil itself possesses a carcinogenic action [4] is given by the fact that administration of this compound together with thyroxin prevents the formation of neoplasms in the thyroid gland [8, 14] and also in the liver [5].

LITERATURE CITED

1. R. N. Akimova, Vrach. Delo, No. 6, 7 (1962).
2. N. S. Lebedeva, Arkh. Anat., 15, No. 4, 29 (1936).
3. N. P. Napalkov, Vopr. Onkol., No. 6, 738 (1958).
4. N. P. Napalkov, in: Current Problems in Oncology [in Russian], Leningrad (1965), p. 34.
5. N. P. Napalkov, in: Current Problems in Oncology [in Russian], Leningrad (1967), p. 78.
6. E. B. Pavlov, Abstracts of Proceedings of the Fifth All-Union Congress of Anatomists, Histologists, and Embryologists [in Russian], Leningrad (1949), p. 249.
7. V. I. Romanov, Byull. Éksperim. Biol. i Med., No. 10, 113 (1964).
8. F. Bielschowsky, Brit. J. Cancer, 9, 80 (1955).
9. A. Chamoro, C. R. Soc. Biol., 140, 499 (1946).
10. J. P. Chu, Endocrinology, 34, 90 (1944).
11. M. R. Curtis, F. D. Bullok, and W. F. Dunning, Am. J. Cancer, 15, 67 (1931).
12. C. S. Dubnic, H. P. Morris, and A. J. Dalton, J. Nat. Cancer Inst., 10, 815 (1950).
13. J. Furth, Cancer (Philadelphia), 10, 842 (1957).
14. J. Furth, Cancer Res., 19, 241 (1959).
15. W. U. Gardner, Cancer (Philadelphia), 10, 726 (1957).
16. A. Gorbman, Cancer Res., 16, 99 (1956).
17. D. N. Gupta, J. Path. Bact., 72, 183 (1956).
18. J. G. Hamilton, P. W. Durbin, and M. W. Parrot, J. Clin. Endocrinol., 14, 1161 (1954).
19. J. Heiman and O. F. Krehbiel, Am. J. Cancer, 273, 450 (1936).
20. S. L. Leonard and R. P. Rees, Endocrinology, 28, 65 (1941).
21. A. Lipschutz, Steroid Hormones and Tumors, Baltimore (1950), p. 174.
22. G. F. Moor and E. L. Bracney, Proc. Soc. Exp. Biol. (New York), 82, 643 (1953).
23. H. D. Purves and W. E. Griesbach, Endocrinology, 56, 374 (1955).
24. E. P. Reineke, A. J. Bergman, and C. W. Turner, Endocrinology, 29, 306 (1941).
25. J. F. Smithcors and S. L. Leonard, Endocrinology, 31, 454 (1942).
26. K. Stein and M. Lisle, Endocrinology, 30, 16 (1942).
27. F. Vazquez-Lopez, Brit. J. Cancer, 3, 401 (1949).