HORMONAL TREATMENT OF PRECANCEROUS DISEASES OF THE TESTIS IN RATS

V. N. Dmitriev

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Tumors and foci of proliferation in the testis derived from the spermatogenic epithelium in rats were treated with estrogens, and those derived from interstitial cells of the testis were treated with androgens and with 17-hydroxyprogesterone capronate. In cases of inhibition of the follicle-stimulating function of the pituitary and simultaneous stimulation of the production of luteinizing hormone (LH) growth of teratomas and seminomas was arrested by the action of estrogens and foci of proliferation were absorbed. The depression of LH production by the use of androgens or 17-hydroxyprogesterone capronate was accompanied by cessation of tumor growth and by absorption of foci of proliferation derived from interstitial cells.

KEY WORDS: *germinogenic tumors; follicle-stimulating hormone; tumors from interstitial cells; luteinizing hormone.*

It can be postulated on the basis of results published previously [1-3, 10] that the development of germinogenic tumors of the testis (teratomas and seminomas) is due to enhancement of the follicle-stimulating function of the pituitary and a simultaneous decrease in the production of luteinizing hormone (LH), whereas the formation of neoplasms from the interstitial cells is due to increased production of LH. It follows from the basic principles of hormone treatment of tumors [5] that the hormone therapy of germinogenic tumors must be aimed at depressing the follicle- stimulating function of the pituitary, whereas treatment of neoplasms from the interstitial cells must be aimed at depressing LH production.

The object of this investigation was to discover if, in principle, neoplasms of the testis can be treated by hormones.

EXPERIMENTAL METHOD

Pretumor and tumor changes of germinogenic character were produced by injecting a caustic emulsion intratesticularly, accompanied by androgenic stimulation [1], whereas the corresponding nongerminogenic changes were produced by subtotal castration. Experiments were carried out on 142 sexually mature male rats, in some of which (59 animals) foci of proliferation and tumors from the spermatogenic epithelium were observed at control biopsy, whereas in the rest (83 rats) corresponding changes derived from the interstitial cells of the testis were present. Foci of proliferation and tumors from spermatogenic cells were treated with large doses of estrogens. During the first 4 weeks the rats were given subcutaneous injections of an oily solution of dihydrostilbestrol (20-30 mg per week); from the 5th through the 10th week of the experiment the dihydrostilbestrol was replaced by an oily solution of diethylstilbestrol (10-12 mg per week). For the treatment of foci of proliferation and tumors from the interstitial tissue of the ovary large doses of androgens or of progesterone, which were injected subcutaneously, were used. One group of animals received injections of an oily solution of testosterone propionate (20 mg per week) for 6 weeks, followed by methyltestosterone (100-150 mg per week as a suspension in physiological saline). Another group of rats received an oily solution of 17-hydroxyprogesterone capronate (20-30 mg per week). Treatment of all groups of the experimental animals continued for 9-11 weeks. On the 4th-6th and 9th-11th weeks of hormone therapy the rats were killed, the morphology of the testes

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TABLE 1. Content of Gonadotropic Hormones in Pituitary of Rats before and during Treatment of Pretumor Diseases and Tumors of the Testis of Germinogenic and Nongerminogenic Character (M ± m)

Group of animals	Number of investigations	Gonadotropic hormone		
		FSH	LH (IU/liter)	LTH (μg)
Intact	34	8,25±0,13	34±6,1	7,25±0,4
Germinogenic foci of proliferation and tumors				
Untreated	50	17,4±1,5	31±1,3	11,9±2,0
Treated with estrogens:				
in 5th-6th week of treatment	27	3,8±0,1	88,3±14,6	9,7±1,1
in 8th-10th week of treatment	15	6,6±0,2	108±17,7	11±0,6
Animals with residual foci of proliferation and tumor	3	16,1±2,1	112,5	12,5
Nongerminogenic foci of proliferation and tumors				
Untreated	27	6,4±0,1	150±1,8	5,4±0,4
Treated with estrogens:				
in 6th week of treatment	19	14,6±0,09	0—2,5±0,3	14±1,5
in 9th-11th week of trratment	24	11,4±0,7	13,7±3,2	11,5±0,6
Treatment with 17-hydroxy-progesterone capronate:				
in 4th week of treatment	17	14,6±0,08	0—1,6±0,1	7,5±0,01
in 10th week of treatment	15	9,07±1,9	10±5,9	8,9±1,0
Animals with residual foci of proliferation and tumor	4	10,1	24±5,2	11,7

Legend. Content of FSH determined from change in weight of ovaries (in mg) of infantile mice after injection of suspension of pituitary glands.

was studied, and the concentration of follicle-stimulating hormone (FSH) [2, 8], LH [4, 6], and luteotropic hormone (LTH) [7, 9] in the pituitary was determined.

EXPERIMENTAL RESULTS

Of 59 rats chosen for hormone therapy, germinogenic tumors (10 teratomas and 2 seminomas) were observed in 12 and foci of proliferation of spermatogenic cells were found in 47 animals. Estrogen therapy of the foci of proliferation and tumors of germinogenic origin was successful in 56 of 59 animals treated (94.4% of cases); treatment of the foci of proliferation was particularly successful. In 96.2% of cases foci of proliferation from the spermatogenic epithelium were absorbed by the end of the experiment (10th week), and only in testes of two animals (3.8%) were foci of proliferation still present. In 16.6% of rats the structure of the testes was almost indistinguishable from normal. As the result of estrogen therapy of teratomas and seminomas, by the end of the experiment further growth of the tumors had ceased in 11 of 12 cases, the neoplasms were reduced in size, and in four animals the teratomas were absorbed. At the site of the previous tumor proliferation of connective tissue was observed, together with large numbers of desquamated cells of the spermatogenic epithelium. Meanwhile, the impression was obtained that in the 5th-6th week of estrogen therapy the results were better than in the 8th-10th week. In fact, by the 5th-6th week of hormone therapy growth of the tumors had ceased in all 12 animals (six rats with tumors present previously were killed at this time), the neoplasms were appreciably reduced in size, and in four animals they were absorbed; in no case were foci of proliferation found in the testes. On the 8th-10th week of treatment of six animals in which neoplasms were present previously, at autopsy foci of proliferation derived from spermatogenic epithelium were found in two rats, and in one animal growth of a seminoma had resumed. The effectiveness of estrogen therapy evidently depends on changes in the gonadotropic function of the pituitary (Table 1).

Whereas in the 5th-6th week of the experiment FSH in the pituitary of more than half of the rats investigated was virtually undetectable, and in the rest its concentration was sharply reduced ($P < 0.01$), by the 8th-10th week of hormone therapy the FSH level had risen ($P < 0.05$) compared with that in the 5th-6th week. This could have led to growth of the seminoma in one animal and to preservation of foci of proliferation from the spermatogenic epithelium in two animals.

Of 83 rats with foci of proliferation and with tumors from the interstitial cells of the testis, 10 had small Leydig-cell tumors and 73 had nodular foci of proliferation. By

the end of treatment, diffuse proliferation was still present in three rats (3.6%) and further growth of the tumor was observed in one rat. In the remaining animals the foci of proliferation were absorbed and the tumors were reduced in size; in two cases (2.4%) Leydig-cell tumors were absorbed and the site of the neoplasm was occupied by desquamated epithelial cells and adipose tissue. A positive result of hormone therapy was reflected in a decrease in the LH level in the pituitary (Table 1). The most marked increase in the LH level ($P < 0.001$) was observed in the fourth to sixth weeks of hormone therapy. Meanwhile, the FSH ($P < 0.02$) and LTH ($P < 0.05$) content in the pituitary was increased. No difference in principle was observed in the effectiveness of treatment depending on the method of hormone therapy (androgens or 17-hydroxyprogesterone capronate). Unfortunately, it was impossible to compare the results with data in the literature on the experimental hormone therapy of ovarian tumors.

The question of whether successful hormone therapy of testicular neoplasms is possible in the early stages of treatment can thus be answered in the affirmative. Success of hormone therapy, it must be noted, depends on the completeness of suppression of pituitary gonadotropic function.

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