THE CAUSES FOR RELAPSE OF MAMMARY CARCINOMA UNDER HORMONE THERAPY

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A. K. Kuralasov

Laboratory of Experimental Hormone Therapy (Head-Doctor of Biological Sciences, N. L. Lazarev)
Institute of Experimental and Clinical Oncology, USSR Academy of Medical Sciences, Moscow
(Director-Corresponding Member AMN SSSR, N. N. Blokhin)
Presented by Corresponding Member AMN SSSR, A. D. Timofeevski
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It has been established that estrogen therapy brings about remission in a significant number of post-menopausal patients with breast carcinoma. However, after some time has elapsed, despite continuation of estrogen treatment, a relapse occurs in almost all patients and they die.

On the basis of data gathered in our laboratory, the mechanism of the anti-tumor action of estrogens on breast carcinoma may be through inhibition of the follicular stimulation function of the pituitary [3].

In the literature there appear indications that the action of inhibitors, directed toward prolonged suppression of separate endocrine gland function, are only temporary and then, despite continued use of the inhibitors, the endocrine function re-establishes itself [1, 2, 4].

In the light of these data we may assume that also in breast carcinoma the prolonged administration of estrogens at first depresses the elaboration of follicle-stimulating hormone (FSH) and then, despite the continuation of estrogen treatment, FSH production resumes. The raised FSH level with the increased content of exogenous estrogen inevitably must condition the remaining malignant cells to resume reproduction, i.e., to lead to a relapse of the breast carcinoma. Verification of the accuracy of this postulation has been the task of our present investigation.

METHODS

In the experiments 180 sexually mature female rats were used. FSH production was inhibited by subcutaneous placement of a synestrol (dihydrostilbestrol) pellet weighing five mg, each 15-17 days implanting a new pellet. The experiments lasted 60 days. Each 10 days after the beginning of the experiment some of the rats were sacrificed (usually 5 controls and 5 experimental animals) and their pituitaries were studied for FSH content. The level of FSH in the pituitary was assayed by the increase in uterine weight in immature mice after subcutaneous administration of weighed pituitary tissue in physiological solution (each mouse received the pituitary from one rat). The injections were made daily for 4 days. On the 5th day the mice were sacrificed and their uterus and ovaries were weighed together on a torsion balance. The FSH content was estimated according to the changes in the ratio of weight of the uterus and ovaries, multiplied by 1000, to the weight of the entire immature mouse (index of increase in uterine weight). The control immature mice were given subcutaneous injections of physiological solution.

RESULTS

The experimental results, presented in Fig. 1, show that introduction of a suspension of normal pituitary caused an increase in uterine weight in immature mice with marked regularity, whereas introduction of a suspension of pituitary from the experimental rats which had undergone prolonged synestrol treatment was not accompanied by this effect. After 10 days of synestrol treatment, the FSH content in the pituitaries of experimental rats had fallen sharply, and by 20, 30, and 40 days the pituitary FSH was almost inapparent, for such a pituitary did not produce a reaction in the immature mouse uterus. However, at the 60th day of uninterrupted synestrol action the FSH content of the pituitary had climbed even higher than in the intact rat.

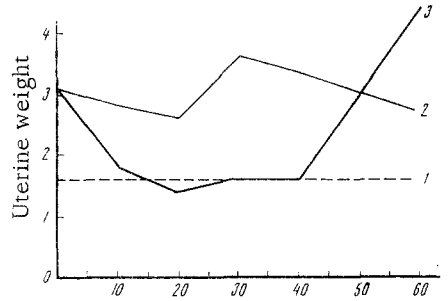

Fig. 1. Change in weight of the immature mouse uterus (1) under the effects of injected suspension of pituitary from rats which had received synestrol (3)

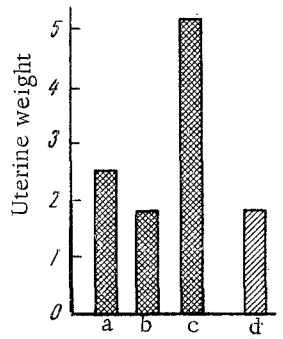

Fig. 2. Change in weight of immature mouse uterus as reflecting the urinary FSH content of patients with breast carcinoma (a), patients in remission after hormone therapy (b), and patients with relapse at the end of synestrol therapy (c). d) Weight of control immature mouse uterus.

Our data show that under conditions of repeated synestrol implantation the follicle stimulating function of the rat pituitary first sharply diminishes but then, despite the synestrol, is again activated.

These data suggest that in patients with breast carcinoma who have undergone synestrol therapy directed toward suppression of FSH production, after prolonged estrogen treatment FSH may again be detected. In order to answer this question we studied the FSH content in the urine of three groups of patients with breast carcinoma: 1) four patients, treated with synestrol, who had returned to the clinic in relapse; 2) three patients who were in remission; 3) two patients before synestrol treatment.

Gonadotropins from 48 h urine collections were isolated in the laboratory of the biochemist N. K. Assonova by the method of Loraine and Brown [6] as modified by G. S. Stepanov [5].

Determination of urinary FSH content and appraisal of the data obtained were carried out by the same technique as in the experimental portion. The urinary extract was divided into three parts in the following ratio: 7:2:0, each of which was injected in equal portions into immature mice over 3 days. As Fig. 2 shows, the patients who had not yet undergone synestrol treatment had high levels of urinary FSH; patients who had undergone synestrol therapy and were in remission had no detectable urinary FSH, and patients who had come to the clinic with relapse of their breast carcinoma during prolonged synestrol therapy had a sharply increased level of urinary FSH.

The clinical data obtained confirm the validity of our hypothesis that resumed FSH production is of decisive importance in relapse of breast carcinoma in patients undergoing prolonged hormone therapy.

SUMMARY

Prolonged action of synestrol on rats was at first attended by a marked reduction of the FSH (follicle stimulating hormone) content in their pituitaries until the hormone was completely depleted; thereupon, the FSH markedly increased above the normal level. Reduction in the FSH content, or its disappearance from the urine, likewise was found in patients with breast carcinoma who underwent synestrol therapy; a high FSH content was found in the patients' urine following prolonged synestrol therapy administered during the relapse. The onset of the latter is possible due to the resumption of FSH production following synestrol therapy.

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