POSSIBILITY OF TUMOR TRANSFORMATION IN AN INTRASPLENIC OVARIAN GRAFT AFTER INHIBITION OF PITUITARY GONADOTROPIC FUNCTION

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In a study of the causes of tumor transformation in an intrasplenic ovarian graft made in castrated females, several authors [6,7,11] have drawn attention to the part played by the enhanced and continuous secretion of gonadotropins developing as a result of the absence of any inhibitory influence exerted by the sex hormones. Previously [1] it has been shown that at late stages of development of an intrasplenic ovarian graft, when transformation into a tumor occurs, there is no continuous and excessive secretion of gonadotropins by the hypophysis.

In the present investigation we attempted to answer the problem of whether an ovarian tumor can arise after inhibition of gonadotropic activity of the hypophysis by testosterone propionate.

METHOD

We castrated 28 infant white rats of a mixed strain, and transplanted the ovary into the spleen. After two months an exploratory laparotomy was performed, and rats in which the graft had been absorbed (Nos. 2 and 5) were discarded. On the next day injections of an oily solution of testosterone-propionate were started.

Animals of the first group (Nos. 1-8) each received 0.1 ml of a 1% testosterone-propionate solution (1 mg), those of the second group (Nos. 9-18) received 0.1 ml of a 5% solution (5 mg). The remaining animals (Nos. 19-28) comprising the third or control group received 0.5 ml of physiological saline.

The injections were continued twice weekly for two months.

Then a second exploratory laparotomy was performed, after which the animals were kept for further study of the growth of the transplant. They were killed seven months after the second laparotomy; the intrasplenic transplant was measured and examined histologically; it was fixed in 10% formalin, and sections were stained by Van Gieson's hematoxylin-eosin.

In a separate experiment the same amounts of testosterone were given to two groups of intact sexually mature rats (10 females in each group), the injections being given twice weekly. They were continued for one month, and then there was a two-week interval, after which the rats were killed. Tissue of the adenohypophysis was tested on infant rats [4], and the ovaries were examined histologically.

RESULTS

At the exploratory laparotomy performed two months after the start of the testosterone-propionate injections we confirmed what had been found previously [6,9], that the male hormone inhibits the initial growth of an intrasplenic ovarian graft. The effects of the 1% and 5% solutions were identical in this respect. However, subsequently the rate of growth of ovarian tissue in these two groups of animals diverged considerably. In three rats of the second group (Nos. 15,17, and 18) the graft was completely absorbed despite the fact that the testosterone injections had ceased. In the remaining animals of this group the grafts continued to shrink ($4.8 \pm 2 mm^2$ after the injection of testosterone, and $2.5 \pm 1.8 mm^2$ at the end of the experiment).

Histological Features of the Ovarian Graft in Rats of the First Group at the End of the Experiment

No. of rats	Structure of ovarian graft
1	Granular-celled tumor. Numerous follicles show cystic changes with massive hemorrhages into their cavity. Between the walls of the follicles there was extensive granulation. Small corpora lutea sometimes present.
3	Massive increase of lutein tissue, locular proliferation of the lutein cells.
4	Mass of cystic follicles. The wall of the cysts consists of elongated connective-tissue cells.
6	Large cysts of follicles lined with a single layer of cubical epithelium. Hemorrhages into the cavity of the cysts. In the wall of the cyst there is a polyp consisting of a granular-celled tumor. Remains of a corpus luteum.
7	Corpora lutea and hemorrhages surrounding them.
8	Focal proliferation of the lutein cells, lipomatosis, hemorrhages.
9	Granular-celled tumor. Great proliferation of the epithelium of the follicles which merge to form a cyst; hemorrhages. Numerous mitoses. At the periphery of the graft there are solitary small corpora lutea.

On the other hand, in rats of the first group after the injections had ceased not only was tissue growth more rapid (8.4 ± 4.7mm^2 after the injection of testosterone and 171.7 ± 208.6 mm^2 at the end of the experiment), but, as was confirmed subsequently, there was also a more marked tumorous growth of ovarian tissue. Thus in our microscopical study of grafts in this group of animals (see table) we found three granular-cell tumors, and in two cases we found a locular proliferation of lutein cells, and in one case a cystic degeneration of the follicles.

In rats of the second group the grafts were all of the same type, and consisted of small corpora lutea. A feature of the grafts of this group was that there were no follicles, whereas in rats of the first group there was extensive cystic degeneration of follicles, and solitary corpora lutea were present.

In the rats of the third (control) group the grafts progressively increased in size (attaining 32.2 ± 14.5mm^2 after four months, and 180 ± 120 mm^2 at the end of the experiment); histological examination showed that they consisted only of luteomas.

Thus under the action of testosterone, transformation into a tumor occurred only in animals of the first group in which cellular elements of the follicles survived in the ovarian grafts. In all animals of the second group, in which after the action of large doses of testosterone there was a progressive necrosis of the cellular elements of the follicular epithelium, there was no transformation into a tumor. It would appear, as has been found by other authors [3], and counter to the findings of certain other investigators [13], that the follicular epithelium plays an important part in the process of transformation of ovarian tissue into a tumor.

In order to determine the reason for the rate of the growth of the grafts after the injection of large or small doses of testosterone, in a special series of experiments we investigated the hypophyseal gonadotropic activity on the structure of the ovaries. Certain authors hold that testosterone acts directly on ovarian tissue [14,15] and others associate its action with inhibition of the luteinizing function of the hypophysis [12].

The results of this set of experiments showed that all the rats on which tissue of the adenohypophysis was tested remained infantile up to the time when the gonadotropic reaction is normally manifest (5 days after the commencement of injections). Although two days later the animals all became sexually mature, there was no

statistically significant difference in the gonadotropic reaction of the two groups of animals which had received different amounts of testosterone. Thus under the condition of our experiment hypophyseal gonadotropic activity had been eliminated.

In a study of the ovaries of animals which had received 1% and 5% testosterone propionate solution we found a greater number than normal of follicles at various stages of maturation; we also found hyperplasia of the estrous tissue, and a marked dilatation of the vessels. However, the corpora lutea were very small, consisting only of small lutein cells. Thus testosterone brings about not only degenerative processes in the corpora lutea but also proliferative changes in the follicular epithelium. This twofold influence has been described previously [5]. The gonadotropic activity of the hypophysis of animals treated with testosterone was suppressed, and therefore changes in the ovary of animals may be attributed not only to inhibition by this hormone of the luteinizing activity of the hypophysis but also to the stimulating influence of the follicular cells.

As has been shown [10], testosterone does not act on ovarian tissue when certain hypothalamic nuclei have been destroyed. We may therefore suppose that because we used small doses of testosterone we were able selectively to eliminate the luteinizing function of the hypophysis, and with higher doses there was characteristic pharmacological "damage" to the hypothalamic nuclei, which, as is well known [2,8], inhibits the initial growth of the ovarian transplant.

As has already been pointed out, published reports have described the selective inhibition of the luteinizing activity of the hypophysis under the influence of testosterone propionate, and therefore from the work we have carried out we may conclude that the tumorous transformation of the intrasplenic ovarian graft may take place after inhibition by small doses of testosterone propionate of the hypophyseal luteinizing activity.

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