On Tumor Formation in Gonadal and Hypophyseal Transplants into the Anterior Eye Chambers of Gonadectomized Rats

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SUMMARY

Small pieces of ovarian, testicular, or ovarian plus hypophyseal tissue were transplanted to the anterior eye chambers of rats, aged 2 months, which were simultaneously gonadectomized. One year after the operations the animals were examined. The ovarian and testicular grafts had taken and had been transformed to tumors in a very high percentage of cases. The ovarian and testicular tumors were morphologically similar to each other, and both had estrogenic as well as androgenic properties. Ovarian and hypophyseal grafts in the same eye grew rapidly into large tumors (granulosa-cell tumors and chromophobie hypophyseal adenomas), with signs of progesterone and prolactin secretion, respectively. One of the animals had a mammary adenocarcinoma, and the mammary glands in all were highly stimulated and secreting milk.

It is concluded that prolactin may stimulate the growth and influence the secretion of granulosa-cell tumors. Gonadal and mammary tumors are discussed in relation to the experimental results.

It has been shown earlier by the present author (12) that ovarian follicles autotransplanted to the anterior eye chamber of 2-month-old spayed rats usually cause granulosa-cell tumors within 1 year. The tumor development might be explained by the fact that the fragment of grafted ovarian tissue has too small a production of steroid hormones to inhibit the hypophysis. The increased amount of hypophyseal gonadotrophins then produced presumably stimulates tumor formation.

This work has now been repeated in a homozygotic rat strain, making it possible also to observe the growth of the follicles and the hormonal action of granulosa-cell tumors formed in gonadectomized male rats. It has been extended to the transplantation of small fragments of testicular tissue instead of ovarian follicles, to ascertain whether it is possible to produce testicular tumors in the same way. In some cases fragments of an anterior hypophyseal lobe have been placed beside the follicles in the anterior eye chambers in an attempt to accelerate the tumor growth by supplying further amounts of hypophyseal hormones. Intact and spayed rats, with only a hypophyseal graft in their eye chambers, served as controls to these last-mentioned animals.

MATERIALS AND METHODS

The experimental animals were about 2 months of age at the time of operation, and all belonged to the inbred homozygotic R strain raised at the Institute. The animals were kept four or five to a cage, and were given commercial pellets and tap water ad libitum and once a week a handful of wheat. Bilateral oophorectomy or orchidectomy was performed through a midline abdominal incision. With the aid of a stereomicroscope (X15), follicles from the interior of an ovary were dissected carefully and transplanted to the anterior eye chambers (also under X15 enlargement) of male and female gonadectomized hosts. In other animals, pieces of testicular tissue of about the same size as a follicle were grafted instead. The testes...
were taken from 1-2-day-old rats. Some animals had an ovarian follicle and a small piece of an anterior hypophyseal lobe transplanted (from 2-month-old female rats) into the right anterior eye chamber and simultaneously a single follicle in the left. Only a hypophyseal graft was placed in the anterior eye chambers of some intact and spayed females. The animals were killed about 1 year later. The grafts were removed, fixed in Susa, embedded in paraffin, and sectioned. The sections were stained with hematoxylin-eosin or with Azan in the case of the hypophyseal or hypophyseal-ovarian grafts. The animals were carefully autopsied in a search for other tumors; and the development of uterus, vagina, the mammary glands, the prostate, and seminal vesicles was studied.

The types and numbers of transplantations are given in Table 1.

### TABLE 1

<table>
<thead>
<tr>
<th>Type of transplantation</th>
<th>No. animals</th>
<th>Grafts studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular transplants to castrated males</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Testicular transplants to spayed females</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Ovarian follicles to castrated males</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Ovarian follicles to spayed females</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Ovarian follicle + piece of hypophyseal anterior lobe into right eye, and ovarian follicle into left eye of spayed female</td>
<td>10</td>
<td>10+10</td>
</tr>
<tr>
<td>Piece of hypophyseal anterior lobe to intact or spayed female</td>
<td>5+5</td>
<td>5+5</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>40</td>
<td>70</td>
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</table>

### RESULTS

**Testicular transplants** grew and were transformed to tumors, mostly of varying sizes in all the ten transplantations made to male hosts, and in nine of the ten transplantations made to female hosts. Macroscopically the tumors were slightly yellowish and had a smooth surface. All were well vascularized from the iris, like all transplants in the present investigation. The cut surface of the tumors was solid, white to yellowish, and fleshy. Microscopically the picture was uniform and essentially the same in male hosts (Fig. 1) and female hosts (Fig. 2). Polygonal to rounded cells with pale nuclei, one or two basophilic nucleoli, and a finely granulated or sometimes vacuolated cytoplasm were lying in cords, sheets, or rounded groups in a sparse stroma with fibriillary network and capillary vessels. Remnants of old, shrunken, seminiferous tubules could be seen, in which only some cells lining the basal membrane were still living. The tumors seemed to have risen through proliferation of cells outside the tubules. No metastases or other tumors were found in these rats. In all hosts there were signs of hormonal activity. The tumors seemed to be both estrogenic and androgenic (Figs. 3, 4), with thick uterine horns, strong proliferation, stratification, and slight cornification of the vaginal epithelium in the female hosts, and growth and stimulation of the prostate and seminal vesicles in the male hosts.

**Ovarian transplants** also had taken and had been transformed to tumors in seven cases out of ten in males and in seven cases out of ten in females. Macroscopically they appeared the same as the testicular tumors. Microscopically (Figs. 5-7) they proved to be granulosa-cell tumors, very reminiscent of the testicular tumors. In females the granulosa tumor cells were small, with small nuclei.

Neither metastases nor other tumors were seen. The hormonal activity was similar in type and degree to that seen in hosts with testicular tumors, both estrogenic and androgenic (Figs. 8-10), with stimulation of uterus and vagina (proliferation, stratification, and slight cornification of the mucosa) in females, and of the prostate and seminal vesicles in the males.

**Hypophyseal + ovarian transplants** in all cases had grown and had been transformed to large tumors, bulging and destroying the eyes. These tumors were soft and richly vascularized. On the cut surface, there were bluish-red spots (blood-filled spaces) between solid yellowish or white parts. The follicles in the opposite eyes had also grown and had become tumors in all cases. Microscopically the combined hypophyseal-ovarian transplant had been transformed to a mixed hypophyseal-ovarian tumor (Fig. 11), a chromophobe hypophyseal adenoma, and a granulosa-cell tumor. In the opposite eye there was a pure granulosa-cell tumor (Fig. 12). The granulosa-cell tumor that was growing together with the hypophyseal adenoma was far bigger than that in the opposite eye, though of about the same histological picture. The mammary glands of these animals were strongly developed. The glands could easily be recognized. They were filled with a milky fluid. This was not found in the animals of the other series. Histologically an active picture with secretion could be seen (Fig. 13). In one animal a mammary tumor (30 X 30 X 10 mm.) had developed that histologically was a highly differentiated adenocarcinoma with wide ducts. Polymorphism and mitoses were seen. This mammary tumor was remarkable, since the mammary tumor frequency of this rat strain is very low.

In the vaginal mucosa, a picture of progestero-
genic activity with mucification, not seen in the animals of the other series, was detected (Fig. 14). Besides the progesterogenic activity there must have been estrogenic activity as well, because the vaginal epithelium was proliferated. The uterine horns were thick.

Hyphyseal transplants to intact or spayed females had taken in all cases (ten out of ten grafts) but had only grown slightly and had not formed tumors.

**DISCUSSION**

Chromophbic prolacting-producing adenomas of the anterior pituitary occur spontaneously in old rats but can also be experimentally induced by chronic administration of estrogens (1, 3, 6, and others). The prolactin causes hyperplasia of all elements of the mammary glands, in which milk secretion is induced (6).

It is probable that estrogen from the follicles placed beside the hypophyseal transplant in the present experiments had a stimulatory action on the hypophyseal cells, which then formed the hypophyseal chromophbic tumors. Direct circulatory connection between hypothalamus and hypophysis thus seems unnecessary for this action of estrogen.

A transplanted pituitary seems to have almost no other function than that of producing prolactin (see 15). This function has probably been accentuated in the present experiments with an ovarian transplant (stimulated by the spayed host own hypophyseal activity) beside the pituitary graft. Desclin (4) claims that the luteotrophic activity of a hypophyseal graft is considerably stimulated by estrogen.

In rats there is a positive correlation between the occurrence of spontaneous chromophbic hypophyseal adenomas and mammary tumors (13). Prolactin and prolactin-producing hypophyseal transplants or tumors have been strongly related to mammary tumor genesis in mice, besides the ovarian factors, estrogen and progesterone (see 15 and others). It is possible that in the present experiments a continuous increased prolactin production in the animals with combined hypophyseal-ovarian grafts to the anterior eye chambers is taking place. In addition, there must be an ample supply of steroid hormones from the induced granulosa-cell tumors. The remarkable development of the mammary glands and the occurrence of mammary carcinoma could thus be explained.

The growth of granulosa-cell tumors seems to be accelerated by hypophyseal adenomas, probably by prolactin. This hormone seems also to act locally on the tumor tissue, since the ovarian tumor growth was more pronounced near the adenoma than in the opposite eye without hypophyseal tissue. The type of hormone production of the granulosa-cell tumor is also changed to progesterogenic-giving vaginal mucification under the influence of prolactin. Although the morphology seems similar in different granulosa-cell tumors it is possible that the type of hormone produced may differ according to the prolactin-producing capacity of the hypophyses of the animals, thus explaining differences sometimes seen in target organs. According to the present experiments, there seems to be no certain relation between the cell type in the granulosa-cell tumors and the function, although there may be one between the rate of cell growth and the function. The steps in the biosynthesis of steroids from progesterone via androgens to estrogens might not all be made in rapidly growing tumor cells.

Testicular tumors of interstitial cells (Leydig cells) have been induced earlier, though only in mice, by prolonged administration of estrogens. Estrogen treatment gives impairment of spermatogenesis and tumors of intertubular primitive mesenchymal cells more or less similar to interstitial cells (for references see 7).

The induction of interstitial-cell tumors (in one case the tumor looked like a granulosa-cell tumor) in testicular grafts has been reported to be successful, but only in rats (2, 10, 17) after testes were grafted to the spleens of gonadectomized animals. However, in these tumors, sex hormones, if secreted, are largely inactivated in the livers of the hosts. Metastases have not been reported, and only a single subtransplant—to the spleen of a castrated rat—is reported to have grown successfully. This method is based on the principle that by castration the normal pituitary-testis balance is broken, with an excess secretion of interstitial cell-stimulating hormone from the hypophysis. The androgens produced by the intrasplenic testicular transplant are inactivated in the liver, the production of interstitial cell-stimulating hormone not being inhibited. In only about 50 per cent of animals tested with this procedure, however, have tumors been reported. The same induction mechanism may be postulated in the present experiments with intraocular testicular grafts that give a high percentage of testicular tumors 1 year after transplantation. With this method, the cryptorchid environment involved in the transplantation to the spleen is ruled out. Recent experimental evidence suggests that cryptorchism plays an important role in testicular tumor induction (8).

The intraocular micrografting technic also pro-
vides a method of studying the sex hormone production of the tumors formed. Estrogen production by the male gonad is well established, but the cell type that secretes testicular estrogen is uncertain. The intratubular Sertoli cells are most generally considered the primary source, but high levels of estrogens were found in the urine of a male dog bearing a Leydig-cell tumor (14). That the interstitial tumor may have a bisexual hormone production is confirmed by the present experiments. Estrogens as well as androgens seem to be produced. Androgen secretion from granulosa-cell tumors in rats has previously been suggested by Kullander (11) and Johnsson (9) and is confirmed in the present experiments.

Morphologically, the testicular tumors found were similar to the granulosa-cell tumors formed in ovarian transplants. Since granulosa-cell tumors in rats very probably may form from theca interstitial cells (12) and the testicular tumors seemed to rise from proliferation of interstitial cells—and both the ovarian and the testicular tumors produced both androgens and estrogens—it is tempting to postulate that in both types of gonads there are interstitial mesenchymal cells capable of forming tumors when influenced by increased amounts of hypophyseal gonadotrophins, and capable of a bisexual hormone production as well. Since progesterone is a probable intermediate in biosynthesis of both androgens and estrogens (5), progesterone secretion may also occur in the same cells by loss of inhibition of certain enzymes.

A disturbed “feed-back” mechanism may explain the tumor formation in both the ovarian and testicular micrografts, and it is probable that the pathogenesis of ovarian and testicular tumors is similar. When the tumors have developed and peripherally exert a strong hormonal effect, the situation is the same as in spontaneous gonadal tumors. Then the tumor cells may be independent of a raised blood level of hypophyseal gonadotrophins, since this is probably depressed by estrogens-androgens.

REFERENCES


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1 See also (16).
Fig. 5.—Ovarian tumor in a female host. 5μ. H. & E. ×200.
Fig. 6.—Ovarian tumor in a male host. 5μ. H. & E. ×200.
Fig. 7.—Compare Figure 6. The ovarian tumor in the opposite eye. 5μ. H. & E. ×200.
Fig. 8.—The vaginal mucosa in a female host with ovarian tumor. 5μ. H. & E. ×200.
A transplanted pituitary seems to have almost no other function than that of producing prolactin. Consequently, the hypophysis thus seems unnecessary for this action of estrogen.

Placed beside the hypophyseal transplants in the animals of the other series, was detected (Fig. 14). Besides the progesterogenic activity there must have been estrogenic activity as well, because the males had taken in all cases (ten out of ten grafts)remained inactive in the grafts to the spleens of gonadectomized animals. However, in these tumors, sex hormones, if secreted, are largely inactivated in the livers of the animals tested with this procedure, however, have not been reported. The same induction mechanism may be postulated in the present experiments.

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Fig. 9.—The ventral prostate lobe in a male host with ovarian tumor. 5μ. H. & E. X200.

Fig. 10.—The seminal vesicle in a male host with ovarian tumor. 5μ. H. & E. X200.

Fig. 11.—Hypophyseal-ovarian tumor. 5μ. Azan. X200.

Fig. 12.—Ovarian tumor in a female host with a hypophyseal-ovarian tumor in the opposite eye. 5μ. H. & E. X200.
The hypothalamus and hypophysis have a direct connection, which is essential for the production of prolactin. The function of estrogen in the mammary glands is not only limited to producing prolactin but also involves other functions such as hyperplasia of the anterior pituitary (see 15). This function has probably been accentuated in the present experiments with an ovarian transplant (stimulated by the spayed host's own hypophyseal activity) besides the pituitary graft.

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Fig. 13.—The mammary gland in a host with one hypophysial-ovarian and one ovarian tumor. 5μ. H. & E. X200.

Fig. 14.—The vaginal mucosa in a host with one hypophysial-ovarian and one ovarian tumor. 5μ. H. & E. X300.
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Chromophobie tumors and the function, although diminished, are largely inactivated in the livers of the animals, thus explaining the disappearance of estrogen from the blood. In only about 50 per cent of animals tested with this procedure, however, have tumors been reported. The induction of interstitial-cell tumors (in one instance the tumors looked like a granulosa-cell tumor) has been induced earlier, though only in rats (~, 10, 17) after testes were grafted to the spleens of gonadectomized animals. Metastases have not been reported, and it is probable that estrogen from the follicles is broken, with an excess secretion of interstitial cell-stimulating hormone from the hypophysis. The androgens produced by the intrasplenic testicular transplant are inactivated in the liver, the spleen is ruled out. Recent experimental evidence suggests that cryptorchism plays an important role in testicular tumor induction (8).

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