Spontaneous Testicular Tumors in Mice*

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Testicular interstitial cell tumors have appeared in estrogen-treated mice of at least three different inbred strains (1, 2, 11, 12, 13, 21), rarely in those of other strains treated in a comparable manner (2, 11, 21). Spontaneous testicular tumors were not described in those inbred strains that acquired such tumors subsequent to prolonged treatment with estrogens. In fact such tumors occur rarely in mice. Among 19,000 mice autopsied, of which approximately one-half were males, only 28 primary tumors of the testes were found (27). All except one of the 28 mice bearing a testicular tumor were from one family or its hybrids, an observation indicating a tendency to hereditary predisposition. Only one of the 28 tumors consisted of the interstitial cells of Leydig; the others were spindle cell sarcomas or composed "of cells closely resembling the epithelium of the seminiferous tubules arranged in alveolar structure."

Mice of the Strong A strain, when adequately treated with estrogens, show hypertrophy of the Leydig cells (1, 7, 8, 13) and finally testicular tumors composed largely of such cells. Estrogen-treated mice of several other inbred strains failed to show a hypertrophy of the Leydig cells, and testicular tumors rarely or never appeared. The tendency for such tumors to occur in estrogen-treated animals was thus strain-limited.

The question arises whether or not estrogen merely results in the attainment of potentialities for testicular neoplasia that are usually not realized. The appearance of spontaneous tumors among mice that would acquire a high incidence of tumors if estrogens were injected is reported here.

MATERIALS AND METHODS

In order to determine to some extent the mode of transmission of the tendency to develop testicular tumors, mice of the A strain were hybridized with mice of either the C57 or the C3H strain (24, 25). Because both male and female mice of the A strain were used four groups of hybrids were obtained as shown in Table I. Both males and females from the A strain transmitted the tendency to acquire testicular tumors to their estrogen-treated first generation hybrids, obtained by matings with mice of the C3H and C57 strains. The studies to be reported here are limited, however, to the untreated control mice of each group. A total of 61 untreated hybrid male mice from the four groups were observed throughout their lives. Twenty-four male mice of the A strain were studied also. All mice were maintained on Purina fox chow and water. The males were kept in cages with one or more males and females until the latter died. From that time on 3 to 5 males were kept together in one compartment. When the conditions of the animals indicated that death was imminent they were killed and an autopsy was performed. If the testes were grossly abnormal they were fixed in Bouin's fluid, sectioned, and stained with hematoxylin and trichosin.

OBSERVATIONS

In 3 of the 61 male mice from two of the four hybrid groups primary testicular tumors were discovered at autopsy. The tumorous testis of one of the mice of the A72 group killed when 810 days old was approximately twice the size of a normal testis (Fig. 1) and measured 1.2 cm. × 0.8 cm. The tumorous testis had a smooth surface and was of mottled yellow and brown color. The nontumorous testis had a smooth surface and was of normal size but contained no secretion; they did not differ from those of a number of other old mice of this group that had no testicular tumors.

<table>
<thead>
<tr>
<th>Group</th>
<th>Parental strains</th>
<th>Number of mice</th>
<th>Average age, days</th>
<th>Number of tumors</th>
<th>Age at death, tumors, days</th>
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<tr>
<td>AC1</td>
<td>A ♀ × C3H ♂</td>
<td>15</td>
<td>757</td>
<td>—</td>
<td>—</td>
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<tr>
<td>AC2</td>
<td>C3H ♀ × A ♂</td>
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<td>752</td>
<td>1</td>
<td>952</td>
</tr>
<tr>
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<td>A ♀ × C57 ♂</td>
<td>16</td>
<td>823</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>A72</td>
<td>C57 ♀ × A ♂</td>
<td>20</td>
<td>752</td>
<td>2</td>
<td>810–816</td>
</tr>
<tr>
<td>A</td>
<td>A ♀ × A ♂</td>
<td>24</td>
<td>514</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

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1 The mice from these strains were supplied by Dr. L. C. Strong.
The tumor was composed of two types of tissue. One part contained small cells, not unlike some non-vacuolated interstitial cells, and many macrophages, some containing a brown pigment similar to that observed frequently in the testicular interstitial tissues of estrogen-treated mice (Fig. 2). Another part, constituting approximately half the tumor, was composed of small round cells and cells resembling fibroblasts. Mitotic figures were abundant among the interstitial cells that formed the first mentioned portion of the tumor. Vestiges of seminiferous tubules were found near the periphery (Fig. 1). This tumor resembled more closely those neoplasias described as seminomas than the usual interstitial cell tumors. The nontumorous testis showed a few "brown cells" and small glandular interstitial cells with a granular cytoplasm. It appeared that Leydig cells were smaller and fewer than in the testis of other old mice.

The second testicular tumor in a mouse of the A72 group was small, only slightly enlarging the testis (Fig. 3). It was detected at autopsy as a hyperemic, yellow body in the proximal half of the testis. Histologically it consisted of large glandular cells with either a clear, vacuolated or a granular cytoplasm, and large vesicular nuclei containing one or two large nucleoli (Fig. 4). This tumor was histologically much like those described previously in estrogen-treated mice of the A, C, and JK strains. The tumor occupied a large part of the testis; the tubules remaining at the periphery contained few spermatids or spermatocytes. The nontumorous testis was similar to those of other old mice of the group, only a few small granular Leydig cells and "brown" cells representing the interstitial elements of interest at this time. The seminal vesicles were very large and distended with secretion.

The tumor arising in the mouse of the AC2 group occupied approximately half the testis and was observed upon gross examination in its mediastinal portion. The area of the tumorous nodule in which the tubules were entirely destroyed was extremely hyperplastic, and surrounded by a more fibrous tissue that widely separated the seminiferous tubules (Fig. 5). This tumor was composed of small cells with scanty cytoplasm and nuclei containing peripheral chromatin aggregates and one or two small nucleoli (Fig. 6). The growth was not sharply circumscribed; at the periphery it encompassed the more or less atrophic seminiferous tubules (Fig. 5). This tumor was composed of cells similar to those of the "third generation" described by Hooker and Pfeiffer (13) in their estrogen-treated mice.

Hyperplasiases or tumors of the interstitial cells sufficiently large to be detected upon gross examination were not observed in any testes of the mice of the A strain.

**DISCUSSION**

It has been observed by several investigators that estrogen-treated mice of some inbred strains acquire interstitial cell tumors of the testis. Although such tumors may occur also among untreated animals of some families of mice, as indicated by the work of Sley, Holmes, and Wells (22), no evidence has been reported that they will occur in mice of those strains or groups in which they appear when estrogens are injected. Testicular tumors have not been described among untreated mice of the A, C, and JK strains kept under the same conditions as those animals that, when given estrogen, acquired such tumors (1, 11, 21). The hybrid mice, however, survived 200 to 300 days longer on the average than their A strain parents (Table 1), and it may be that the increased longevity afforded an adequate period for the materialization of inherent tendencies that might be elicited precociously in estrogen-treated animals. Spontaneous testicular interstitial cell tumors tend to appear among aged animals (see reference 27 for literature).

The recent experiments on the induction of testicular interstitial cell tumors in inbred mice thus indicate that two influences are essential for the inception of such neoplasia; namely, the humoral environment maintained by estrogen injections and some genetic predisposition. The present observations reveal that the more vigorous and longer lived hybrid mice with an adequate genetic predisposition may acquire testicu-
lar tumors in the absence of extrinsic hormonal factors. Testicular neoplasias have not been observed among hybrid mice obtained by crossing mice of other inbred strains, although these animals were kept under similar conditions (9, 10).

Since the testicular interstitial cells atrophy after removal of the hypophysis their morphological integrity apparently depends upon the hypophysial hormones. It is probable that the estrogens act on the pituitary gland (14), the latter being more directly associated with the initiation of the hypertrophic and finally the neoplastic changes, a theory substantiated by the observation that a gonadotropic preparation, pregnant mare serum, induced local hyper trophy of the interstitial cells of mice of the A strain (18). The inherited factors that limit the testicular tumors to mice of certain strains may therefore involve peculiarities of either the testicular or hypophysial physiology or both.

The possibility that trauma might play an etiological role in testicular neoplasia in mice has been suggested (22) and should not be overlooked. Inguinal and scrotal wounds occur frequently during fights, especially between male mice. That lesions might have occurred in the testes of the mice that spontaneously developed testicular tumors is possible. At the time of death, however, evidence of such lesions was lacking. As far as is known experiments have not been undertaken in which controlled lesions have been made in the testes of animals of these strains. Maximow (15), however, observed abundant mitotic figures among the interstitial cells in the vicinity of sterile testicular lesions, indicating that trauma may incite proliferation. Ovarian grafts placed in the testes of mice of other strains may elicit an increase of interstitial cells among the damaged tubules that accompany such procedures (6).

The size and structure of the cellular elements of the spontaneous testicular neoplasia in these mice varied greatly, not only from one tumor to another but between different parts of the same growth. In some tumors islands of hematopoietic tissue have been observed (11). Interstitial cells have been described as arising from lymphocytes (16, 17), or more frequently from cells indistinguishable from fibroblasts (15, 17, 19, 26, 28). The undifferentiated cells from which the Leydig cells may arise may undergo changes in several directions. The glandular cells, hematopoietic cells, and macrophages may all have a common origin from undifferentiated intertubular elements.

The presence of "brown pigmented" cells in the testes of the old mice with and without testicular tumors, and among the peripheral cells of the tumors, has been mentioned previously (1, 3, 4, 5, 8, 11, 13). Such cells have been described in the testes of birds and mammals by several investigators and are found usually when there is evidence to indicate a regression of the testis (see reference 20 for review). In old mice the number of interstitial cells decreases as age advances (23), and as observed in the present study the brown pigment was found in the interstitial cells of old mice.

**SUMMARY AND CONCLUSIONS**

1. Testicular tumors arose in 3 of 61 untreated hybrid mice obtained by mating the animals of the A with those of the C3H and C57 strains. Two of these were interstitial cell tumors and histologically resembled those arising in estrogen-treated mice of similar origin. The third, composed of fibroblastic cells and small round cells, was probably an interstitial cell tumor but resembled a seminoma rather than the usual interstitial cell tumor.

2. Testicular tumors were not observed in untreated mice of the A strain, but these animals survived on the average 200 to 300 days less than their F1 hybrids.

3. It is possible that in mice of certain strains estrogens may act to reveal or augment tendencies to acquire testicular interstitial cell tumors that otherwise would not be attained during the usual life span.

**REFERENCES**


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