The Transformation of Rat Mammary Adenofibroma to Fibroma by Androgens*

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In the course of experiments on the hormonal factors influencing the growth and transplantability of mammary adenofibroma in rats (6) it was observed that in males the tumors often become pure fibromas, while in females the tumors retained their original adenofibromatous structure. The objects of the present experiments were, first, to determine the hormonal factors responsible for the fibromatous transformation; second, to determine the time required for the transformation to occur; and third, to determine the constancy of the phenomenon in different strains of transplantable adenofibroma.

Since these experiments were started other workers have reported changes in the morphology of mammary adenofibroma under various conditions. Thus, Heiman (3) reported a relative increase of fibrous tissue in adenofibromas growing in old males, in castrate females with or without gonadotropic hormone injections, and in castrate males receiving either gonadotropic or estrogenic hormone injections. Heiman (4) also reported inhibition of the glandular components of adenofibroma by large doses of androgens. Murphy et al. (8) found that estrogens failed to prevent the fibromatous transformation of adenofibroma growing in males.

EXPERIMENTAL

Grafts of actively growing tumor tissue 8-10 mm. in diameter, obtained from 11 different strains of transplantable mammary adenofibroma were implanted in the left groin of the following groups of rats: (a) normal young mature males and females, (b) castrates of both sexes with or without gonadotropic hormone injections, and in castrate males receiving either gonadotropic or estrogenic hormone injections. Heiman (4) also reported inhibition of the glandular components of adenofibroma by large doses of androgens. Murphy et al. (8) found that estrogens failed to prevent the fibromatous transformation of adenofibroma growing in males.

Estrogen-injected groups received 6 rat units of Amniotin 1 in oil every other day starting 2 days before implantation and continuing for the duration of the experiment. Androgen-injected groups received 0.25 mgm. of testosterone propionate 2 in oil twice a week starting 2 days before tumor implantation and continuing for the duration of the experiment.

The implants were left in their hosts for intervals varying from 3 to 76 weeks. Specimens from viable parts of the growing tumors were then removed for microscopic study.

RESULTS

The presence of androgenic hormone proved to be the main factor responsible for the transformation of adenofibroma to fibroma, but for the change to occur the tumor usually had to be exposed to this hormone for 25 or more weeks. Thus, in 47 "androgen-present" rats (normal males and androgen-injected castrates) transformation to fibroma occurred in 28 or 59.6 per cent after a period of 25 or more weeks, but in 18 similar rats in which the tumor was exposed to the androgens for a period of 3 to 25 weeks the incidence of fibroma development was only 27.8 per cent. (Table I.) Although the fibroma-producing effect of physiological amounts of androgens is delayed it is quite abrupt after about 25 weeks and it is for this reason that the results are grouped under the headings of "3-25 weeks" and "25-76 weeks" in Table I.

In the absence of androgenic hormone, adenofibroma only rarely underwent fibromatous change. Thus, fibroma developed in none of 37 "androgen-absent" rats (normal females, castrates, and estrogen-injected castrates) in the "3-25 week" group and in only 3 of 49 similar rats in the "25-76 week" group (Table I). The 3 instances of fibromatous change in the latter group occurred in 2 castrate males and 1 castrate female, and in each of these cases the tumor had grown very little, if at all, since implantation, suggesting that the unfavorable growth conditions had caused

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1 Amniotin was supplied by Dr. John Anderson of E. R. Squibb & Sons.
2 Testosterone propionate was supplied by Dr. Erwin Schwenk of the Schering Corporation.
epithelial atrophy but that the more resistant fibrous elements had not yet become nonviable. That the fibromatous transformation produced by androgens is not due to inhibition of the tumor as a whole is indicated by two findings: first, the microscopic structure of the resulting tumor is that of an actively growing cellular fibroma, and second, the rate of growth of the tumors becoming fibromatous is as great as that of those retaining the adenofibromatous structure. Thus, the average diameter, at 26 weeks, of 19 tumors which had become fibromas in male or androgen-injected hosts was 3.5 cm., while the average diameter of 42 tumors which remained adenofibromatous was 3.2 cm.

To test this possibility, testosterone propionate in biweekly doses of 0.25 mgm. was injected into 4 castrate males and into 4 castrate females for 30 weeks. The result as shown by whole mounts and microscopic sections of the mammary glands was stimulation of mammary epithelium in the females in almost the same degree as in the males. There was no evidence of inhibition of the female mammary epithelium, and therefore the retardation of the epithelium of adenofibromas cannot be due to a sex difference in the response of mammary epithelium to androgens.

Another possible explanation of the transformation to fibroma by androgen is based on the differential response of the various mammary gland elements to the hormone. Thus, as Astwood and Geschickter (1) have pointed out, the androgens stimulate a characteristic type of acinar development with no stimulation of the duct tree itself. The fact that the epithelium of adenofibroma is largely of duct origin may well account for the lack of stimulation by androgens. However, there is no demonstrable inhibition of normal mammary duct epithelium by androgens and hence the inhibition of adenofibroma epithelium is not satisfactorily explained on this basis.

The possibility that androgens may cause a slight stimulation of the fibrous components of adenofibroma causing them to crowd out the epithelium was considered. However, since mammary glands which had been stimulated by androgens for long periods showed no tendency to fibrosis, this explanation is untenable. Moreover, the fact that androgens had little or no stimulatory effect on transplanted mammary fibroma (7) is further evidence against this explanation.

Therefore, at present no adequate explanation based on normal mammary physiology can be given for the

<table>
<thead>
<tr>
<th>Androgen-present groups</th>
<th>Interval: 3-25 weeks</th>
<th>Number of rats receiving implants</th>
<th>Fibromatous transformation No.</th>
<th>Per cent</th>
<th>Interval: 25-76 weeks</th>
<th>Number of rats receiving implants</th>
<th>Fibromatous transformation No.</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal males</td>
<td>12</td>
<td>4</td>
<td>33.3</td>
<td></td>
<td>33</td>
<td>19</td>
<td>57.6</td>
<td></td>
</tr>
<tr>
<td>Testosterone-injected castrate males</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>7</td>
<td>61.6</td>
<td></td>
</tr>
<tr>
<td>Testosterone-injected castrate females</td>
<td>1</td>
<td>100.0</td>
<td>1</td>
<td>2</td>
<td>66.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: Androgen-present groups</td>
<td>18</td>
<td>5</td>
<td>27.8</td>
<td>47</td>
<td>28</td>
<td>59.6</td>
<td></td>
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</tr>
</tbody>
</table>

The tendency for the 11 different strains of adenofibroma to change to pure fibroma by the action of androgens varied from zero to 100 per cent. However, the tumors of each strain showed some relative increase in fibrous tissue after prolonged androgenic action. Therefore, while complete transformation to fibroma occurred in only 59.6 per cent after 25 weeks or more, a tendency for at least partial fibromatous change occurred in practically every instance.

**DISCUSSION**

The fact that androgenic hormone stimulates rather than retards the epithelium of the normal rat mammary gland (5, 11) makes it difficult to understand how this hormone can cause the disappearance of the epithelium of mammary adenofibroma, a tumor which ordinarily responds like the normal gland to hormonal influences (6).

Since all the adenofibromas were originally derived from females, the possibility was considered that epithelium derived from female mammary glands might react to androgens in a manner different from that of epithelium from male mammary glands. To test this possibility, testosterone propionate in biweekly doses of 0.25 mgm. was injected into 4 castrate males and into 4 castrate females for 30 weeks. The result as shown by whole mounts and microscopic sections of the mammary glands was stimulation of mammary epithelium in the females in almost the same degree as in the males. There was no evidence of inhibition of the female mammary epithelium, and therefore the retardation of the epithelium of adenofibromas cannot be due to a sex difference in the response of mammary epithelium to androgens.

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Therefore, at present no adequate explanation based on normal mammary physiology can be given for the
Effect of Androgens on Adenofibroma

fibromatous transformation of adenofibroma by androgens. It would seem that in the process of becoming neoplastic the epithelium of rat adenofibroma becomes sensitive to an inhibitory effect of androgenic hormone.

That the effects of androgens are exerted upon the mammary structures through the mediation of the anterior pituitary gland is probable (9, 10), but since in these experiments the pituitary gland was always present it is permissible to speak of an androgenic effect upon the mammary gland even though it is conceded to be an indirect effect.

A clinical observation of interest is that benign mammary tumors in males tend to be predominantly fibrous while in females epithelial tumors predominate (2, 12). On the basis of the present experimental findings it may well be that the frequency of fibrous tumors in males is the result of the inhibition of the glandular components of fibro-epithelial tumors by androgenic hormone. Of some 400 benign mammary tumors studied in this laboratory all occurred in females with 1 exception and in this male the tumor was a pure fibroma.

While the complete obliteration of 1 component of a mixed tumor by a hormone is of fundamental interest, the phenomenon has no value in the treatment of adenofibroma since the remaining fibromatous component continues to grow unabated. There is the possibility, however, that the prolonged action of androgens upon pure adenoma of the mammary gland may produce complete regression of this tumor. Further experiments to test this hypothesis are in progress.

SUMMARY AND CONCLUSIONS

1. Androgenic hormone tends to transform mammary adenofibroma to pure fibroma in rats.
2. After 25 or more weeks of exposure to physiologic amounts of androgens fibromatous transformation of adenofibromas occurred in 28 of 47 rats (59.6 per cent) and partial transformation took place in the rest. Less than 25 weeks' exposure produced relatively little change in tumor histology.
3. Adenofibroma was never transformed to fibroma in females or in estrogen-injected castrates, and only rarely so in untreated castrates.
4. The fibromatous transformation produced by androgens does not depend upon inhibition of the growth of the tumor as a whole.
5. Different strains of adenofibroma vary in the degree to which they respond to the fibroma-producing influence of androgens.
6. No adequate explanation based on normal mammary physiology was found for the transformation of adenofibroma to fibroma. Only when the mammary epithelium is a part of a benign mammary tumor does it become sensitive to the inhibitory effect of androgenic hormone.

REFERENCES

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