Estrogen Receptor in Normal and Neoplastic Mouse Mammary Tissues

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SUMMARY

The soluble cytoplasmic fractions of lactating mammary glands, parenchyma-free mammary fat pads, and spontaneous and transplanted mammary tumors from a number of inbred mouse strains were assayed on sucrose density gradients for their specific estradiol-17β-3H-binding capacities. There is no apparent correlation between the susceptibility of a strain to mammary tumor development and the ability of its normal mammary gland receptors to bind estradiol. The receptor appears to be in the parenchymal elements of the gland. The spontaneous mammary tumor showed binding capacities significantly lower than the normal gland, based on wet weight tissue and DNA content. There is no correlation between the binding capacity of a tumor and that of the normal glands from the same strain. Spontaneous mammary tumors appeared to maintain whatever receptor binding capacity they had, when transplanted for one generation into normal or ovariectomized syngeneic hosts.

INTRODUCTION

Hormones have an important role in the tumorigenic process in a variety of target tissues (22). However, the exact nature of the role of hormones in this process is as yet unknown. Estrogen is known to be involved in mouse mammary tumorigenesis (12). Estrogen apparently has both a direct effect on the mammary cell (3) and an indirect effect through its ability to cause release of prolactin from the adenohypophysis. Prolactin is known to be necessary for mammogenesis and lactogenesis in the mouse (17) and has been implicated in mouse mammary tumorigenesis (16).

Mammary tumors can be classified as ovarian hormone-dependent or -independent, depending on their growth response to ovariectomy. In humans about 30% of the carcinomas of the breast are described as hormone-dependent, in that they show remission after endocrine ablative therapy (5).

Studies on the mechanism of action of steroid hormones lead to the concept of the steroid receptor; according to this, cells responsive to a given steroid(s) contain specific, high-affinity, steroid-binding proteins called receptors (9). The levels of receptor in any target tissue tend to parallel the sensitivity of the tissue to the hormones. The presence of cytoplasmic estrogen receptors has been reported for both normal and neoplastic mouse mammary tissue (23, 24, 29, 30, 34), from a limited number of mouse strains. Many previous investigators have attempted to find a correlation between some measurable physiological phenomenon and the mammary tumor incidence in different mouse strains (27). However, no physiological phenomenon has been shown to correlate well with the tumor incidence. Conceptually, it appears possible that genetically controlled differential hormone sensitivity of the mammary tissue might be one of the factors determining strain difference in mammary tumor incidence. The recent development in the concept of steroid receptors suggests the possibility that the mammary tissue sensitivity to a hormone may be correlated with its receptor levels. With this in mind a series of studies was undertaken to analyze the cytoplasmic estrogen receptors in normal and neoplastic mammary tissues of different strains of mice. The specific purposes for these studies were the following. (a) Are there quantitative differences in estrogen receptor levels in the normal mammary tissue of mice of strains differing in their susceptibility to mammary cancer development? In addition experiments were conducted to determine whether the estrogen receptors are located in the parenchymal and/or stromal elements of the mammary tissues, since the mammary tumors originate from the parenchymal elements. (b) Are there estrogen receptors in the spontaneous mammary tumors from different mouse strains and does any correlation exist between the quantities of receptor in the normal mammary tissues and in the tumors originating from it? Attempts were also made to determine the fate of these receptors in tumors following transplantation into ovariectomized hosts.

MATERIALS AND METHODS

Mice. All mice were from the colony of the Cancer Research Laboratory. The origin and mammary tumor incidence of these strains of mice has been described previously (18, 33). The following strains and hybrids were used: C-3; C*; 1; C57BL; C57BL X I F1; GR; RIII; and C3H. Among these strains C57BL, I, C57BL x I F1, and C-3 mice are considered

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to be free of MTV. However, C57BL and I mice are highly resistant to mammary tumor development while C57BL × I F₁ and C⁻ mice are highly susceptible, since introduction of MTV results in high mammary tumor incidence only in the latter group of mice. The remaining strains are all infected naturally with different variants of MTV and are highly susceptible to mammary tumor development.

**Tissue Sources.** Lactating mammary glands (2nd, 3rd, and 4th pairs) were obtained from primiparous, 7- to 10-day postpartum females which were 4 to 8 months old at the time of sacrifice. The lymph nodes were removed from the glands.

Parenchyma-free mammary fat pads were obtained by removing the parenchymal elements of 3-week-old C⁻ females which were later bred, and their fat pads were used on the 7th to 10th day postpartum (7). Spontaneous mammary tumors were obtained from all of the above strains except I and C⁻, from which no tumors were available during the course of the study. In order to obtain the transplanted tumors, 1-sq mm pieces of 4 spontaneous mammary tumors (2 from RIII, 1 each from C3H and GR) were transplanted s.c. into intact and ovariectomized 4-week-old female syngeneic hosts. Host animals were palpated biweekly. Pieces of all tumors were fixed in Tellesniczky's solution, sectioned, and stained with hematoxylin and eosin.

**Sample Preparation and Sucrose Density Gradient Analysis.** All tissue samples were placed in cold 0.01 M Tris buffer, pH 7.4 cut into small pieces and washed 3 times with the buffer. The tissue was weighed and then homogenized in a ground glass Duall-23, conical homogenizer (Kontes Glass Co., Vineland, N. J.) at 4°, with an appropriate volume of the Tris buffer to yield a wet weight tissue per ml homogenate concentration of 330 mg for normal lactating glands and 500 mg for tumors. The DNA content of the homogenate was estimated by the method of Webb and Levy (35) using calf thymus DNA as the standard. The homogenates were centrifuged at 12,000 × g at 4° for 30 min, and the resulting supernatants were collected. The protein concentration of the supernatants was estimated by the method of Lowry et al. (13) using bovine serum albumin as the standard.

Varied quantities of the appropriate hormone(s) were mixed with 0.4-ml aliquots of the supernatant and incubated at 4° for 1 hr. The mixture was layered on 5 ml 0.01 M Tris 0.015 M EDTA, pH 7.4, linear 10 to 30% sucrose gradients and centrifuged at 240,000 × g in a SW 50.1 rotor with a Beckman L2-65B (Beckman Instruments, Inc., Fullerton, Calif.) ultracentrifuge for 15 hr at 4°. The gradients were fractionated from the bottom into scintillation vials to yield 35 equal fractions. To each vial were added 3 ml of 100% ethanol and 10 ml of scintillation fluid (5 g PPO per liter toluene). The samples were counted in a Beckman LS-250 liquid scintillation counter at a counting efficiency for ³H of 52%. Beef liver catalase (11.3 S) was used as a sedimentation marker and its location in the gradient was determined by the method of Beers and Sizer (2). From the location of the catalase, the S values for other parts of the gradient were determined by the method of Martin and Ames (14).

**Enzymatic Treatment.** DNase, RNase, and Pronase (Sigma Chemical Co., St. Louis, Mo.) were all dissolved in 0.01 M Tris buffer and used at a concentration of 250 μg/ml. An aliquot of the supernatant was incubated at 4° with each of the enzyme preparations and simultaneously estradiol-17β-³H (40 Ci/mmol; New England Nuclear, Boston, Mass.) of a known concentration was added. The incubation with DNase also contained 8 mM MgCl₂. After 1 hr of incubation, the samples were assayed on sucrose gradients as described above.

**RESULTS**

The sucrose density gradient analysis of the normal lactating gland (Chart 1) showed that there were 2 estradiol-³H binding peaks, one in the 8 S region which saturated at an estradiol concentration of 3 to 9 nM, and one in the 4 S region, which did not saturate with the highest concentration of estradiol used (0.1 μM).

The hormone specificity of the 8 S binding was confirmed by a series of competition experiments. Supernatant samples of normal lactating gland were incubated with a saturating concentration of estradiol-³H and a 100- or 1000-fold greater concentration of an unlabeled estrogenic compound or a nonestrogenic steroid known to have an effect on the mammary gland. Charts 2 and 3 show that only unlabeled estradiol, diethylstilbestrol, and [(1-2-p-[9p-methoxy-
Chart 2. Sucrose density gradient analysis of the specificity of estradiol-17β-3H binding by the soluble fraction. Competition with nonestrogenic steroids. The soluble fraction of C± lactating mammary tissue was incubated at 4° for 30 min with: estradiol-17β-3H (3 nM), *, estradiol-17β-3H (3 nM) and aldosterone (1 μM), ○; estradiol-17β-3H (3 nM) and progesterone (1 μM), □; estradiol-17β-3H (3 nM) and hydrocortisone (1 μM), ×; estradiol-17β-3H (3 nM) and testosterone (1 μM), ♦. Sample (0.3 ml) was layered on 5 ml 0.01 M Tris, 10 to 30% sucrose density gradient and centrifuged at 240,000 X g for 15 hr at 4°. Beef liver catalase was used as a sedimentation.

Specific estradiol-3H binding was thus taken as the cpm under the 8 S binding peak in the gradient. From these data Scatchard (26) plots were made to estimate the Kdis value and the molar concentration of binding sites present. Chart 5 shows a typical Scatchard plot, obtained from normal lactating and neoplastic mammary tissues. The binding capacity of the normal lactating tissue was expressed as moles of binding sites per mg, wet weight, of tissue and as moles of binding sites per Hg DNA. Assays of the protein concentration in the supernatants revealed that the ratio of mg, wet weight, tissue per ml homogenate to mg soluble protein per ml homogenate was 15.35 ± 1.5. An estimate of the number of binding sites per cell was also made by using 6.6 pg of DNA per cell nucleus (6).

In an attempt to determine whether the stromal elements of the mammary gland had an estrogen receptor, parenchyma-free fat pads from 7- to 10-day postpartum C± mice were assayed for estradiol-3H binding, along with the normal glands from the same animal. As can be seen in Chart 6, the parenchyma-free fat pads showed no detectable binding, but the gland-filled pads showed a normal binding profile. A comparison of estradiol-1H binding in the normal lactating glands of the various mouse strains used showed that all the sucrose density gradient patterns were similar to that seen in Chart 1. Table 1 shows the binding capacity and the Kdis values for the normal lactating and neoplastic mammary tissues of the mouse strains used. The Kdis values for the normal lactating glands were all similar, ranging from 2.8 to 5.4 x 10^-10 M. Statistical analysis by the Mann-Whitney U test (31) revealed that the binding capacities of lactating mammary tissue from C±, C*, C57BL, C57BL × I F1, and C3H mice were not significantly different from each other. Similarly, there was no significant difference in the estradiol-binding capacities of lactating mammary tissues from I, GR, and RIII mice. There was, however, significant difference (p < 0.05) in the binding capacities of lactating mammary tissues from these 2 groups of mouse strains.

A comparison of estradiol-3H binding (Chart 7) in spontaneous mouse mammary tumors showed that there were also 2 binding peaks, similar to those seen in the normal lactating gland. The 8 S peak saturated at an estradiol concentration between 3 and 9 nM, and the 4 S peak did not saturate at the highest concentration used (specific binding was again taken as the cpm under the 8 S peak). From these data Scatchard plots were made to estimate the Kdis values...
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Chart 4. Sucrose density gradient analysis of the effect of enzymes on the estradiol-17β-3H binding by the soluble fraction of C+ lactating mammary gland. The soluble fraction was incubated at 4°C for 30 min with: estradiol-17β-3H (3 nM), •; estradiol-17β-3H (3 nM) and DNase (250 µg/ml), ○; estradiol-17β-3H (3 nM) and RNase (250 µg/ml), △; estradiol-17β-3H (3 nM) and pronase (250 µg/ml), •. Sample (0.2 ml) was layered on a 5 ml 0.01 M Tris, 10 to 30% sucrose density gradient and centrifuged at 240,000 X g for 15 hr at 4°C. Beef liver catalase was used as a sedimentation standard.

and the molar concentrations of binding sites. Chart 5 shows the Scatchard plot for neoplastic and normal lactating mammary tissues. As with the normal lactating tissue, the binding capacity of the tumor was expressed as moles of binding sites per mg, wet weight, tissue and as moles of binding sites per µg DNA. Table 1 shows the binding capacity and the Kdₘₜ values for the neoplastic and normal lactating tissues of the mouse strains used. The Kdₘₜ values for all the tumors were effectively the same as those of the normal lactating tissues, ranging from 3 to 6.5 x 10⁻¹⁰ M. However, the binding capacity values for the tumors were lower and varied more than those for the normal lactating tissue, ranging from undetectable to about 50% of that of the normal lactating gland.

The following experiments were undertaken to determine whether the receptor concentration of the primary tumor correlated with its ability to grow in ovariectomized animals and to see whether growth in ovariectomized animals in any way affected the receptor concentration. Portions of 4 primary mammary tumors (RIII 1 and 2, GR 20, C3H 300), were assayed for their binding capacities and the rest were transplanted, as described above, into syngeneic hosts. In all cases the transplants grew well in both the ovariectomized and the intact control animals. However, different growth rates were observed for the different tumor transplants. Tumors grew in 18 of 18 ovariectomized animals and in 35 of 36 intact controls. The fastest growing was the RIII 2 tumor, which took approximately 43 days to reach 20 sq mm, and the slowest growing was the GR 20 tumor which took approximately 80 days to reach the same size. When the tumors reached a size of approximately 20 sq mm, they were removed and their binding capacities were assayed. The results can be seen in Table 2. Of the 4 primary tumors used, RIII 1 had the highest binding capacity and C3H 300 the lowest. The binding capacities of transplanted RIII 1 tumors derived from both intact and ovariectomized hosts were similar to that of the values obtained from the primary tumor. The binding capacity of RIII 2 transplanted tumor developing in the ovariectomized hosts was effectively similar to that of the primary tumor. However, the value for the transplanted tumors that developed in intact hosts was significantly higher (p<0.05). With the transplanted tumor GR 20, from intact hosts, the binding capacity value was lower than that of the primary tumor. The same tumor growing in ovariectomized hosts showed a higher binding capacity compared to the tumor transplants from intact hosts. These values were, however, not significantly different from the value of the primary tumor. Finally, the binding capacity value of the primary tumor C3H 300 was so
DISCUSSION

The results show that the lactating mammary glands of all the mouse strains studied have a specific 8 S cytoplasmic estrogen receptor similar to that reported for the mouse uterus (1, 9) and mammary gland (24, 28, 30). The 8 S receptor is primarily associated with the epithelial portion of the gland and not the fat cells or connective tissue. The epithelial elements are the secretory component of the gland and make up about 80% of the lactating gland (21). It is from the epithelial components that the mouse mammary carcinoma arises. Although the parenchyma-free fat pad of a lactating mouse may not be at the same physiological state as the normal lactating gland fat pad, it served as the best control available to confirm that effectively all the receptor binding being measured was from the parenchymal elements in the gland.

There were no correlations between the levels of estrogen receptor in the lactating mammary tissue and the tendency of a strain to develop mammary cancer. For example, I mice had the lowest binding capacity (45 X 10^-17 mole/µg DNA) of those strains studied and C57BL mice had one of the highest (120 X 10^-17 mole/µg DNA), yet both are known to be highly resistant to mammary tumor development. The C57BL X I F1 hybrid, which is very susceptible to mammary tumor induction (19), has a binding capacity value (90 X 10^-17 mole/µg DNA) intermediate to the parental strains. The fact that this hybrid had an intermediate value and the fact that there were statistically significant differences between the binding capacities of the strains studied suggest that genetic factor(s) may be involved in determining the level of estrogen receptor in the normal mouse mammary gland. There is little current information on factor(s) regulating the receptor levels in a given tissue.

The sensitivity of a target tissue to the steroid hormone is probably proportional to the concentration of receptor present (1). The binding capacity values for the different strains probably represent the sensitivity of their mammary cells to estrogen, but in light of the involvement of other hormones, viruses, and immunological factors (20) in mouse mammary tumorigenesis, estrogen receptor levels alone need not correlate with tumor incidence.

The results show that the tumor of all the strains studied have an 8 S estrogen receptor similar to that of the normal lactating mammary gland and are also similar to those in the rat (11, 15, 36) and human (10, 32) mammary tumors. The 4 S region of the sucrose density gradient did not show saturation even at estradiol-3H concentrations as high as 90 nM. There have been reports of specific 4 S receptors in some human mammary tumors (11); however, no specific 4 S component were observed in our study.

All of the tumors assayed had binding capacity values lower than that of the normal lactating gland. This was seen to range widely from a rare high of near 50% of normal value to a few cases of no detectable binding. Thus no correlation was found between the binding capacity value of the normal lactating tissue of a strain and that of the tumor originating from it. Similar binding patterns have also been observed in the rat (36).

From the transplantation experiments it was apparent that the absence or presence of the estrogen receptor had no effect on the ability of the tumor to grow in normal or ovariectomized syngeneic hosts. The different growth rates of the tumors are apparently controlled by factors not related to the receptor levels, since there was no correlation between the growth rate of the tumor and its receptor content. After growth in normal or ovariectomized hosts, the transplanted tumors maintained their basic morphology and had binding capacity values effectively unchanged from that of the primary tumor. The 1 exception was the RIII 2 tumor. The primary
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Table 1
Estimates of the estradiol-17β-3H-binding capacities of the normal lactating and neoplastic mouse mammary tissues

See text for details.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Tissue</th>
<th>Estradiol-17β-3H binding capacity (10⁻¹⁷) X (moles/mg tissue)</th>
<th>Estradiol-17β-3H binding capacity (10⁻¹⁷) X (moles/μg DNA)</th>
<th>Estradiol-17β-3H binding capacity (10⁻¹⁵) X K₅₀ M⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>C⁻</td>
<td>N²  (22)</td>
<td>155.0 ± 60.0°</td>
<td>154.0 ± 60.0°</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>T-not available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C⁺</td>
<td>N−primiparous (12)</td>
<td>95.3 ± 9.0</td>
<td>90.0 ± 8.0</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>N−multiparous (5)</td>
<td>135.6 ± 58.0</td>
<td>128.0 ± 54.0</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>T (8)</td>
<td>15.6 ± 7.6</td>
<td>4.1 ± 2.0</td>
<td>5.9</td>
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<tr>
<td>C57BL</td>
<td>N (7)</td>
<td>180.0 ± 105.0</td>
<td>120.0 ± 70.0</td>
<td>3.5</td>
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<tr>
<td></td>
<td>T (4)</td>
<td>14.3 ± 8.8</td>
<td>3.7 ± 2.3</td>
<td>6.5</td>
</tr>
<tr>
<td>I</td>
<td>N (6)</td>
<td>93.0 ± 4.1</td>
<td>45.0 ± 2.0</td>
<td>3.8</td>
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<td></td>
<td>T-not available</td>
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<td></td>
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<tr>
<td>C57BL × 1 F₁</td>
<td>N (10)</td>
<td>139.0 ± 61.0</td>
<td>90.0 ± 40.0</td>
<td>3.4</td>
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<tr>
<td></td>
<td>T (4)</td>
<td>12.0 ± 2.2</td>
<td>3.2 ± 0.6</td>
<td>5.4</td>
</tr>
<tr>
<td>GR</td>
<td>N (19)</td>
<td>87.0 ± 33.0</td>
<td>57.0 ± 22.0</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>T (8)</td>
<td>32.0 ± 23.0</td>
<td>8.4 ± 6.0</td>
<td>3.0</td>
</tr>
<tr>
<td>C3H</td>
<td>N (6)</td>
<td>106.0 ± 18.0</td>
<td>95.0 ± 17.0</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>T (9)</td>
<td>23.9 ± 16.0</td>
<td>6.3 ± 4.3</td>
<td>6.0</td>
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<tr>
<td>RIII</td>
<td>N (6)</td>
<td>63.0 ± 28.0</td>
<td>58.0 ± 26.0</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>T (12)</td>
<td>24.5 ± 13.0</td>
<td>6.4 ± 3.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

aN, normal lactating; T, neoplastic.
bNumbers in parentheses represent number of samples.
cMean ± S.E.

tumor had a binding capacity of 3.3 X 10⁻¹⁷ mole/μg DNA. The tumors from the ovariectomized hosts had effectively the same value while the transplants from the intact hosts had a significantly higher binding capacity value. The range of values for this latter group was 4.8 to 15.4 X 10⁻¹⁷ mole/μg DNA with a mean of 9.7 X 10⁻¹⁷ mole/μg DNA. Whether there was a selection in the normal hosts for tumor cells with a higher receptor content or whether there was an experimental error in estimating the binding capacity value of the primary tumor is not certain. If it were selection, it might be expected that the tumor cells with the receptors would grow at a different rate in the normal hosts compared to those in the ovariectomized hosts; however, this did not occur.

Tumors are known to be heterogeneous for almost any of the examined differentiated functions of the normal tissue (27). The fact that the tumors had the 8 S receptor, yet always at a level below that of the normal gland, suggested that there was a decrease in either the receptor content per cell or the number of cells with a normal receptor content. This point cannot be resolved until autoradiographic studies are carried out.

The transplantation studies confirmed that the mouse mammary tumor is ovarian independent for its growth. The fact that the tumors transplanted in ovariectomized animals maintained their receptor levels indicates that estrogen is probably not involved in the maintenance of the receptor.

4° for 30 min with the following concentrations (nM) of estradiol-17β-3H: 0.4, 0.9, 0.3, 9.0, 90.0, 5. Sample (0.3 ml) was layered on 5 ml of 0.01 M Tris, 10 to 30% sucrose density gradient and centrifuged at 240,000 X g for 15 hr at 4°. Beef liver catalase was used as a sedimentation standard.
Table 2
Estimates of the estradiol-17β-3 H-binding capacities of primary and transplanted mouse mammary tumors

Tumors were transplanted into intact or ovariectomized host.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Tissue</th>
<th>Estradiol-17β-3 H binding capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(10⁻¹⁷) x (moles/ mg tissue)</td>
</tr>
<tr>
<td>RIII</td>
<td>Tumor 1 (1)°</td>
<td>34.9</td>
</tr>
<tr>
<td></td>
<td>Transplanted N° (4)</td>
<td>26.7 ± 13.6e</td>
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<tr>
<td></td>
<td>Transplanted OV (2)</td>
<td>27.4 ± 3.7</td>
</tr>
<tr>
<td>RIII</td>
<td>Tumor 2 (1)</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>Transplanted N (5)</td>
<td>31.3 ± 15.9</td>
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<tr>
<td></td>
<td>Transplanted OV (5)</td>
<td>16.6 ± 6.9</td>
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<tr>
<td>GR</td>
<td>Tumor 20 (1)</td>
<td>13.2</td>
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<tr>
<td></td>
<td>Transplanted N (5)</td>
<td>10.6 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>Transplanted OV (4)</td>
<td>12.7 ± 5.4</td>
</tr>
<tr>
<td>C3H</td>
<td>Tumor 300 (1)</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Transplanted N (7)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Transplanted OV (2)</td>
<td>3.9 ± 3.8</td>
</tr>
</tbody>
</table>

° Numbers in brackets represent the number of samples.
° N, intact; OV, ovariectomized.
° Mean ± S.E.

Similar results were found in ontogeny studies of estrogen receptor in the rat uterus (4).

Attempts to correlate the tumor incidence of a strain or the hormone dependency of the mammary tumors with some physiological characteristic such as receptor levels makes the assumption that the population of cells being studied is homogeneous with respect to the characteristic being measured. However, measurement of a physiological characteristic gives a value that may represent the average of a heterogeneous population. It may well be that the cells giving rise to tumors or the cells capable of growing within a tumor represent the extremes of the heterogeneous distribution. If such is the case, trying to correlate response or sensitivity with quantitative values may not resolve one population from another. Thus the ultimate approach may be to analyze the receptors on the individual cell level.

ACKNOWLEDGMENTS

We wish to thank John King, Walter Jackson, and Mitchell Webb for their expert technical assistance. We are also thankful to John Underhill and Emily Reid for photography and for the preparation of the charts, respectively.

REFERENCES


Fig. 1. a, photomicrograph of the primary mammary tumor RIII 1. b, photomicrograph of the RIII 1 tumor after the 1st transplant generation. It has maintained its basic morphology. H & E, x 400.
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