The Relationship of the Inherited Hormonal Influence to the Production of Adrenal Cortical Tumors by Castration

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The work of Loeb (21, 22), Cori (6, 9) and Murray (23, 24) demonstrated that ovariectomy of mice in certain stocks at an early age was associated with a reduction in incidence of spontaneous mammary tumors. Hyperplasia and/or adenoma of the adrenal cortical cells in castrated male and female mice was later described in several inbred stocks (dba, ce, C3H, CBA, NH, Balb) (13, 14, 27, 29). The altered adrenal cortical cells in the castrated mice were linked with gross and histological evidences of estrogenic stimulation of the mammary glands, uterus and vagina. Dorfman and Gardner (10) supported the evidence of physiological activity of adrenal tumors in studies upon ovariectomized mice of the NH strain in which the urinary output of estrogenic substances was increased approximately 4 times over that found in the intact female. Transplants of adrenal tumors (32) and the structure of the submaxillary gland (30) in castrated mice of the extreme dilution stock demonstrated that secretions from the adrenal lesion also contained compounds with androgenic activity.

The presence of the adrenal lesions in castrated mice was not correlated with the occurrence of mammary tumors in the stocks mentioned above, in spite of the fact that the original observation of the adrenal lesion occurred coincidentally with the unexpected appearance of mammary tumors in castrated mice (27). The development of mammary tumors in mice is known to be influenced by 3 factors including (a) the genetic susceptibility of the animal, (b) the presence in the milk of the nursing female of an agent transmissible to the offspring, and (c) adequate hormonal stimulation of the mammary gland (3). The tumors in the adrenal cortex were observed in castrated animals of those strains (27, 28) in which a high incidence of spontaneous mammary cancer had been established and associated with the presence of the three factors (2, 4, 6), and had also been observed in low mammary tumor stocks as well (14, 28). Because all stocks have not been completely tested for the presence of the 3 factors influencing the growth of mammary tumors, the importance of these 3 factors in the development of adrenal tumors was studied in the present experiment.

The genetic nature of 2 of these factors, the hormonal mechanism and the mammary tumor susceptibility, was suggested by Bittner and his co-workers (7). Female mice of the high mammary tumor A and C3H stocks and reciprocal hybrids between the 2 stocks were studied. In the 2 inbred strains, a high incidence of mammary tumors was observed among the breeding animals. If the mice were maintained as virgins, the incidence of mammary tumors was high in the C3H stock but low in the A strain (4, 7). The genetic susceptibility for mammary tumor development and an active agent in the milk were present in mice of both groups. Precancerous nodules and tumors of the mammary glands were found consistently in virgin mice of the C3H and hybrid stocks but were rarely present in mice of the A strain.

The difference in mammary gland structure and mammary tumor incidence between the virgin mice of the A strain, and virgin mice of the C3H and hybrid strains was explained on the supposition that "all three of the primary factors (3) responsible for mammary tumor development must be present in order for nodules to develop with any frequency," and in the virgin mice of the A strain there was inadequate hormonal stimulation (6). The effective hormonal mechanisms as measured by the mammary tumor incidence was thought to be a dominant genetic factor transmitted from the C3H stock to hybrid animals between the A and the C3H stocks of the F1 and F2 generation, and was termed the inherited hormonal influence (7).
The hormonal difference in genetic complex influencing mammary tumor formation in these 2 strains and in the F₁ hybrids was confirmed by Heston and Andervont (17).

To examine the action of the inherited hormonal influence, castration of mice in the A and C3H strains was suggested to determine what relationship might exist between the inherited hormonal factor, mammary tumor development and adrenal cortical hyperplasia. Preliminary evidence has been reported that the inherited hormonal influence as it governs hormonal metabolism may be associated with the adrenal cortical hyperplasia in castrated mice of the A and C3H stocks and their hybrids (25). Final data will be presented at this time.

**MATERIALS AND METHODS**

Intact and castrated females of several groups of animals were studied: mice of 2 high mammary tumors strains (A and C3H), and 6 groups of reciprocal hybrids between these 2 stocks (4 with the active milk agent (AZF₁, ZAF₁, AZ-ZBC, ZA-ZBC) and 2 without this agent (AxZb-ZBC, ZbAx-ZBC). The mice were derived from the Bittner colony.

The breeding female mice in both the A and the C3H stocks have a high incidence of mammary tumors. Most of the virgin female mice of the C3H stock also had mammary tumors. The virgin mice of the A strain rarely had mammary tumors (Table I).

The reciprocal hybrid mice were separated into 2 groups: one with a high incidence of mammary tumors and the other with a low incidence of mammary tumors. The high tumor hybrids (AZF₁, ZAF₁, AZ-ZBC, ZA-ZBC) were offspring resulting from the reciprocal cross between the A and the C3H (Z) strains, and the mating of these offspring with C3H males. The animals in these groups have a high incidence of mammary tumors comparable to that observed among breeding female mice in the inbred strains from which they were derived (Table I), (5).

The low tumor hybrids (AxZb-ZBC, ZbAx-ZBC) were derived by mating offspring of reciprocal crosses between fostered mice of the A and C3H strains with males of the C3H strain. In this manner hybrids were obtained with the genetic susceptibility and hormonal mechanisms of the parent strains but were lacking an active milk agent. The tumor incidence in these fostered mice has been 1 to 2 per cent (5).

The 3 factors known to influence the production of mammary tumors in mice were present in the following groups: (a) breeding and virgin female mice of the C3H stock; (b) the F₁ and F₂ hybrid mice between the A and the C3H stock; (c) the hybrid animals derived from the backcross to the C3H males, and (d) breeding females only of the A strain. The hormonal mechanism was lacking in the virgin mice of the A strain. The milk agent was not present in the groups of fostered mice.

All animals were castrated at 4 weeks of age. Both the intact and the castrated mice were checked at weekly intervals for the appearance of mammary tumors. Four months after ovariectomy vaginal smears were taken at intervals of 4 to 6 weeks to determine the presence of vaginal cornification. The cotton swab technic was used. A few animals with vaginal cornification were selected at random from each group and were smeared daily for a 2 week period to determine whether or not cyclic variations occurred. The smearing was discontinued when the animals were 18 months old. Smears were considered positive and indicative of estrus only when cornified epithelial cells were the chief cellular constituent of the smear.

All animals that acquired mammary tumors were killed shortly after the nodule was noted. Mice in poor condition were also sacrificed for study. Tissues removed at autopsy were fixed in either Bouin's or Helly's fluid, and were stained with Delafield's hematoxylin and eosin. Whole mounts of the second and third pair of mammary glands, stained with Mayer's hemalum, were also prepared.

The animals were housed in wooden boxes, 5 or 6 in a group, with an unlimited supply of Purina

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**Table 1: The Incidence of Mammary Cancer in Breeding and Virgin Female Mice of the A and the C3H Stock, and in Hybrid Animals Between These Two Stocks**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>86.7</td>
<td>10.0 mo.</td>
<td>15.0 mo.</td>
<td>3.9</td>
<td>15.0 mo.</td>
<td>19.3 mo.</td>
</tr>
<tr>
<td>C3H(Z)</td>
<td>95.1</td>
<td>9.1</td>
<td>10.4</td>
<td>63.0</td>
<td>13.3</td>
<td>15.9</td>
</tr>
<tr>
<td>AZF₁</td>
<td>98.0</td>
<td>9.7</td>
<td>11.5</td>
<td>92.5</td>
<td>15.2</td>
<td>18.9</td>
</tr>
<tr>
<td>ZAF₁</td>
<td>97.6</td>
<td>10.1</td>
<td>7.5</td>
<td>73.2</td>
<td>19.1</td>
<td>22.5</td>
</tr>
<tr>
<td>AZF₂</td>
<td>95.8</td>
<td>11.2</td>
<td>8.5</td>
<td>70.4</td>
<td>16.2</td>
<td>21.8</td>
</tr>
<tr>
<td>ZAF₂</td>
<td>100.0</td>
<td>10.0</td>
<td>—</td>
<td>38.8</td>
<td>17.2</td>
<td>22.0</td>
</tr>
</tbody>
</table>

cells in width, regarded as Type A cells (Figs. 2, 3).

**RESULTS**

**A. OBSERVATIONS UPON THE ADRENAL**

**Gross.**—The adrenal glands in intact mice of all groups were comparable. Among the older animals the glands were usually firm and pink with the connective tissue capsule occasionally mottled by small circumscribed yellow or deep red areas. Rarely the entire adrenal was yellow.

Comparison of the adrenal glands from the control animals with those glands from the castrated mice brought forth several dissimilarities in the latter. Normal appearing adrenal glands as described in the preceding paragraph were observed among the castrated groups only in mice of the A strain. The adrenal glands from mice of the C3H and hybrid groups had developed definite bulges or nodules. Frequently the glands were yellow and swollen so as to obscure the nodular formations. Differences in size and distortion were noted between the two adrenals of the same animal. The left adrenal was usually the larger. The largest nodules measuring 40 to 50 mm. were found only in the hybrid mice irrespective of the presence or absence of the active milk agent.

**Microscopic.**—The cortex of the adrenal was principally involved. The distribution of cells throughout the cortex into 3 major zones (zona glomerulosa, zona fasciculata and zona reticularis or X zone) followed the customary pattern in the mouse (11). In the older animals localized regions beneath the capsule were composed of small cells with heavily stained nuclei but with relatively little cytoplasm, many of which were in different stages of mitosis. Cord-like trabeculation of the cells was not involved. No metastases were observed.

1. Adrenal glands showing normal cellular arrangements in the cortex constituted one group. Some glands were included, therefore, in which the so-called Type A cell had accumulated beneath the capsule (Fig. 1).

2. The adrenal glands in the second group had cords of the cortical zones disrupted to different extents by cells of Type A and Type B. Type B cells were observed first in the outer cortex where the fasciculata cells appeared swollen (Fig. 2). The glands with more extensive involvement of the zona fasciculata usually showed an increased number of subcapsular Type A cells between the aggregates of Type B cells. Brown degeneration cells were distributed throughout the cortex and in the juxtap-medullary zone in variable numbers. Nodules were visible grossly in glands with such cortical rearrangement.

3. Small adenomas were noted in the adrenal glands classified in this group. Large numbers of elongated, spindle-shaped cells of the subcapsular type extended into the main body of the cortex between the groups of Type B cells. The Type B cells themselves were smaller, had less cytoplasm, still stained lightly, were vacuolated but with heavily staining nuclei, many of which were in different stages of mitosis. Cord-like trabeculation of the cells was not observed (Fig. 3).

4. The glands placed in group 4 had the cortical tissue replaced by histologically malignant cells and were considered to be adenocarcinoma (Fig. 4). Resemblance to Type A or B cells was lacking. Cell boundaries were also poorly defined. The undifferentiated cells comprising the tumor were arranged in lobules of different sizes and separated from one another by strands of connective tissue. The blood supply was scant and necrosis was common in the larger tumors.

Amyloid degeneration was observed in the adrenal glands of each of the 4 groups in differing amounts. The medulla was frequently compressed to one side by the overgrowth of cortical tissue but otherwise was not involved. No metastases were observed.

Strain differences among the castrated mice were apparent in the extent of adrenal gland involvement. The glands in mice of the A strain showed no marked pathological lesions. The usual cord-like arrangement of the cortex in the adrenal was modified by subcapsular Type A cells. Adenomas were present in 4 animals. In none of the mice were the normal contours of the organ disturbed (Table II).

More extensive adrenal lesions were noted in the other groups of mice studied. The C3H strain mice,
TABLE II: THE DISTRIBUTION OF ADRENAL CORTICAL LESIONS IN CASTRATED FEMALE MICE OF THE A AND C3H STOCKS AND HYBRIDS BETWEEN THESE STOCKS AS DETERMINED BY HISTOLOGICAL EXAMINATION

<table>
<thead>
<tr>
<th>Strain</th>
<th>No. of animals</th>
<th>Normal Adrenal glands No.</th>
<th>Subcapsular cells and hyperplasia No.</th>
<th>Adenoma No.</th>
<th>Adenocarcinoma No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>33</td>
<td>24</td>
<td>72.9</td>
<td>5</td>
<td>15.2</td>
</tr>
<tr>
<td>C3H(Z)</td>
<td>33</td>
<td>5</td>
<td>3.3</td>
<td>9</td>
<td>27.3</td>
</tr>
<tr>
<td>ZAF1*</td>
<td>14</td>
<td>5</td>
<td>35.7</td>
<td>2</td>
<td>14.2</td>
</tr>
<tr>
<td>AZF1*</td>
<td>14</td>
<td>2</td>
<td>14.2</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>Hybrid ZBC*</td>
<td>55</td>
<td>3</td>
<td>5.4</td>
<td>6</td>
<td>10.9</td>
</tr>
<tr>
<td>Fostered ZBC†</td>
<td>24</td>
<td>2</td>
<td>8.3</td>
<td>5</td>
<td>20.8</td>
</tr>
</tbody>
</table>

* High tumor hybrids with active milk agent.
† Low tumor hybrids lacking active milk agent.

the high tumor hybrid mice with the milk agent (ZAF1, AZF1, hybrid-ZBC) and the low tumor mice without the active milk agent (fostered ZBC) showed considerable cortical involvement. The alterations in the adrenals of the C3H strain mice were less than in the mice of the hybrid groups. Hypertrophied cortical cells were found in the adrenals of all but one mouse of the C3H strain. Sixty per cent of those examined showed adenomatous development and 3 animals (9.0 per cent) showed adenocarcinomas. Brown degeneration in the juxta-medullary zone was conspicuous.

The majority of the hybrid mice with or without the milk agent showed adenomatous or adenocarcinomatous changes of the adrenal cortical cells. Brown degeneration was not localized as among the C3H mice but was scattered throughout the cortex. Although the tumors did not invade surrounding organs, the cortical cells frequently infiltrated through the capsule of the adrenal. Tumors of the lung were present in 9 mice of the high tumor hybrid group and 11 mice of the fostered hybrid group. The pulmonary tumors were characteristic of primary lung tumors of the A strain. The presence or absence of the milk agent had no relationship to the extent of cortical pathology.

B. OBSERVATIONS OF FUNCTIONAL ACTIVITY OF ADRENAL LESIONS

1. Vaginal smears.—Daily examination of the vaginal mucosa of intact animals representing the four main groups of mice being studied indicated: (a) that individual cycles in the animals of each group lasted four to six days, (b) that the resting phase, if present, was short. No attempt was made to determine the time when estrous cycles began in these mice but a high percentage of the animals 3 months old had periodic cornified vaginal smears.

Among the castrated mice the failure of the vaginal orifice in the females of the A strain to open until the animals were 5 or 6 months old made observations previous to this period impossible. At no time during subsequent examinations were smears of the estrous type obtained (Table III).

Animals of the other groups showed cornification as early as 3 months following castration. The vaginal canal was open at the time of castration or shortly thereafter. A series of daily observations of

TABLE III: PERCENTAGE OF INTACT AND CASTRATED FEMALE MICE OF THE A AND C3H STOCKS AND HYBRIDS BETWEEN THE TWO STOCKS OBSERVED WITH ESTROUS VAGINAL SMEARS (4 TO 18 MONTHS)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Intact mice</th>
<th>Castrated mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>A</td>
<td>15</td>
<td>93.3</td>
</tr>
<tr>
<td>C3H(Z)</td>
<td>8</td>
<td>75.0</td>
</tr>
<tr>
<td>High tumor hybrids*</td>
<td>14</td>
<td>92.0</td>
</tr>
<tr>
<td>Low tumor hybrids†</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Hybrids with active milk agent.
† Hybrids lacking active milk agent.

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exhibited indications of hormonal activity; namely, cystic hyperplastic endometrium, tall columnar epithelia, numerous mitotic figures in the surface glands and in the deeper mucosa, edema, stromal nuclear changes varying from small spindle-shaped cells to enlarged rounded types with vesicular nuclei, leukocytes and an increase in fibrous connective tissue. Different combinations of these indicators suggested estrogenic, androgenic and progesterone influences (Fig. 7).

3. Mammary glands.—A third indicator of hormonal activity was the structure of the mammary glands (1, 16). The mammary architecture in the intact mice of the A strain was primarily ductular (Fig. 8). Greater alveolar development was apparent in mice of the other groups. Hyperplastic nodules and mammary tumors were found only in mice of the C3H strain and of the high tumor hybrid group (Fig. 9). The mammary glands of the fostered mice lacked hyperplastic nodules (Fig. 10).

The glands of the castrated mice had unusually long duct systems. Side branching was slight and the distances between lateral branches were variable. The type and degree of development showed considerable variation even within mice of the same strain. The castrated mice of the A strain showed greatest deviation from the usual appearance. Frequently 1 or 2 of the glands were of the rudimentary male type while the remainder of those studied were more extensively developed. As a rule the glands consisted of a main duct with a few side branches and no hyperplastic nodules (Fig. 11). Two mammary tumors developed (Table IV).

The mammary ducts were similar to those of mice in the C3H strain and high tumor hybrid stocks with extended smaller ducts and irregular alveolar development. No hyperplastic nodules and no mammary tumors were present (Fig. 13, Table IV).

The average age at which the tumors appeared in mice of the castrated series, with the exception of the A strain, was somewhat later than in the groups of virgin mice. There was no consistent correlation in the age of the animals dying noncancerous between the castrated and virgin groups (Tables I, IV). Although the presence of Type A or B cells in the adrenals of the castrated mice and the postulated hormonal activity were related to the extent of mammary tree development, the adrenal lesions influenced mammary tumor development only in the presence of an active milk agent. The few cellular changes in the cortex of the adrenal glands in mice of the A strain are reflected in the immature male-like structure of the mammary gland whereas more extensive cortical changes in mice in the other groups coincide with the greater development of the mammary gland and mammary tumors in the susceptible stocks.

**DISCUSSION**

Removal of the ovaries from mice of certain strains was followed by gross and microscopic changes in the uterus, vagina and mammary glands showing stimulation by estrogenic, androgenic or progesterone-like substances. The adrenal cortical hyperplasia and carcinomas which were observed in these animals were suggested as the source of the stimulating hormones (13, 14, 27, 30). When the ovarian hormones were replaced by administration of diethylstilbestrol (31) or by certain androgenic steroids (26), the hyperplastic cellular changes in the adrenal cortex were prevented, and the adrenal glands were established as the source of the steroids involved.

The nature of the hormones being released by the hyperplastic cells in the adrenal glands of the cas-

<table>
<thead>
<tr>
<th>Strain</th>
<th>No. of animals</th>
<th>No. of mammary tumors</th>
<th>Ave. ca. age, months</th>
<th>Ave. non-ca. age, months</th>
<th>Adrenal tumors,*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>46</td>
<td>2</td>
<td>4.3</td>
<td>6.7</td>
<td>16.3</td>
</tr>
<tr>
<td>C3H(Z)</td>
<td>53</td>
<td>29</td>
<td>54.7</td>
<td>14.2</td>
<td>16.0</td>
</tr>
<tr>
<td>ZAF,†</td>
<td>14</td>
<td>10</td>
<td>71.5</td>
<td>20.9</td>
<td>19.5</td>
</tr>
<tr>
<td>AZF,‡</td>
<td>35</td>
<td>19</td>
<td>54.4</td>
<td>19.3</td>
<td>20.0</td>
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<tr>
<td>Hybrid ZBC,†</td>
<td>69</td>
<td>36</td>
<td>52.0</td>
<td>16.4</td>
<td>17.5</td>
</tr>
<tr>
<td>Fostered ZBC,‡</td>
<td>55</td>
<td>0</td>
<td></td>
<td></td>
<td>20.0</td>
</tr>
</tbody>
</table>

*Tumors include adenomas and adenocarcinomas.
†High tumor hybrids with active milk agent.
‡Low tumor hybrids lacking active milk agent.

Table IV: Summary of Data Showing the Incidence and Time of Occurrence of Mammary Tumors in Castrated Female Mice of the A and C3H Stocks and Hybrids Between the Two Stocks with the Percentage of Adrenal Tumors in Each Group

Castrated mice of the C3H strain and mice of the high-tumor hybrid stocks had mammary glands similar to those of mature virgin mice of that stock. The lateral branching and alveolar development were somewhat less than that in the intact animal. The ducts and alveoli in parts of the gland were distended with secretion. Hyperplastic nodules and mammary tumors were present (Fig. 12, Table IV).

In the castrated mice lacking the milk agent, the mammary ducts were similar to those of mice in the C3H strain and high tumor hybrid stocks with extended smaller ducts and irregular alveolar development. No hyperplastic nodules and no mammary tumors were present (Fig. 13, Table IV).
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trated mice was ill-defined. Present evidence has suggested that the secretions from the pituitary gland influenced the liberation of hormone from the adrenal cortex in the castrated animals. The administration of gonadotrophic hormones has been demonstrated to discharge the hormones from adrenals in castrated animals (14). Adrenotrophic hormone has not been effective in the doses tried (20). Caloric restriction has lowered the hormonal content and activity of the hyperplastic adrenal cortical cells (19). Because the type of cellular change observed in the adrenals of the castrated mice of the several strains was essentially similar but the extent of the lesion varied considerably, a differential pituitary action upon the adrenal cortex was probable. A differential response to pituitary stimulation by the adrenal may also not be excluded.

The variability in mammary gland development, the difference in uterine development and the superimposition of leukocytes upon cornified epithelial cells in the vaginal smears suggested that, (a) several types of steroid hormones were being released from the adrenal cortex in the castrated mice, (b) the hormones were being released in varying quantities, (c) the metabolism of the hormones present was being handled differentially, or (d) the end organ response to the several steroids was peculiar to the individual strain and animal. The quality and quantity of the secretion in the present experiment could be determined only insofar as was observed that castrated mice of the A strain with scant adrenal cortical change following castration which were present in the majority of the animals in the other groups. No ovariectomized mice of the A strain had estrous cycles. There was little or no uterine growth. The mammary gland development was slight. No precancerous nodules and but 2 mammary tumors were present.

The animals in the C3H strain and in the high tumor hybrid stocks in which all 3 factors for mammary tumor development were present, had extensive adrenal cortical pathologic change following castration. Vaginal cornification was observed. Mucosal changes indicative of hormonal stimulation were present in the uterus. Mammary glands were comparable to those in the intact animals and contained hyperplastic nodules and tumors. The low tumor hybrids, derived from mice lacking the milk agent, showed changes in the adrenal, uterus, and vagina similar to those observed in the C3H and high tumor hybrid stocks. No precancerous lesions in the mammary glands and no mammary tumors were observed.

Because only slight changes were found in the adrenal glands of mice in the A strain following castration, and because mice of this strain are also believed to lack the inherited hormonal influence, the extensive changes in the C3H and hybrid groups of mice, in which the inherited hormonal influence is present, suggest that the inherited hormonal influence functions genetically and may be considered as a mechanism influencing the cellular changes in the adrenal cortex following castration.

### SUMMARY

1. The three factors known to influence the growth of mammary tumors in inbred strains of mice have been studied in relationship to the formation of adrenal tumors following castration.

#### TABLE V: CORRELATION OF OBSERVATIONS UPON CASTRATED MICE OF THE A AND C3H STRAINS AND HYBRIDS BETWEEN THE TWO STRAINS WITH AND WITHOUT THE ACTIVE MILK AGENT

<table>
<thead>
<tr>
<th>Genetic susceptibility to Mammary Cancer</th>
<th>A strain</th>
<th>C3H strain</th>
<th>High tumor hybrids</th>
<th>Low tumor hybrids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk influence</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Inherited hormonal influence</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Adrenal cortical lesions</td>
<td>27.1%</td>
<td>96.7%</td>
<td>91.7%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Uterine stimulation</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Estrous activity</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Mammary gland nodules</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>Absent</td>
</tr>
<tr>
<td>Mammary tumor incidence</td>
<td>4.3%</td>
<td>54.7%</td>
<td>55.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
2. One of these factors, modifying hormonal activity in breeding and virgin mice, and designated as the inherited hormonal influence was observed to be in castrated mice of the C3H stock and to be transmitted as a dominant to the hybrids between the A and C3H stock but to be lacking in the castrated mice of the A strain.

3. Adrenal cortical hyperplasia and tumors occurred in those castrated groups with the inherited hormonal factors (C3H, high and low tumor hybrid stocks).

4. The hyperplastic adrenal glands were suggested as the source of compounds similar to those released by the ovary in the intact animal. These hormones are believed to be responsible for the evidence of hormonal activity in the vagina, uterus and mammary glands.

5. Mammary tumors were present in the castrated mice with the inherited hormonal influence provided an active milk agent was present (C3H, high tumor hybrids).

6. The castrated mice of the A strain, lacking the inherited hormonal influence even in the presence of the genetic susceptibility to mammary tumor formation and an active milk agent, had slight adrenal lesions and little or no indication of hormonal stimulation of the uterus, vagina or mammary glands.

7. The action of the inherited hormonal influence is probably mediated at least in part through the hypophysis.

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29. Woolley, G. W., and Little, C. C. The Incidence of Adrenal Cortical Carcinoma in Gonadectomized Female Mice of the Extreme Dilution Strain. I. Obser-


DESCRIPTION OF FIGURES 1 TO 7

Fig. 1.—Adrenal cortex from mouse of intact group showing slight subcapsular cell proliferation with penetration of these cells into zona fasciculata. Mag. × 300.

Fig. 2.—Adrenal cortex from castrated mouse showing subcapsular cell proliferation, hypertrophy and hyperplasia of cells in zona fasciculata. Mag. × 175.

Fig. 3.—Cross section of adrenal gland from castrated mouse showing dense areas of subcapsular cell proliferation associated with normal portions of cortex, and showing hyperplastic and adenomatous nodules involving remainder of cortex. Mag. × 6.

Fig. 4.—Area of undifferentiated cells undergoing active mitoses from histologically malignant adrenal cortical tumor in castrated mouse. Mag. × 175.

Fig. 5.—Cross section of the uterus from intact mouse. Mag. × 85.

Fig. 6.—Cross section of uterus from castrated mouse of the A strain. Lack of glandular development, compactness of lamina propria and scant muscular elements are characteristic. Mag. × 85.

Fig. 7.—A cross section of the uterus from a castrated hybrid mouse. The cystic endometrium, changes in stromal nuclei and well developed muscle tissue are apparent. Mag. × 85.
DESCRIPTION OF FIGURES 8 TO 13

Fig. 8.—Whole mount of mammary gland from intact virgin mouse of the A strain. The main duct system is complex but alveolar development is scant. Mag. \( \times 35 \).

Fig. 9.—Whole mount of mammary gland from intact virgin hybrid mouse. Hyperplastic nodules and some alveolar development are apparent. Mag. \( \times 35 \).

Fig. 10.—Whole mount of intact virgin mouse lacking the milk agent. No hyperplastic nodules are present. Mag. \( \times 35 \).

Fig. 11.—Whole mount of mammary glands from castrated mouse of the A strain. The glands are of rudimentary male type. Mag. \( \times 35 \).

Fig. 12.—Whole mount of mammary gland from castrated hybrid mouse. Hyperplastic nodules are present as in normal virgin mice but there is less alveolar development. Mag. \( \times 35 \).

Fig. 13.—Whole mount of mammary gland from castrated hybrid mouse lacking the milk agent. Extensive but irregular development of duct system is present. Mag. \( \times 35 \).
The Relationship of the Inherited Hormonal Influence to the Production of Adrenal Cortical Tumors by Castration

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