Studies on the Inherited Susceptibility and Inherited Hormonal Influence in the Genesis of Mammary Cancer in Mice*

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Additional observations will be presented in this report on the development of mammary cancer in mice, especially virgin females, associated with the action of an inherited hormonal influence, termed the inherited hormonal influence. Comparisons will also be made for the genic make-up of the inherited susceptibility versus the inherited hormonal influence.

While the role of the hormonal stimulation in the genesis of mammary cancer has been known for many years (see review by Loeb [26]), not until 1944 was it demonstrated that the genic control of the hormonal mechanism was related to the appearance of these tumors in virgin mice (15, 21). This was found by mating females of the A strain, where the incidence in virgin females was known to be low (6), with males of the Z or C3H stock, in which strain both the virgins and breeders have a high incidence. When the F1 females were maintained as nonbreeders, a high incidence was noted. Thus, the hormonal mechanism which determined the high incidence in virgins of the Z strain was transmitted and called the inherited hormonal influence (9).

In this cross, the females of the A strain contributed the mammary tumor agent and the inherited susceptibility for mammary cancer, while the Z fathers transmitted the inherited hormonal influence, as well as the inherited susceptibility. The three primary factors (7) considered to be needed for a high incidence were represented.

Further studies from this laboratory indicated that in the A and Z cross (23, 28–30), as well as in other strains (10, 11, 13, 14, 23), the inherited hormonal influence was associated with postcastrational adrenal cortical hyperplasia, previously observed by Woolley et al. (33–35). Mice of strains which show adrenal lesions following gonadectomy have been tested for the transmission of hormonal mechanisms and their influence upon the development of mammary cancer.

METHODS AND MATERIALS

The three strains of mice used in these studies were developed by Strong (31) and include the A, C3H, and I stocks. As in former reports, to simplify the hybrid designations, the C3H will be referred to as the "Z" stock.

The A and Z stocks were obtained from Strong more than 20 years ago and have been continued only by brother-to-sister matings. In both strains 65 successive generations of spontaneous mammary tumors have been observed.

After being used for various studies, including the reciprocal Z X I cross in co-operative work which showed the maternal influence on mammary cancer in mice (5, 25), the I line was discontinued. In 1944 representatives of the I stock were again obtained, this time from Andervont, who had observed (2, 8) that, when they receive the mammary tumor agent from C3H females, I mice were found to be relatively nonsusceptible to mammary cancer. However, following ovariectomy, females of the I strain developed adrenal cortical hyperplasia with hormonal stimulation of the secondary sex organs (23). This suggested that mice of the I stock might transmit the inherited hormonal influence, although they were "nonsusceptible" to mammary cancer.

To designate the hybrid crosses, the maternal stock is always given first. Thus, A females mated with I males produced AIF1 hybrids. The F1 hybrids resulted from mating the I females inter se. When the AIF1 females were crossed with males, the resulting back-cross animals were called AIF1-IBC1; the F1 females mated with A males gave AIF1-ABC1 hybrids.

The AIF1 (A9 X ZcP) females were crossed with males of the A stock to produce the AIF1-ABC1 mice, and when the ABC1 females were again back-crossed with A males, the next generation mice were called AIF1-ABC1 hybrids.

All the experimental animals received Purina Fox Chow and tap water. At least some animals of the various groups were observed during the same periods.

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RESULTS

The observations on the occurrence of spontaneous mammary cancer are reported in Table 1 for breeding and virgin females of the various inbred stocks and their hybrids. The incidences were determined by including all mice which survived to the age at which the youngest mouse was observed to have mammary cancer. Also tabulated are the average ages for the appearance of tumors and the death of the noncancerous mice.

Eleven females of the I stock were foster-nursed by females of the Z or A cancerous strains, so they would obtain the mammary tumor agent, and later were maintained as breeders. All I mice of the fostered series and their 42 descendants of the following three generations failed to develop mammary cancer. Since breeders did not die cancerous, virgin females of the I stock with the agent were not observed.

Five females of the I stock of the fostered generation were mated with Zb (without the agent) males, and the incidence of mammary cancer was observed in their F1 progeny. Among the nineteen hybrids with mothers obtaining the agent from A females, only one had cancer. Three I females, of one litter and nursed by a female of the Z stock, had 32 FI progeny. The incidences in the IZbFi progeny of these mothers were 10, 25, and 83 per cent. The average cancer age for those with the high incidence was 242 days; for the others it was 343 days.

The fostered females of the I stock had fifteen descendants of the first or second generation tested, by mating with susceptible, usually Zb, males. Two per cent of their 134 F1 progeny developed cancer.

In the inbred A strain, the nonbreeding females gave the usual low incidence of mammary cancer (6), but the incidence increased to over 80 per cent when the females were subjected to the hormonal stimulation associated with the production of young and lactation. Virgins of the Z stock had a rather high incidence, and this was increased by breeding with an acceleration in the time of appearance (Table 1).

In the breeding AZF1 and AZF2 hybrids, as well as the back-cross generations to the A stock, approximately the same incidence was observed as in the inbred maternal A strain. With the exception of the AZF1-ABC2 generation, where only nineteen breeders were continued, the average cancer ages were also the same.

The percentage of AZF virgins to have mammary cancer was greater than that found in the Z strain, or 89 and 66 per cent, respectively. In virgins of the AZF2 generation, the incidence dropped to 62 per cent, with further reductions being noted in the first and second "A" back-cross generations.

At least seven of the AZF1-ABC2 progeny of fourteen ABC2 mothers were continued in use as nonbreeders. These mothers had 151 offspring with the same incidence, 19 per cent, as the total number (Table 1); and they are listed, according to when the mothers either developed mammary cancer or died noncancerous, in Table 2, with data for their AZF1-ABC2 young.

One female died noncancerous, as did her nine AZF1-ABC2 progeny. Among the offspring of ABC2 cancerous mothers, the incidence ranged from 0 per cent to 44 per cent. The average cancer ages could not be correlated with the incidence in the ABC2 mice, although the highest incidence occurred in some at the earliest age. However, the average age of groups with incidences of 27 and 37 per cent, above the average, was over 600 days, or 4 months later than the entire group.

After the females of the A strain had been mated with I males, their AIF1 hybrids, when main-

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Table 1

<table>
<thead>
<tr>
<th>Stock or generation</th>
<th>Matings</th>
<th>No.</th>
<th>Per cent cancer</th>
<th>Av. age in days cancer</th>
<th>Per cent noncancer</th>
<th>Av. age in days noncancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A x A</td>
<td>569</td>
<td>54</td>
<td>350</td>
<td>367</td>
<td>111</td>
</tr>
<tr>
<td>Z(CMH)</td>
<td>Z x Z</td>
<td>835</td>
<td>65</td>
<td>278</td>
<td>322</td>
<td>135</td>
</tr>
<tr>
<td>I</td>
<td>I x I</td>
<td>53</td>
<td>0</td>
<td>65</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AZF1</td>
<td>A x Z</td>
<td>85</td>
<td>94</td>
<td>320</td>
<td>414</td>
<td>121</td>
</tr>
<tr>
<td>AZF2</td>
<td>AZF1 x AZF2</td>
<td>110</td>
<td>83</td>
<td>337</td>
<td>387</td>
<td>155</td>
</tr>
<tr>
<td>AZF1-ABC2</td>
<td>AZF1-ABC2</td>
<td>22</td>
<td>91</td>
<td>328</td>
<td>606</td>
<td>82</td>
</tr>
<tr>
<td>AZF1-ABC1</td>
<td>AZF1</td>
<td>19</td>
<td>89</td>
<td>359</td>
<td>540</td>
<td>159</td>
</tr>
<tr>
<td>AIF1</td>
<td>A x I</td>
<td>97</td>
<td>95</td>
<td>284</td>
<td>389</td>
<td>50</td>
</tr>
<tr>
<td>AIF2</td>
<td>A x IAF1</td>
<td>68</td>
<td>68</td>
<td>302</td>
<td>549</td>
<td>155</td>
</tr>
<tr>
<td>AIFABC1</td>
<td>AIF1</td>
<td>23</td>
<td>78</td>
<td>314</td>
<td>609</td>
<td>80</td>
</tr>
<tr>
<td>AIFABC2</td>
<td>AIF2</td>
<td>25</td>
<td>56</td>
<td>274</td>
<td>651</td>
<td>84</td>
</tr>
</tbody>
</table>

* Eleven females of the I stock, fostered by Z or A females, and 48 descendants.
tained as breeders, had an incidence of 95 per cent; and in the succeeding generation, AIF₂, it was 68 per cent. Only small numbers of breeders were continued in the AIF₂-ABC₁ and AIF₂-IBC₁ generations; in the former the incidence was the same as in the maternal A strain, but in the IBC₁ breeders it was only 56 per cent. The shortest latent period

In Table 3 the number of mice to have mammary cancer or to die noncancerous is given by age periods. The percentage of the total number of virgins in each group to develop cancer during the various age periods has been tabulated in Table 4. The distribution would give a normal curve for every group except the AIF₂-ABC₁ mice, where, with only thirteen cancerous virgins, tumors appeared in three at an early age and in four after they were 21 months of age. The percentage of mice, living to the beginning of each age period or longer, to develop mammary cancer has been tabulated in Table 5.

### DISCUSSION

Spontaneous mammary cancer will occur with a high incidence only in females with the mammary tumor agent, with an inherited susceptibility, and after an adequate hormonal stimulation of the mammary glands (7). In addition to the genetic susceptibility, the hormonal mechanism associated with its development in virgin females has also been found to be under genetic control (15, 21) and has been termed the inherited hormonal influence (9).

### TABLE 2

OBSERVATIONS FOR MAMMARY CANCER IN VIRGIN AZF₁-ABC₁ HYBRIDS, LISTED ACCORDING TO MOTHERS WITH SEVEN OR MORE PROGENY

<table>
<thead>
<tr>
<th>Cancer (+) or nonca. (—)</th>
<th>No. of AZF₁-ABC₁ progeny</th>
<th>Incidence in AZF₁ progeny (per cent)</th>
<th>Av. ca. age in progeny</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZF₁-ABC₁ mothers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+257</td>
<td>8</td>
<td>10</td>
<td>669</td>
</tr>
<tr>
<td>+350</td>
<td>12</td>
<td>9</td>
<td>675</td>
</tr>
<tr>
<td>+372</td>
<td>7</td>
<td>14</td>
<td>553</td>
</tr>
<tr>
<td>+372</td>
<td>11</td>
<td>9</td>
<td>446</td>
</tr>
<tr>
<td>+392</td>
<td>14</td>
<td>7</td>
<td>571</td>
</tr>
<tr>
<td>+310</td>
<td>9</td>
<td>44</td>
<td>327</td>
</tr>
<tr>
<td>+380</td>
<td>11</td>
<td>11</td>
<td>449</td>
</tr>
<tr>
<td>+353</td>
<td>10</td>
<td>10</td>
<td>478</td>
</tr>
<tr>
<td>+368</td>
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<td>+376</td>
<td>15</td>
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<td>629</td>
</tr>
<tr>
<td>+399</td>
<td>19</td>
<td>37</td>
<td>611</td>
</tr>
<tr>
<td>+517</td>
<td>10</td>
<td>10</td>
<td>571</td>
</tr>
<tr>
<td>+568</td>
<td>11</td>
<td>9</td>
<td>422</td>
</tr>
<tr>
<td>—623</td>
<td>9</td>
<td>0</td>
<td>422</td>
</tr>
</tbody>
</table>

In Table 3 the number of mice to have mammary cancer or to die noncancerous is given by age periods. The percentage of the total number of virgins in each group to develop cancer during the various age periods has been tabulated in Table 4. The distribution would give a normal curve for every group except the AIF₂-ABC₁ mice, where, with only thirteen cancerous virgins, tumors appeared in three at an early age and in four after they were 21 months of age. The percentage of mice, living to the beginning of each age period or longer, to develop mammary cancer has been tabulated in Table 5.

### DISCUSSION

Spontaneous mammary cancer will occur with a high incidence only in females with the mammary tumor agent, with an inherited susceptibility, and after an adequate hormonal stimulation of the mammary glands (7). In addition to the genetic susceptibility, the hormonal mechanism associated with its development in virgin females has also been found to be under genetic control (15, 21) and has been termed the inherited hormonal influence (9).

### TABLE 3

NO. VIRGIN FEMALES DYING DURING EACH AGE PERIOD (CANCER/NONCANCER)

<table>
<thead>
<tr>
<th>Months</th>
<th>A</th>
<th>Z</th>
<th>AZF₁</th>
<th>AZF₁</th>
<th>AZF₁-ABC₁</th>
<th>AIF₁</th>
<th>AIF₁</th>
<th>AIF₁-ABC₁</th>
<th>AIF₁-IBC₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>-6</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>6-8</td>
<td>0/0</td>
<td>0/0</td>
<td>2/0</td>
<td>0/0</td>
<td>2/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>9-11</td>
<td>1/3</td>
<td>2/3</td>
<td>1/3</td>
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<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
</tr>
<tr>
<td>12-14</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
</tr>
<tr>
<td>18-20</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
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<tr>
<td>21-23</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
</tr>
<tr>
<td>24-26</td>
<td>0/2</td>
<td>0/2</td>
<td>0/2</td>
<td>0/2</td>
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<td>0/2</td>
<td>0/2</td>
<td>0/2</td>
<td>0/2</td>
</tr>
<tr>
<td>27-29+</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

No. cancer/nonca: 4/107; 101/28; 108/13; 95/58
Percent cancer: 3.6
Av. ca. age: 450
Av. nonca. age: 573
of the C57BL stock did not, and neither was there evidence of hormonal stimulation. When breeders of this stock possessed the mammary tumor agent, either a low (2, 8) or high (3, 4, 18) incidence of mammary cancer was noted, depending upon the subline being tested, while nonbreeders had few tumors (27, 32).

That the hormonal mechanism was transmitted was determined by making reciprocal crosses between the A and Z stocks and finding a high incidence of mammary cancer in the virgin hybrids (15). Comparable findings were reported by Heston and Andervont (21) at approximately the same time. Further observations indicated that ability that mice with the inherited hormonal capacity for developing mammary tumors as virgins might show postcastrational adrenal cortical hyperplasia, this theory has been tested in several crosses. To demonstrate this hormonal mechanism, females of the A strain were mated with males of the stock being tested. In several crosses, the high incidence of mammary cancer in virgin F₁ females showed that other strains (in addition to the Z strain) have been found to transmit the inherited hormonal influence (10-12). Stocks not previously reported include the C and I⁻. Other hormonal mechanisms and their influence upon the development of mammary cancer have been discussed (10) and will be considered in future reports. In every cross, the inherited hormonal influence appears to be dominant over these other mechanisms.

As reported here, and in confirmation of the observations of Andervont (1, 3), females of the I stock are relatively nonsusceptible to mammary cancer, since they remained noncancerous after they obtained the agent and were maintained as breeders. However, ovariectomized females of the I stock developed adrenal cortical hyperplasia (23), suggesting that they might possess the inherited hormonal influence. This was proved by mating males of the I stock with females of the A strain and finding a high incidence of mammary tumors in the F₁ virgin females.

By observing the hybrids of the two crosses con-
sidered here (A♀ × Z♂ and A♀ × I♂) as either virgins or breeders, it is possible to obtain information on the respective role of the inherited susceptibility and the inherited hormonal influence in the genesis of mammary cancer in mice. And, by considering the various groups, some comparisons may be made regarding the segregation of the genes controlling these inherited factors.

In the A♀ × Z♂ cross, the incidence of mammary tumors was as high in breeders of the four groups of hybrids (F₁, F₂, and two back-cross generations to the A strain) as was seen in breeders of the maternal strain. The lowest incidence, 83 per cent, was observed in the AZF₁ generation. Several of the noncancerous mice of this group died following alterations in the animal room, and this is reflected by the early age at death of the noncancerous mice, viz., 367 days—nearly 200 days before other series. The AZF₁ breeders of 24 litters, consisting of 73 mice, all had mammary cancer at an average age of 388 days.

From the data observed in these hybrids, it is possible to assume either that the mice of the A and Z stocks possessed the same susceptibility for spontaneous mammary cancer, or, if different genes were involved, that any combination of these genes would produce susceptible hybrids.

Eighty-nine per cent of the virgin AZF₁ females had mammary cancer, an increase of 23 per cent over that found in virgins of the Z strain. The incidence in the AZF₁ virgins of 68 per cent would indicate that the segregation of at least one primary gene was involved in controlling the inherited hormonal influence from the Z stock. Further evidence for this was apparent in the virgins of the AZF₁-ABC₁ and AZF₁-ABC₂ generations, where the incidences were 41 and 19 per cent, respectively.

The mothers of the AZF₁-ABC₂ generation have been tabulated, and only three had progeny with a total incidence of 40 per cent (Table 2). The average cancer age for mice of this group, 579 days, was later than that observed for the entire group. The incidence for the progeny of other AZF₁-ABC₁ mothers ranged from 0 to 27 per cent. Two females, one cancerous and one noncancerous, had no cancerous progeny. From these results, it appears probable that, while the ratio for the entire group might be explained on the segregation of a single gene, multiple factors determined the transmission of the inherited hormonal influence.

A breakdown of the AZF₁-ABC₂ data also revealed that the highest incidence was found in the progeny born to mothers which developed mammary cancer when they were from 300 to 400 days of age. When the mothers had tumors before they were 300 days of age, 17 per cent of their offspring developed cancer; and, when cancer did not appear in the mothers before 500 days, the incidence in their offspring was 10 per cent. No importance may be attached to these tabulations at present.

In the AIF₁ breeders, the same incidence of mammary cancer was observed as in the AZF₁ breeders; but the tumors appeared, on an average, 100 days earlier in mice of the former group. The incidence of 78 per cent in the AIF₁-ABC₁ breeders compares with the observations for the maternal stock, both as regards the incidence and average cancer age. Since the AIF₁-ABC₁ group consisted of only 23 mice, the incidence was influenced by the fact that three of the four mice in one litter died noncancerous. Five other females born to the same mother were also continued as breeders, and all had cancer; thirteen were kept as virgins, whose incidence was 28 per cent.

Breeders of the AIF₂ and AIF₁-ABC₁ generations possessed different susceptibilities for mammary cancer and had incidences of 68 and 56 per cent. Their tumors appeared slightly earlier than the average age observed in the A stock. Thus, at least one primary gene was indicated for the inherited susceptibility, with perhaps modifying genes acting to influence the average cancer age.

Although only 4 per cent of the virgins of the A and I stocks and none of the breeders of the I stock with the mammary tumor agent had spontaneous mammary cancer, the cross between A females and I males produced hybrids with an incidence of 72 per cent, even when the females were observed as virgins. In this cross the mothers of the A stock contributed the inherited susceptibility for mammary cancer and the mammary tumor agent, while the inherited hormonal influence was transmitted by the I males.

Although the incidence of 79 per cent was lower than that observed in the AZF₁ virgins, it was comparable to that found in several groups with mothers of the same maternal strain (AIP₁, AIF₁, ACF₁) where the range was from 72 to 75 per cent (11, 13, and unpublished data).

The incidence of mammary cancer in virgins of the AIF₁ generation was determined by the segregation of the genes controlling both the inherited susceptibility and the hormonal influence. Based upon the observed incidence in the F₁ virgins, at least three genes were active—possibly more. The data for the AIF₁-ABC₁ virgins indicate that two or three genes controlled the inherited hormonal influence, and, in the AIF₁-IBC₁ group, one or two genes controlled the inherited susceptibility.

Females of the AZF₁-ABC₁ and AIF₁-ABC₁ generations would be expected to have approximately
the same proportion of chromatin from the A strain. The variation in the incidence of mammary cancer in breeders of the two groups was due primarily to three mice of one litter dying non-cancerous in the latter series, referred to above. The incidence in the virgin females of the two generations would be influenced by the genes, transmitted by either the Z or I mice, which determine the inherited hormonal influence. In the virgins of the AZF1-ABC1 generation, 41 per cent had cancer, while the incidence in the AIF1-ABC1 group was only 16 per cent. On the basis of the incidence observed in the two virgin F1 populations, the action of the inherited hormonal influence from the Z stock required at least one primary gene, while that from the I stock showed the action of multiple genes. Furthermore, the distribution of mammary tumors among the virgins of the AIF1-ABC1 generation was quite different from that observed in the other groups (Tables 3-5). This may have some significance, but the number of cancerous mice was not adequate for any interpretation.

From the observed incidence found in hybrids of these two crosses, and from comparisons with the theoretical ratios to be expected on a genetic basis, it is possible to summarize the data as follows:

Either the inherited susceptibility for spontaneous mammary cancer, transmitted by animals of the cancerous A and Z stocks, is controlled by the action of the same genes, or, if different genes are involved, any combination of these genes will produce susceptible hybrids in generations where segregation might be expected.

In the AI cross, the transmission of the inherited susceptibility from mice of the A strain may be explained upon the action of a single primary gene.

The incidence of mammary cancer in virgin females of the hybrid generations of the AZ cross may be interpreted according to the theory that the inherited hormonal influence of the Z stock is dependent upon one primary gene.

The inherited hormonal influence transmitted by mice of the I stock, resulting in mammary cancer in hybrids when maintained as virgins, involved the action of multiple genes.

The data suggest that the inherited hormonal mechanisms contributed by mice of the Z and I stocks may result from the action of not only different genes but also of different numbers of genes.

If it is possible that, in the Z stock, one or more genes common to both the inherited susceptibility and the inherited hormonal influence exists, then segregation of these genes could not be demonstrated in this study.

The genetic make-up of the two inherited factors considered in this report was based upon the theoretical relationship between the observed and expected ratios of cancer. As published previously (9), data on the transmission of the inherited susceptibility for mammary cancer by the A stock could not be explained by such a simple interpretation; it is more likely that multiple factors may be active to characterize both inherited factors under consideration.

One may also theorize regarding the difference in the average cancer ages observed in the hybrids, as compared to animals of the inbred strains. The hybrids continued as virgins, in every generation, later average cancer ages than did those of the inbred Z strain; and yet the incidence in the AZF1 and AIF1 virgins was higher. The latent period for mammary cancer in the hybrids generally increased in proportion to the amount of chromatin they received from the A stock.

In the breeders of the AZ cross, the average cancer ages approximated more closely that seen in the A strain, whereas tumors in the AIF1 breeders appeared 2 months earlier in females of the Z strain. This early age was also observed in breeders of the AIF1-IBC1 group or in mice with increased chromatin from the I stock.

It may be suggested that either factors associated with the inherited hormonal influence or other inherited factors transmitted by mice of the I stock have some physiological effect which accelerates the time of development of mammary cancer in breeders of some generations.

Attempts have been made to investigate possible differences in the physiological nature of the hormonal patterns of mice with and without the inherited hormonal mechanism. Deringer, Heston, and Andervont (16) observed that the vaginas opened later in females of the A stock than in females of the C3H strain and their F1 hybrids. There was also a difference in the initiation of estrus, but females of the A strain had cycles of shorter duration than did the C3H females.

By the transplantation of organs into either ovariectomized or adrenalectomized-gonadectomized F1 hybrids, the grafted organs would be subjected to comparable or identical pituitary stimulation, and the hormones produced by the transplants would act upon and be metabolized by genetically identical tissues.

Ovaries from A, Z, and F1 females were grafted into gonadectomized F1 females, and the recipients were observed for many months (14, 23). The morphological difference, noted in intact animals, between the ovaries of the A and Z females was not evident after the ovaries had been maintained for 3 months in F1 hybrids, in that the ovaries from...
donors of the A strains were found to be indistinguishable from those of the Z or F1 mice. This suggested a difference in pituitary function, and other findings indicated a variation in inherited hormonal properties of the ovaries of the parental strains, as well as other organs of the endocrine system. In another study (24), the change noted in adrenal corticosteroid levels in A donors of the A strains was found to be attributable to differences inherent in the adrenal tissue itself.

Other possible mechanisms by which inherited factors may operate, either the influencing of factors associated with the etiology of mammary cancer in mice or other physiological effects, have been suggested (17, 19, 20, 22).

These studies on the comparative action of the inherited susceptibility and the inherited hormonal influence indicate that other factors, in addition to the mammary tumor agent, are essential for the development of mammary cancer in mice. While some may be extrinsic in nature, others may be due to the action of genes and be inherited. A future report will be concerned with another hormonal effect which, although inherited, either inhibits or delays the time of appearance of mammary cancer, so that many animals die noncancerous in a group where a high incidence might be expected. Further basic research is needed to understand these mechanisms, since they may be fundamental to the problem of the genesis and control of cancer, at least in experimental animals.

**SUMMARY**

Further observations are presented on the action of another inherited factor, an inherited hormonal influence, which, along with the inherited susceptibility and the mammary tumor agent, has been found to be a primary cause of mammary cancer in virgin mice.

In several stocks there is an association between the presence of the inherited hormonal influence and the development of adrenal cortical hyperplasia in gonadectomized mice.

The inherited hormonal influence may be transmitted by mice of strains which are either susceptible or relatively nonsusceptible to the development of spontaneous mammary cancer.

The inherited susceptibility and the inherited hormonal influence, when transmitted by mice of the same stock, may be due to the action of different genes, although genes common to both factors may exist.

The inherited hormonal influence, when possessed by mice of different stocks, may not involve the same genetic make-up in the two stocks.

The determination of the exact number of genes to produce either the inherited hormonal influence or the inherited susceptibility is difficult to ascertain because of the influence of other factors, intrinsic and/or extrinsic, and the source of the mammary tumor agent, in the development of mammary tumors. It seems probable that multiple genes are needed.

Possible physiological effects of the hormonal mechanism are discussed.

**REFERENCES**

2. ———. The Influence of Foster Nursing upon the Incidence of Spontaneous Mammary Cancer in Resistant and Susceptible Mice. Ibid., pp. 147-59.


Studies on the Inherited Susceptibility and Inherited Hormonal Influence in the Genesis of Mammary Cancer in Mice

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