The Effect of Foster Nursing on the Incidence of Spontaneous Mammary Carcinoma in Two Inbred Strains of Mice

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When the important results of Bittner’s work on the foster nursing of mice became known (8), and as a sequel to the hybridization experiments reported from this laboratory (19), it was decided to test the effect of cross-fostering on the mammary tumor incidence in the Simpson (high tumor) and CBA (low tumor) strains. The work was begun in September, 1938, with a number of young breeding pairs of both strains. There were a number of initial difficulties and progress was slow; some of the mice did not breed, others killed the fostered litters, and still others littered at a time when no foster mother was immediately available. With the outbreak of war it was decided, in view of the necessity for reducing stock and because of the extensive and thorough nature of the investigations being carried out in the United States, to stop further breeding but to allow the fostered animals then living to die naturally. For this reason far fewer mice were fostered and fewer raised in the second and third generations than had been intended. Nevertheless, the results have been more successful than had been expected and are worth communicating.

From a number of Simpson pairs, belonging to inbred generations 13 to 18 and chosen from lines having a high incidence of mammary tumors, 9 pairs produced 17 litters (consisting of 31 females and 27 males), which were successfully fostered to CBA mothers, and another 11 litters that were killed by the foster parents. For perfect comparison, unfostered litter mates of these mice should have been set aside as controls, but this would have caused further delay in the completion of the experiment; consequently, only 4 females from the same families were available as controls, and comparison had to be made with the rest of the strain.

Eight CBA pairs produced 16 litters (comprising 18 females and 19 males), which were successfully fostered to Simpson mothers, and another 6 litters that were killed by the foster parents. There were only 11 female controls from the same families.

1. SIMPSON MICE FOSTERED BY CBA

The Simpson breeding pairs came from 7 inbred lines having the following mammary tumor incidences in virgins and breeders combined: 68.8, 72.5, 70.6, 76.2, 64.5, 63.6, and 71.4 per cent. The average was 69.5 per cent. In a previous communication (19) Table III gave an analysis of the incidences in each line in virgins and breeders separately, and it was shown that in 5 lines out of the 7 the incidence was higher in virgins.

Five of the Simpson mothers bred from in the experiment developed mammary tumors, 3 died before tumor age, and one died nontumorous at 19 months. The litters were removed as soon as possible after birth. The time that elapsed before fostering depended on when a foster mother was available, and only 8 litters were successfully fostered within 24 hours after birth; in other cases from 2 to 5 days elapsed, and in two instances 10 and 11 days passed before fostering. The longer periods are not included in the results shown in Tables I and II.

The CBA strain has a low incidence, about 5 per cent, of mammary carcinoma. None of the foster mothers was tumorous, but on analyzing the separate lines to which they belonged it was found that in 7 there were no tumorous females and in the other 7 the incidence varied from 2.5 to 8.5 per cent (Table I, column 4). None of the tumor mice had been bred from, however, and in any case it has already been shown (19) that breeding from such CBA females does not raise the tumor incidence, these mammary tumors being of the noninheritable type.

The results of the experiment are summarized in Tables I and II, in which only mice aged 6 months and over are included, and from which the following conclusions may be drawn. The numbers concerned are small; nevertheless, there is no evidence that tumor incidence is lower in litters fostered within 24 hours.
than in those in which fostering was delayed; this point will be discussed later. The tumor incidence in the line to which the CBA foster mother belonged did not affect the result; thus litters fostered by CBA mice of lines without mammary carcinoma might still produce tumors (litters 1a and 1b), while litter 7a (of only 2 mice), fostered by a mother belonging to a line with an incidence of 7.5 per cent, had no tumors. In the first (fostered) generation the tumor incidence (55 per cent) shows a slight decrease compared with the parent Simpson lines (63.6 to 76.2 per cent. Table 1, birth all the conditions were such as to favor a high incidence, as in the parent strain, and this section of the experiment merely proves the unreliability of small numbers.

The average age at appearance of tumors in fostered mice was 12.4 months (range of variation = 6 to 17 months); the average age at death of nontumor fostered mice was 13.6 months (6 to 27 months). The average tumor age in Simpson mice is 14.5 months.

A number of fostered mice were bred from; 3 developed tumors (in litters 2a and 4a) and 3 of their 6

<table>
<thead>
<tr>
<th>Simpson litter no.</th>
<th>Simpson parent line</th>
<th>CBA foster mother’s line</th>
<th>Interval between birth and fostering</th>
<th>Total no.</th>
<th>No. with mammary tumors</th>
<th>No. with mammary tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.0</td>
<td>0-24 hrs.</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2a</td>
<td>68.8</td>
<td>2.5</td>
<td>0-24 hrs.</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2b</td>
<td>0.0</td>
<td>0-24 hrs.</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3a</td>
<td>72.5</td>
<td>8.5</td>
<td>0-24 hrs.</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4a</td>
<td>70.6</td>
<td>7.1</td>
<td>0-24 hrs.</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5b</td>
<td>76.2</td>
<td>0.0</td>
<td>0-24 hrs.</td>
<td>2</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>6a</td>
<td>71.4</td>
<td>2.2</td>
<td>0-24 hrs.</td>
<td>2</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>6b</td>
<td>64.5</td>
<td>8.5</td>
<td>2 days</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7a</td>
<td>63.6</td>
<td>0.0</td>
<td>3 days</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table II: Total Mammary Tumor Incidence in Fostered Simpson Mice**

<table>
<thead>
<tr>
<th>Generation</th>
<th>Total no. of females over 6 mos.</th>
<th>Total incidence of mammary tumors</th>
<th>No. of females</th>
<th>Incidence of mammary tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>20</td>
<td>11</td>
<td>13</td>
<td>55.0</td>
</tr>
<tr>
<td>F2</td>
<td>36</td>
<td>7</td>
<td>25</td>
<td>19.4</td>
</tr>
<tr>
<td>F3</td>
<td>29</td>
<td>5</td>
<td>28</td>
<td>17.2</td>
</tr>
</tbody>
</table>

In addition to the data given in Tables I and II, 3 Simpson litters comprising 5 females were fostered by a CBA mouse that had herself been fostered by a Simpson mouse; there were 2 tumors amongst the 5 mice (40 per cent incidence), and in the second (unfostered) generation there was one tumorous female in a litter of 3 (33 per cent incidence). The original fostering took place 5, 10, and 11 days after daughters were tumorous (50 per cent incidence); the rest of the second generation had noncancerous mothers and there were 4 tumor mice out of 30 (13 per cent incidence). The average incidence in the second generation was 19.4 per cent.

Two tumor mice of the second generation were bred from; they had 4 daughters, one of which was tumorous (25 per cent incidence). There were 25 third generation females with noncancerous mothers; 4 of these developed tumors, an incidence of 16 per cent.

These figures show that there is a tendency for the young of tumorous fostered mice to have a higher incidence of mammary cancer than the young of non-tumorous mice.

There were 4 control females from later litters of
the same families as those to which the fostered mice belonged. Two of these (50 per cent) produced mammary tumors.

The incidence of lymphadenopathy in the fostered and succeeding generations is worth recording. There is no sex difference in incidence in any generation. Analysis of the figures for both sexes shows that family 7 has an unusually high incidence (Table III) and, since most of the F₂ mice were raised from this family, is almost entirely responsible for the great increase shown in the second generation. In the other families the incidence is within the range of variation for the strain. It is difficult to account for the high incidence in family 7. The inbred line had a total incidence of lymphadenopathy of 20.4 per cent in 13 generations; in the first 3 generations the incidence was 3 per cent, in the next 6 it was 23.3 per cent; there was a double lymphadenopathy mating in the tenth generation, the incidence in the last 4 generations being 31.1 per cent, i.e., only slightly more than in the preceding generations. The Simpson mother of the fostered mice, a mouse of the 12th inbred generation, had a mammary tumor but no lymphadenopathy.

The incidence of lymphadenopathy in the fostered generation (family 7), 63.6 per cent, was therefore double the immediately previous incidence. The CBA foster mother died at 6 months without lymphadenopathy; there were a few cases of the disease in her ancestry, and the incidence in her own generation was 25 per cent (2 out of 8 mice), a figure considerably higher than the average for the strain (8 per cent). According to Barnes and Cole (7), and to Furth, Cole, and Boon (16), mice belonging to low leukemic strains are not rendered leukemic when nursed by high leukemic stocks, but the incidence in a high leukemic strain is lowered by fostering on a low stock; these 4 were paired with brothers that later developed the disease; the disease was, however, as frequent in the offspring of nonaffected mice as in the young from these 4 pairs.

The high incidence of lymphadenopathy may well have reduced the apparent incidence of mammary carcinoma in F₂, since the average age for lymphadenopathy was 11.9 months (range of variation, 4.5 to 19 months) and the presence of a tendency to develop mammary cancer would therefore remain hidden owing to premature death; in 3 mice the 2 neoplasms occurred together at 15, 15, and 17 months. If the females of family 7 are excluded from Table II, the mammary tumor incidence in those fostered within 24 hours after birth becomes 80 per cent instead of 61.5 per cent in F₁, and 42.9 per cent instead of 24 per cent in F₂. With the exception of 2 mice, 1 male and 1 carcinomatous female, the third generation was raised entirely from family 7. It is worth noting that every female bred from in family 7 in a direct line for 13 generations from Simpson mouse No. 1 of this laboratory developed mammary carcinoma.

Lung tumors were moderately frequent in the experiment: the incidence was 29 per cent in F₁, 37 per cent in F₂, and 34 per cent in F₃. Hepatomas are of common occurrence in the CBA strain but are unknown in the Simpson strain. None appeared in the fostered generation of Simpson mice and only 2 in their unfostered descendants (1 in an 18 month old F₂ female and 1 in a 21.5 month old F₃ male). Such sporadic occurrences have been noticed recently in inbred strains that formerly never produced these tumors.

The only other tumors noted in the present work

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Table III: Incidence of Lymphadenopathy in Fostered Simpson Mice

<table>
<thead>
<tr>
<th>Generation</th>
<th>Total no. of mice</th>
<th>Total incidence of lymphadenopathy</th>
<th>No. of mice</th>
<th>Incidence of lymphadenopathy</th>
<th>No. of mice</th>
<th>Incidence of lymphadenopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁</td>
<td>45</td>
<td>15</td>
<td>34</td>
<td>8</td>
<td>23.5</td>
<td>11</td>
</tr>
<tr>
<td>F₂</td>
<td>73</td>
<td>39</td>
<td>22</td>
<td>5</td>
<td>20.0</td>
<td>51</td>
</tr>
<tr>
<td>F₃</td>
<td>67</td>
<td>46</td>
<td>2</td>
<td>1</td>
<td>50.0</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>185</td>
<td>100</td>
<td>58</td>
<td>14</td>
<td>24.1</td>
<td>127</td>
</tr>
</tbody>
</table>
were two hemangiomas, and one squamous epithelioma of the jaw.

2. CBA MICE FOSTERED BY SIMPSON

Eight pairs of CBA mice produced litters that were successfully fostered by Simpson females. None of the CBA mothers developed mammary tumors and in 6 of the inbred lines to which they belonged no instances dying at 6 months and over, since 6 months was the earliest tumor age in the Simpson strain. Three F₁ and 7 F₂ nontumor females died before 10.5 months, and if these are excluded the average nontumor age becomes 26.8 months (range of variation 19.5 to 35 months); the majority of nontumor mice therefore had ample opportunity to develop tumors. As Table IV shows, most of the litters were fostered within 24 hours.

### Table IV: Incidence of Mammary Tumors in CBA Litters Fostered to Simpson Females

<table>
<thead>
<tr>
<th>CBA litter no.</th>
<th>(1) CBA parent line</th>
<th>(2) Simpson foster mother's line</th>
<th>Interval between birth and fostering</th>
<th>No. of CBA females over 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F₁</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total no.</td>
</tr>
<tr>
<td>1a</td>
<td>0.0</td>
<td>68.8</td>
<td>0-24 hrs.</td>
<td>1</td>
</tr>
<tr>
<td>1b</td>
<td>0.0</td>
<td>71.4</td>
<td>0-24 &quot;</td>
<td>0</td>
</tr>
<tr>
<td>2a</td>
<td>0.0</td>
<td>63.6</td>
<td>6 days</td>
<td>1</td>
</tr>
<tr>
<td>2b</td>
<td>0.0</td>
<td>68.8</td>
<td>6 &quot;</td>
<td>1</td>
</tr>
<tr>
<td>3a</td>
<td>0.0</td>
<td>68.8</td>
<td>0-24 hrs.</td>
<td>2</td>
</tr>
<tr>
<td>4a</td>
<td>0.0</td>
<td>76.2</td>
<td>0-24 &quot;</td>
<td>2</td>
</tr>
<tr>
<td>5a</td>
<td>0.0</td>
<td>68.8</td>
<td>0-24 &quot;</td>
<td>4</td>
</tr>
<tr>
<td>5b</td>
<td>0.0</td>
<td>68.8</td>
<td>0-24 &quot;</td>
<td>1</td>
</tr>
<tr>
<td>5c</td>
<td>0.0</td>
<td>71.4</td>
<td>10 days</td>
<td>1</td>
</tr>
<tr>
<td>6a</td>
<td>0.0</td>
<td>63.6</td>
<td>0-24 hrs.</td>
<td>2</td>
</tr>
<tr>
<td>7a</td>
<td>0.0</td>
<td>68.8</td>
<td>2 days</td>
<td>3</td>
</tr>
<tr>
<td>7b</td>
<td>0.0</td>
<td>68.8</td>
<td>0-24 hrs.</td>
<td>1</td>
</tr>
<tr>
<td>8a</td>
<td>0.0</td>
<td>68.8</td>
<td>68.8</td>
<td>3</td>
</tr>
<tr>
<td>8b</td>
<td>0.0</td>
<td>68.8</td>
<td>0-24 hrs.</td>
<td>1</td>
</tr>
</tbody>
</table>

Indices = number dying at less than 10.5 months.

### Table V: Total Mammary Tumor Incidence in Fostered CBA Mice

<table>
<thead>
<tr>
<th>Generation</th>
<th>Total no. of females over 6 mos.</th>
<th>Total incidence of mammary tumors</th>
<th>Fostered at less than 24 hrs.</th>
<th>Fostered at more than 24 hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>F₁</td>
<td>18</td>
<td>44.4</td>
<td>12</td>
<td>58.3</td>
</tr>
<tr>
<td>F₂</td>
<td>20</td>
<td>35.0</td>
<td>15</td>
<td>33.3</td>
</tr>
<tr>
<td>F₃</td>
<td>29</td>
<td>58.6</td>
<td>24</td>
<td>58.3</td>
</tr>
</tbody>
</table>

The tumor incidence in the fostered females was much less than in the control females. As shown in Tables IV and V, mammary tumors appeared in a number of fostered females and in their unfostered descendants. The average age at which tumors appeared was 20.3 months (range of variation 10.5 to 28 months), while the average age at death of nontumor females was 21.1 months (6.0 to 35 months). The average tumor age for the CBA strain is 27.8 months. Although 10.5 months was the earliest age at which mammary carcinoma appeared in the fostered mice, the analysis is based on the numbers after birth, but in others there was a delay of from 2 to 12 days before a foster mother was available. This delay is probably of less importance when a low tumor strain is fostered by a high tumor strain than vice versa, since, as proved by Andervont and his collaborators (5, 6), young mice are still susceptible to the milk influence when 12 days old, although there was evidence that 7 day old mice were more susceptible than those 14 days old. Admittedly Andervont was working with the C3H strain, which is known to be highly susceptible, and is of course a high tumor strain. There is some evidence in the present work that the period of susceptibility may be shorter in strain CBA (see Discussion).

In the fostered CBA generation, the percentage of tumors in mice fostered after more than 24 hours was much less than the percentage in those fostered...
before 24 hours. In the former group, only 1 tumor
litter 2a) appeared in 6 females. This tumorous
mouse, fostered when 6 days old, was the mother of
both the F2 tumor females in that family; 1 of the
latter was bred from and her 1 daughter was cancer-
ous. The only sister of the same F1 tumor female
latter was bred from and her 1 daughter was cancer-
free at 24 months and had a nontumorous daughter
more than 24 hours are similar to those in the corre-
sponding generations from mice fostered within 24
hours, show that an interval up to 6 days between birth
and fostering does not affect the susceptibility of low
tumor strain mice to the milk influence, and also that
noncancerous fostered mice can absorb the influence
and transmit it to their offspring (10).

As already stated, no mammary tumors occurred
before the age of 10.5 months. If the tumor incidence
is calculated for mice living to that age and over, the
following figures are obtained: There were 7 tumorous
mice out of 9 fostered at less than 24 hours, an inci-
dence of 77.8 per cent; in the second generation there
were 9 descendants of those fostered within 24 hours,
and 5 were cancerous (55.6 per cent), while of the
4 descendants of those fostered after 24 hours 2 de-
veloped tumors (50.0 per cent). The other figures are
unchanged, the remaining classes all having lived more
than 10.5 months. These incidences show an even
more striking increase, compared with the normal
incidence for unfostered CBA mice (5 per cent),
than those based on a minimum age of 6 months; they
also show that although there is a real drop in tumor
incidence in the second and third generations (in the
group fostered within 24 hours), it is exaggerated in
F2 owing to the number of mice dying between 6 and
10.5 months.

The incidence of lymphadenopathy in the fostered
mice and their descendants of both sexes appeared to
be increased (Table VI). The incidence in unfostered
mice of the same inbred lines was 9.4 per cent (limits
of variation 5.8 to 14.1 per cent). The average age at
death from the disease in the fostered animals was
24.6 months (8 to 35 months); there was only 1 death
at 8 months, however, the next being 19.5 months.
The incidences calculated for mice living more than
8 months (the lowest age for lymphadenopathy in the
strain as well as in this experiment) show only a slight
increase over those given in Table VI for mice dying
over 6 months; the figures for 3 generations be-
come 20, 17, and 35 per cent respectively, with a total
average of 25 per cent. The cases were distributed
throughout all the families and none showed a greater
proportion than any other, nor was there any signifi-
cance difference in incidence between the two sexes.
Relatively few breeders (fostered) died of lymphadeno-
pathy, but many died young and they may possibly
have been susceptible. The average age for lymphadeno-
pathy was higher than that for mammary carcino-
ma, and, unlike the fostered Simpson mice, it is
therefore unlikely that many potentially carcinomatous
cases were hidden by lymphadenopathy. In some mice
lymphadenopathy occurred together with mammary
cancer, in others with lung adenoma or hepatoma.

The occurrence of hepatomas was not affected by
fostering. In contrast to the first experiment, in which
no hepatomas were found in Simpson mice fostered
by CBA females, the incidence in CBA mice fostered
by Simpson females was moderately high and similar
to that in unfostered CBA mice. This is in agreement
with Andervont's statement for the C3H strain (4, 5,
20). In the inbred lines from which the fostered mice
came, to the generations used in the experiment, the
average incidence for both sexes was 30 per cent (limits
of variation, 21.5 to 37.5 per cent). The earliest cases
of hepatoma in the experiment were 22 months (fe-
male) and 20 months (male), compared with 13
months (female) and 19 months (male) in the rest
of the strain. Table VII gives the incidences in the
fostered and subsequent generations based on females
dying at 13 months and over and on males dying at
19 months and over. The total average incidence for
both sexes and all 3 generations was 33.3 per cent,
which closely resembles the strain average given above;
as usual, the neoplasm is much more frequent in
males than females. The average hepatoma age was
26.9 months (20 to 36 months); this is higher than
the average mammary tumor age. The hepatoma inci-
dence may therefore be expected to be lower than
normal on account of the number of mice dying of
mammary carcinoma before hepatoma age; this ap-
pears to be the case, since the incidence in females is
below the normal (18 per cent) for females of the
strain (19).

The high incidence of hepatomas in the F2 males
may possibly be explained by the longer life of these
males. The average age at death of 13 F2 males was

Table VI: Incidence of Lymphadenopathy in Fostered
CBA Mice

<table>
<thead>
<tr>
<th>Generation</th>
<th>Total no. of mice (both sexes) over 6 mos.</th>
<th>Incidence of lymphadenopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>F1</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>F2</td>
<td>59</td>
<td>9</td>
</tr>
<tr>
<td>F3</td>
<td>60</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>155</td>
<td>37</td>
</tr>
</tbody>
</table>

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26.3 months, of 38 F₂ males 24.3 months, and of 30 F₃ males 27.2 months; the average hepatoma ages in the 3 generations were 29.8, 26, and 28.4 months respectively; the males of the third generation therefore had the greatest chance to develop hepatomas. There was no evidence that a greater number of these neoplasms appeared in the young of hepatomatous parents. No hepatomatous F₂ females and only 2 hepatomatous males were bred from; only 2 of the 18 hepatomas in F₃ males appeared in the offspring of these 2 males. These facts suggest that some of the F₂ mice must have been potentially hepatomatous but died before developing the neoplasm.

There were 5 unfostered control litters, comprising 11 females and 6 males; of these, 4 females (36.4 per cent) and 5 males (83.3 per cent) were hepatomatous. The average ages at death were high, 29.1 and 28.6 months respectively.

<table>
<thead>
<tr>
<th>Generation</th>
<th>Total number of mice</th>
<th>Incidence of hepatomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males over 19 mos.</td>
<td>Females over 13 mos.</td>
</tr>
<tr>
<td>F₁</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>F₂</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>F₃</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>81</td>
<td>51</td>
</tr>
</tbody>
</table>

Lung adenomas occurred in the fostered generation (25 per cent) and in the subsequent generations (23.7 and 31.7 per cent respectively); the incidence in the control litters was 25.3 per cent.

Other neoplasms observed in this experiment, and which have also been noted in the CBA strain, were as follows:—several hemangiomata at different sites (subcutaneous, liver, mammary tissue), ovarian tumors, sarcoma of the heart, adrenal tumor, and adenoma of the lacrimal gland.

DISCUSSION

When a high mammary tumor strain is fostered by a low mammary tumor strain, the incidence in the fostered mice depends to a very great extent on the time they spent with their own mothers before being fostered. Thus no mammary tumors were obtained in dba mice born from ova transferred to C57 mice soon after fertilization (12, 15). When C3H mice were fostered by C57 mice, Andervont and McEleney (3) showed that mammary tumors appeared in 25 per cent of those fostered within 17 hours after birth, and in 63 per cent of those fostered between 17 and 24 hours, giving an average incidence for both classes of 46 per cent; Andervont (1) found that when C3H young were fostered by strains I, Y, and C, 50 per cent of those fostered up to 17 hours after birth and 86 per cent of those fostered 24 hours after birth developed tumors; similar results were obtained by Bittner (10). It is therefore supposed that, by even one nursing from their own mothers, the young mice receive enough of the milk influence to cause the production of a certain number of tumors (20, 5).

In the first of the present experiments, the incidence in fostered Simpson mice is lower than the average incidence for the strain, but still moderately high; the fostered mice had therefore probably obtained a certain amount of the milk influence from their own mothers. The number of animals concerned is small, and there is possibly no significant difference between those fostered at less than 24 hours and those fostered at greater intervals after birth; as it stands, with a higher incidence in the 24 hour group, the result does not agree with previous work (3, 11).

After allowing for the effect on mammary tumor incidence of the high incidence of lymphadenopathy, there is still a real fall in the incidence of mammary carcinoma in F₂. This may be explained by Bittner's theory (10), which postulates that young mice of a high tumor strain, which have spent a short time with their mothers before being fostered, may obtain enough of the milk influence to produce mammary tumors in themselves, but not enough to pass on to their descendants in sufficient quantity to maintain the high incidence.

Strong's CBA strain is well known for its low incidence of mammary carcinoma, but although used in one of Bittner's earliest experiments (9) very few fostering experiments have been carried out with it. Bittner obtained tumors in 3 of 9 (33.3 per cent) A strain females fostered by CBA, and an incidence of 4.9 per cent in A strain mice fostered by C57. Various facts concerning the CBA strain are reviewed by Bittner (11), and it seems likely that there are different substrains, some of which are more susceptible than others to breast cancer production by estrogenic stimulation or by forced breeding. Thus Bonser, Stickland, and Connal (13) obtained 5 tumors in 32 females treated with estrogens, although their line had until that time never produced a spontaneous mammary
carcinoma. In this laboratory, no mammary tumors were produced with estrone (18), in either males (castrated or noncastrated) or females (ovariectomized or nonovariectomized), but the mammary tissue was stimulated to a preneoplastic degree of activity; yet a number of spontaneous mammary tumors have appeared in the strain, the incidence being about 5 per cent. The tumors are of the noninherited variety, and breeding does not increase the incidence (19).

In the present investigation, when CBA mice were fostered by Simpson females the mammary tumor incidence was raised to an average of 44.4 per cent, or 77.8 per cent in those living over 10.5 months and fostered within 24 hours. This proves that the CBA strain is susceptible to the milk influence. The strain has a low mammary tumor incidence, therefore, not because the mice are genetically nonsusceptible like the C57, but because they lack the milk influence. In this, strain CBA resembles strain C (1); Andervont was able to raise the tumor incidence in the latter from 0 to 64 per cent by fostering on C3H females. Andervont (2) has also raised the tumor incidence in C57 to 63 per cent by fostering on C3H; this is a remarkable increase in a strain that has always been regarded as being genetically nonsusceptible to the milk influence. The usual incidence obtained in C57 by fostering is about 10 to 15 per cent (1, 11), but higher incidences, 20.9 per cent, by fostering on strain A, were reported by DeOme (14), and 20 per cent in breeders fostered by dba by van Gulik and Korteweg (21), while Fekete and Little (15) obtained an incidence of 50 per cent by transfer of fertilized ova. Possibly different substrains of C57 have been developed, with different susceptibilities to the milk influence; there is also the possibility that different high tumor strains used as foster mothers may be able to produce different incidences in the low tumor fostered strain by transmitting different concentrations of the milk factor.

Having acquired the milk influence from the Simpson foster mothers, CBA females are able to transmit it to subsequent generations; in the present experiment the tumor incidence in the second and third generations remained high. In several instances tumors appeared in the second and third generations bred from fostered females that had died tumor-free. In this connection, the low incidence in the group fostered at more than 24 hours after birth is of interest, since the mice had obviously acquired the milk influence and were able to transmit it to their descendants, as proved by the increased tumor incidence, yet had not themselves (with one exception) developed tumors, although dying at 24, 17.5, 28.5, 26.5, 29, and 24.5 months respectively (average=25 months); the 1 tumorous mouse was that which died at 17.5 months. Although such small numbers are involved, the result suggests that during the time the young CBA mice spent with their own mothers before fostering (from 6 to 12 days), their mammary tissue had already passed the susceptible stage. The mammary glands of fostered and unfostered mice have been shown to develop differently (21). In a high tumor strain like C3H, the young mice are known to remain susceptible to the milk influence up to 14 days (5, 6). Probably the period of susceptibility varies in different strains. This seems a more likely hypothesis than the possibility of the young CBA mice acquiring some influence from their own mothers in 12 days that is able to neutralize the immediate effect of the mammary tumor inciter without preventing its transmission to the offspring of the fostered mice. The latter hypothesis could scarcely be reconciled with previous work (5, 6), in which young C3H mice were fostered by C57 for varying periods before being returned to their own mothers.

SUMMARY

When females of the Simpson (high mammary tumor) strain were fostered by mice of Strong's CBA (low mammary tumor) strain, the incidence was reduced from 69.5 per cent (average age=14.5 months) to 55 per cent (average age=12.4 months). There was unavoidable delay in fostering some of the litters, and even some of those fostered within 24 hours after birth had probably been suckled by their own mothers.

There were fewer mammary tumors in the offspring of the fostered Simpson mice, partly because of a greatly increased mortality from lymphadenopathy. The offspring of fostered tumorous females had a higher tumor incidence than the young of fostered nontumorous mice.

The mammary tumor incidence in CBA females fostered by Simpson mice was raised from 5 per cent (average age=27.8 months) to an average of 44.4 per cent (average age=20.3 months) in all those dying over the age of 6 months, and to 77.8 per cent in those fostered within 24 hours and dying over the age of 10.5 months.

The CBA fostered females were able to absorb the milk influence and transmit it to their offspring even when they themselves died nontumorous; tumors appeared in the young of nontumorous as well as of tumorous fostered females.

There was a very great increase in lymphadenopathy in fostered Simpson mice and their offspring; there was also a definite though smaller increase in the disease in fostered CBA mice and their descendants.

Fostering had no effect on the incidence either of lung adenomas or of hepatomas, except in so far as mice developed mammary carcinomas before reaching the normal lung or liver tumor age.
When young CBA mice had spent from 6 to 12 days with their own mothers before being fostered to Simpson females, they were no longer susceptible to the action of the milk influence, although they were able to transmit it to their young. Possible reasons for this are discussed.

REFERENCES

The Effect of Foster Nursing on the Incidence of Spontaneous Mammary Carcinoma in Two Inbred Strains of Mice

E. W. Miller and F. C. Pybus