The Effect of Pregnancy on Sarcoma 180 in Albino Swiss Mice*

F. Homburger and Abraham Tregier

(Cancer Research and Cancer Control Unit, Tufts College Medical School, Boston, Mass.)

It has been observed that transplanted tumors in rats and mice sometimes regress during pregnancy (3, 6), the tumor growth usually being more noticeably inhibited in the later stages of pregnancy (1). Spontaneous breast adenocarcinoma in F1 hybrids (from C57BL females mated to RIII males) have been reported to regress after parturition or “a little before” parturition (4).

This report summarizes the effects of mating1 and pregnancy on the growth of tumors in albino Swiss mice as observed in four experiments that ran from 2 to 4 months each,2 each experiment comprising animals in the same age group. The mice used were virgin females from 8 to 16 weeks old, taken from our own stock colony in which Sarcoma 180 from the Jackson Memorial Laboratory has been grown since 1951. In the previous 35 passages of this tumor, which has been transplanted every 7 days, spontaneous regression has occurred in 16 per cent of 177 animals.

MATERIALS AND METHODS

A total of 281 mice was used. All were fed Purina Laboratory Chow and water ad libitum and were kept in an air-conditioned room maintained at 72°F. The 103 controls that were not mated were segregated in groups of not more than six to a cage.

The 178 mice that were to be mated were placed with healthy males 12 weeks old, generally one female and one male to a cage but sometimes two females and one male, and were kept together throughout the experiment. Some mothers had two, and some had three litters. The offspring were weaned when they were 3 or 4 weeks old.

In experiments I and II, cytologic studies of vaginal smears from 60 mated animals were performed twice weekly for 3 weeks, but uterine infection in five animals and the consequent death of two prompted discontinuance of such studies. In experiments III and IV the date of conception was therefore calculated by subtracting 19 or 20 days from the date of delivery.

The customary trocar method was used for transplanting fragments of freshly cut tumor, suspended in small amounts of saline, into both axillary regions. Only well preserved tumors free of necrosis were used. Special care was taken to minimize contamination by blood or other tissues.

Body weights were taken before transplantation of tumors and at the end of the experiment. The tumors were measured with calipers in two diameters every 2 days. Grading was based on the size of the tumor relative to its size on the 7th day after transplantation (see Chart 1). The tumors

---

1 As used in this report, the term “mating” is to be understood as “inferred copulation,” the date taken as the time of mating being the date when males and females were placed together.

2 Some of the animals in which Sarcoma 180 was transplanted 1 year ago are still in good health.

Received for publication February 4, 1954.

490
Homburger and Tregier—Effect of Pregnancy on Sarcoma 180

were thus self-related by data that illustrate their behavior with time and varying conditions. All animals were eventually autopsied, and histologic sections were taken from the tumors—from the transplant sites in those animals in which the tumors had regressed, and from any organ which did not appear normal on gross inspection.

Experiments

Experiment I.—Tumors were implanted into 75 mice. The tumors were measured 7 days later. Then 48 of the mice were mated, 7, 10, and 16 days after tumor transplantation.

Experiment II.—Tumors were implanted into 56 mice after 40 of them had been mated for periods of from 6 to 12 days.

Experiment III.—Tumors were implanted into 84 mice. Four days later, 50 of the mice were mated.

are not always fruitful, or to a disturbance in the estrous cycle of the tumorous mouse, or to rapid tumor growth.

The average rate of regression in these nonpregnant mated mice was 23 per cent (26 out of 114), almost twice that in the virgin controls. Specifically, in the first three experiments, in which the time between transplantation and mating was at least 4 days, it was 2-3 times higher. In experiment IV, in which the interval was only 24 hours, regressions in the virgin controls were 2½ times those in the nonpregnant mated animals.

The spontaneous regressions required from 3 to 8 weeks, whereas regressions due to pregnancies or sterile mating were often considerably more rapid. There was occasionally a "secondary" tumor (see Chart 2), due either to small tumor implants scattered by the trocar or to subcutaneous

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGRESSION OF SARCOMA 180 IN FEMALE ALBINO SWISS MICE</td>
</tr>
</tbody>
</table>

Comparative Data Summarizing Four Experiments*

<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>TUMORS IMPLANTED</th>
<th>PREGNANT MATED MICE</th>
<th>NONPREGNANT &quot;MATED&quot; MICE</th>
<th>CONTROLS NONHATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>75</td>
<td>22</td>
<td>90</td>
<td>26</td>
</tr>
<tr>
<td>II</td>
<td>56</td>
<td>25</td>
<td>68</td>
<td>15</td>
</tr>
<tr>
<td>III</td>
<td>84</td>
<td>10</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>IV</td>
<td>66</td>
<td>7</td>
<td>71</td>
<td>53</td>
</tr>
<tr>
<td>Totals</td>
<td>281</td>
<td>64</td>
<td>81</td>
<td>114</td>
</tr>
</tbody>
</table>

* Tumors transplanted in virgin mice 8-16 weeks old.
† Experiment I: 7, 10, 16 days before mating. II: 6, 11, 18 days after mating. III: 4 days before mating. IV: 24 hours before mating.

RESULTS

Only the end-point—either complete regression of the tumor or progression of the tumor and death of the animal—has been considered in our interpretation of the data. The data of all four experiments have been summarized in Table 1.

Spontaneous regression was complete in thirteen of the 103 nonmated controls. This rate of 13 per cent is close to the over-all regression rate of about 16 per cent observed in the previous generations of transplants of this same tumor in albino Swiss females.

Only 64 of the 178 mated animals became pregnant. In this group there were 52 regressions, an average of 81 per cent. It is understood that "mating" refers to the opportunity for copulation; the 114 nonpregnant females kept with males may never actually have been inseminated, but this is highly unlikely. Nonfertility may have been due to the fact that these were first matings, which

spread of the primary tumor. If such a tumor progressed and killed the animal, it was considered progression even though the primary tumor may have regressed; but if the secondary tumor also regressed completely, the case was classified as a regression.

In all regressing secondary tumors the mode of regression was by absorption without skin break. In the others, regression went on to complete disappearance either by sequestration and necrosis or by absorption without skin break.

Downloaded from cancerres.aacrjournals.org on July 19, 2017. © 1954 American Association for Cancer Research.
The histology of the tumors at various stages of regression was studied in a number of animals, and in some instances counts of mitoses were made. The first sign of regression appeared as a rim of necrosis at the periphery of the tumors, followed by a fibrous reaction of the surrounding stroma, resulting in many cases in replacement of the necrotic portions of the tumor by granulation and fibrous tissue and eventually in sequestration of the tumor. Regressing and progressing tumors showed similar mitotic rates.

**DISCUSSION**

The data on the pregnant mice may be summarized as follows: When the tumor was transplanted from 7 to 16 days before mating (experiment I), the rate of regression was 91 per cent. When the tumor was transplanted 4 days before mating (experiment III), the rate of regression was 100 per cent. Tumors implanted 24 hours before mating (experiment IV) regressed at the rate of 71 per cent, whereas tumors implanted from 6 to 12 days after mating (experiment II) regressed at the rate of 69 per cent. Since implantation of the tumor in experiment II must have been made during pregnancy, there may be a slight basis for postulating that tumors having their inception during pregnancy or shortly before it (experiment IV) regress less frequently than those arising from 4 to 16 days (in the case of the mouse) before conception.

In the case of the nonpregnant mated mice when the tumor was transplanted from 7 to 10 days before mating, from 6 to 12 days after mating, or within 4 days of mating, the rate of regression was about the same, 31, 38, and 28 per cent, respectively. It was only 6 per cent when implantation and mating were simultaneous.

The mechanism of tumor regression during pregnancy, which seems largely independent of the time relationship between transplantation, mating, and pregnancy, is poorly understood. It is possible that the predominance of estrogen during pregnancy approaches the conditions of the experiment of Nathanson and Salter (5) on the inhibiting effect of estrogens on the growth of transplanted tumors. The histologic evidence in our experiments, indicating primarily a host defense reaction as a cause of tumor regression, renders this interpretation even more likely.

Our histologic studies showed that mitosis in regressing and progressing tumors was similar. In the regressing tumors, peripheral necrosis was followed by intensive connective tissue formation; in the progressing tumors, the necrosis that frequently occurred was always located in the center of the tumors. This could be interpreted as indicating that the regression of Sarcoma 180 observed in our studies is the result of a host reaction to the tumor growth rather than a direct inhibition of malignant cellular proliferation.

Bischoff and Maxwell (2) have credited gonadotropins with causing regressions in Sarcoma 180. Their animals lost weight, however, whereas the mice in the present study gained weight as the tumors regressed.

In contrast to Baatz's observations of accelerated growth of Ehrlich's carcinoma in the lactation period (1), our observations were that some regressions of Sarcoma 180 continued during lactation.

In our studies acceleration of tumor growth was observed in experiment IV, in which transplantation and mating took place within 24 hours. Only 6 per cent of tumors regressed in the nonpregnant mated mice, compared to 15 per cent in the controls. A similar observation is that made in our laboratory (unpublished data) on F1 offspring of noninbred albino Swiss parents, in which Sarcoma 180 had spontaneously regressed. In adult offspring of these animals a high incidence of spontaneous regression prevailed. However, when Sarcoma 180 was implanted into such offspring at the time of sexual maturation rapid and fatal tumor growth ensued.

It might be hypothesized that transplantation of Sarcoma 180 in Swiss mice at period of hormonal imbalance, such as at puberty or at first mating, renders the growth of the tumor more malignant.

A positive explanation of the observed regression and acceleration of the growth of Sarcoma 180 is still to be had. Besides the hormonal, immunologic, and metabolic changes in pregnancy, competition for nutrients between the fetuses and the tumor must also be considered as a possibility affecting the influence of pregnancy on the growth of the tumor. These studies, however, appear to warrant the conclusion that pregnancy can induce complete regressions of Sarcoma 180 in Swiss mice. Even sterile mating can have a similar effect under certain conditions. Under conditions of simultaneous transplantation and first sterile mating, however, the tumor may be rendered more malignant. Because of the relatively high percentage of spontaneous regressions (16 per cent and 13 per cent) in previous generations and in the experimental controls of this Sarcoma 180, the basic
malignancy of our tumor might be questioned. However, when implanted in albino Swiss mice intraperitoneally, Sarcoma 180 invariably caused death by very malignant and rapid tumor growth. Fatal growth of this tumor nearly always occurred in C57BR/a and C57BL/6 hosts.

SUMMARY

In four experiments with 281 female albino Swiss mice, it was observed that pregnancy effected from 68 to 100 per cent complete regressions of Sarcoma 180. The higher rates of regression occurred in fertile females, mated from 4 to 16 days after transplantation of the tumor.

Regressions also occurred in from 28 to 31 per cent of sterile females, mated from 4 to 16 days after and from 6 to 12 days before transplantation of the tumor. The percentage of regressions was 2–3 times greater than that observed in the non-mated virgin controls. The progression of tumors resulting in death of the nonpregnant animal was greatest (94 per cent) when the tumor was transplanted within 24 hours before sterile mating.

It is concluded that pregnancy may present conditions unfavorable to tumor growth and that sterile mating (not coincident with inception of tumor) may also change the receptivity of the host.

REFERENCES

The Effect of Pregnancy on Sarcoma 180 in Albino Swiss Mice

F. Homburger and Abraham Tregier


| Updated version | Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/14/7/490 |

**E-mail alerts**

Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.