The Effect of Castration, Theelin, and Testosterone on the Incidence of Leukemia in a Rockefeller Institute Strain of Mice*

James B. Murphy, M.D.

(From the Laboratories of the Rockefeller Institute for Medical Research, New York 21, N. Y.)

The pronounced difference in susceptibility to leukemia between the sexes has as yet received no satisfactory explanation. In man, with the several types of the disease, 60 to 79 per cent of the cases are in males (1, 6, 7). In the majority of strains of mice showing a high leukemia incidence the ratio of susceptibility is the reverse, with the females showing an incidence often a third higher than the males. In considering an explanation there is a possibility that one sex may be more susceptible to the effect of inciting agents that are supposed to play some role in initiating the disease process. In support of this idea there is some evidence that the blood-forming tissues of men are more receptive than those of women to the stimulating effect of benzol (5). It seems more likely, however, that the differences in the incidence of leukemia between the sexes is in some way influenced by the endocrine system. The following investigation was undertaken to test this possibility.

MATERIALS AND METHODS

The mice used in the tests were from the highly inbred Rockefeller Institute Leukemia Strain (R.I.L.). At approximately 4 weeks of age the females were divided into 3 groups, with litter mates in each group when possible. The animals in one group were ovariectomized and each given subcutaneously a pellet of testosterone propionate 2 mgm. in weight, and 26 of the group were normal, untreated controls.

The results of this experiment are given in Fig. 1.

EXPERIMENTS

Females.—The 93 female mice in this test were divided as follows: 31 were ovariectomized, 36 were ovariec
these 2 groups, as shown by the form of the curves on
the time of development or the total incidence of leu-
kemia. The curve for the castrated females treated
with testosterone propionate is distinctly different.
The disease not only appeared at a later age period,
but only 58.3 per cent of the mice developed leukemia,
which contrasts with 88.4 per cent and 90.3 per cent
respectively for the controls and the untreated castrated
animals. The later onset of the disease in the treated
castrates is shown by the fact that the average age at
death from leukemia was 299 days, while the other
2 groups averaged 248 days and 253 days.

Males.—Of the 99 male mice in this group 34 were
castrated, 37 were castrated and given subcutaneously
a pellet of theelin weighing approximately 3 mgm.,
and 28 were untreated to serve as controls.

The results, as shown in Fig. 2, demonstrate a sharp
contrast between the castrated and control males. The
97 per cent incidence of leukemia for the former is
the highest so far encountered in any group from the
strain, and this is significantly different from the
53.5 per cent for the controls. The average ages at
death from leukemia, 260 days for the castrated as
compared to 300 days for the controls, indicate the
later onset of the disease in the latter. The toxic effect
of theelin was so great that it caused the death of the
majority of the treated mice before or in the early
leukemia age period. It is considered that the figures
for this group have no significance, but it is interest-
ing to note that between the 20th and 30th weeks of
age the rate was definitely higher than in the controls,
and even a little higher than in the castrated males.

For comparison the results with the 4 important
groups from the foregoing experiments have been
brought together. It will be noted in Fig. 3 that the
curve for castrated males is almost identical with that
for the female controls, and there is the same agree-
ment between the male controls and the castrated fe-
males treated with testosterone propionate. The data
in Table I further emphasize these similarities. The
total incidence of leukemia for castrated male mice is
97 per cent, with 260 days as the average age at death
from leukemia; and these figures closely approximate
those for the control females, which had an incidence
of 88.4 per cent and an average age at death of 253
days. The incidence and survival period for the intact
males closely approximate the figures for the ovariecto-
tomized female mice treated with testosterone.

<table>
<thead>
<tr>
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<th>Average age at death from leukemia, days</th>
<th>Leukemia rate, %</th>
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<tbody>
<tr>
<td>Control females</td>
<td>26</td>
<td>253</td>
</tr>
<tr>
<td>Castrated males</td>
<td>34</td>
<td>260</td>
</tr>
<tr>
<td>Control males</td>
<td>28</td>
<td>300</td>
</tr>
<tr>
<td>Testosterone-treated, castrated females</td>
<td>36</td>
<td>299</td>
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DISCUSSION

Judged by the results of the present study the differ-
ence in leukemia incidence between male and
female mice of the R.I.L. strain appears to be the
result of some inhibitory action exerted by the male
sex hormone, rather than a stimulation from the
ovarian secretion. This conclusion is based on the fact that the leukemia rate in ovariectomized and intact females is almost identical, and these figures are somewhat exceeded by the rate for castrated males. On the other hand, ovariectomized females treated with testosterone propionate have a rate significantly lower than the 3 groups above, and this closely approximates the rate for intact males. Gardner (2) and Lacassagne (4) have reported that the incidence of leukemia is increased in some stocks of mice by prolonged treatment with estrogenic hormones. More recently Gardner, Dougherty, and Williams (3) have reported that estrogenic hormones increase the incidence of lymphoid tumors in some strains but not in others. It is of interest to note that there is no constant sex difference in the rate of occurrence of lymphoid tumors in mice. In the present test of the effect of theelin on castrated males of the R.I.L. strain under observation is due to an inhibitory effect of the male sex hormone rather than to a stimulation of the ovarian secretion.

So many of the castrated males treated with theelin died before or in the early leukemia age period that not a sufficient number were left to give significant figures on the leukemia incidence in this group.

**SUMMARY**

The spontaneous leukemia rate in the females of the Rockefeller Institute Leukemia Strain of mice is consistently higher than in the males. In the present experiments the incidence in ovariectomized females was 90.3 per cent, in intact females 88.4 per cent, and in castrated males 97 per cent. These figures are significantly different from the incidence in intact males, 53.5 per cent, and in ovariectomized females treated with testosterone propionate, with a rate of 58.3 per cent. On the basis of these findings it is suggested that the sex difference in susceptibility in the mouse strain under observation is due to an inhibitory effect of the male sex hormone rather than to a stimulation of the ovarian secretion.

**REFERENCES**

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