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

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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 approximately 3 mgm. in weight, and 26 of the group were normal, untreated controls. The results of this experiment are given in Fig. 1. The curves are based on the cumulative percentage of leukemia estimated at 5 week intervals. The disease does not appear before the 20th week of age, and in the controls and ovariectomized mice the rate increases rapidly thereafter. There is little difference between

![Graph showing the incidence of leukemia in female mice after castration, theelin, and testosterone treatment.

Fig. 1. — The points on the curves represent the number of mice that had developed leukemia by the age indicated, expressed as a percentage of the initial number of animals.

Females. — The 93 female mice in this test were divided as follows: 31 were ovariectomized, 36 were ovariectomized and each given subcutaneously a pellet of testosterone propionate approximately 3 mgm. in weight, and 26 of the group were normal, untreated controls.

The disease, after it develops, runs a fairly acute course and is characterized by considerable enlargement of the lymph nodes and extensive involvement of the thymus. The liver may be infiltrated, but the number of circulating white blood cells does not reflect the severity of the tissue involvement.

EXPERIMENTS

Females. — The 93 female mice in this test were divided as follows: 31 were ovariectomized, 36 were

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these 2 groups, as shown by the form of the curves on the time of development or the total incidence of leukemia. 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 interesting 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 agreement between the male controls and the castrated females 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 ovariectomized female mice treated with testosterone.

<table>
<thead>
<tr>
<th>Number</th>
<th>Average age at death from leukemia, days</th>
<th>Leukemia rate, %</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

**DISCUSSION**

Judged by the results of the present study the difference 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. stock the incidence of leukemia in mice under 30 weeks of age was as high as that in the intact females and the untreated castrated males. Too few animals survived the toxic effect of the hormone to give data of any value for the later age periods. However it seems unlikely that estrogens would increase the rate above that noted in the untreated castrated males (97 per cent).

While the reported results indicate some inhibitory action of the male sex hormone, with the known interrelation between the endocrines this cannot be accepted as necessarily a direct effect on the lymphoid tissue. No attempt is made to correlate the present findings with our observations on the role of the adrenals in susceptibility to a transplanted leukemia of rats (8, 9).

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.

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.

Note: Since this paper went to press the following article has appeared: McENERNEY, D. P., BOON, M. C., and FURTH, J. On the Role of Thymus, Spleen, and Gonads in the Development of Leukemia in a High-Leukemia Stock of Mice. Cancer Research, 4:377-383. 1944. It is reported that in the Ak stock of mice the incidence of leukemia in mice ovariectomized at 23 to 56 days of age was 45 per cent, as compared to 74 per cent for the controls. Among males subjected to orchidectomy at 20 to 56 days the incidence of leukemia was 60 per cent, as compared with 52 per cent among the controls. The results with this stock appear to differ materially from those with the R.I.L. mice. This may be due to the ages at which the gonads were removed. In our experiments the average age at removal was under 4 weeks. The authors mentioned above made no distinction between animals gonadectomized before and after reaching maturity.

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REFERENCES

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