Observations on Leukemia in AKR Mice Born from Transferred Ova and Nursed by Low Leukemic Mothers*

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In some inbred strains of mice a large number die of leukemia. The role of heredity in leukemia has been studied by many investigators, who have observed leukemic incidences in hybrids of high and low leukemic strains. Reviewing these studies, Furth (9) states that the evidence that genes are a strong influence on the incidence of leukemia is conclusive but that environmental factors modify the expression of genetic tendencies.

In the present paper a study of the effects of extrinsic influences on leukemia in AKR/Fe strain of mice is reported. Two new lines were originated from this strain at the F32, 33, and 34th generations of inbreeding. One line was derived from animals which were nursed by low leukemic foster mothers; the other line was derived from mice born from fertilized AKR/Fe ova which were transferred into the uteri of low leukemic mothers and were nursed by them. In genetic composition these new lines were identical with the AKR/Fe mice. They differed in extrinsic influences to which they were exposed. These were (a) the influence of nursing by low leukemic mothers and (b) the combined influences of such nursing and uterine environment of low leukemic mothers. For low leukemic mothers the C3H e mice were used. The origin of this and of AKR/Fe strains have been reviewed by Carter et al. (8). Hereafter, the strains will be referred to by the strain symbols only.

EXPERIMENTAL

THE ORIGIN OF LINE AKR

This line was started from foster-nursed AKR mice in the following way. Two females of the AKR strain were killed on the last day of their pregnancy and their young removed by cesarean section. One of the litters consisted of two males and two females, the other of three males and three females. They were foster-nursed by C3H e mice, which in addition to a low incidence of leukemia have a low mammary tumor incidence.

The foster-nursed AKR designated as AKRf mice were mated to their litter-mates, and this type of mating has been maintained since. The young of later generations have been nursed by their own AKR mothers.

THE ORIGIN OF LINE AKRr

This line was started from fertilized eggs of AKR mice (donors) which were transferred and born to C3H e mothers (recipients).

Both the donors and the recipients were mated to fertile males. In the case of the donors the males were brothers of the females. Two or 3 days after mating, as evidenced by the presence of vaginal plugs in both the donors and recipients, the donors were killed. The ova were collected by cutting up the oviduct in small pieces in a watch glass containing saline. They were transplanted immediately into the uteri of the anesthetized recipients. There were ten young, four males and six females, born from these transferred ova. They were nursed by their C3H e mothers. Five of these animals were born from ova transferred when in the four- to six-cell stage, and five from ova in the morula stage. In this way the ova of the donors were isolated at a very early stage from the high leukemic mothers and developed in a low leukemic uterine environment.

These animals were mated inter se. Among the six females, one never had any litters; two had only one litter each, and the young died before reaching weaning age. The descendants of the remaining three females established the AKR r line.

THE INCIDENCE OF LEUKEMIA

C3H e.—In this line which was used for recipients of AKR ova and for foster mothers, the leukemic incidence was very low (0.4 per cent in 250 animals).

AKR.—The incidence of leukemia in 101 males...
and females of the AKR strain which was used for donors was 84 per cent at an average age of 254 days.

**AKRα**—Females and males of the first four generations are included here. Of the original ten animals which were nursed by CSHα mothers one died young, seven developed leukemia, and two died of other causes. They and their descendants totaled 77 mice of which 64, or 83 per cent, developed leukemia at an average age of 284 days. The remaining thirteen died without leukemia at an average age of 320 days.

**AKRβ**—Females and males of the first three generations are included here. All ten mice born from transferred ova developed leukemia. They and their descendants totaled 107 mice of which 85, or 80 per cent, developed leukemia at an average age of 281 days. The remaining 22 died without leukemia at an average age of 337 days.

### TABLE 1

<table>
<thead>
<tr>
<th>STRAIN</th>
<th>LEUKEMIC MICE</th>
<th>NONLEUKEMIC MICE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of mice</td>
<td>Per cent</td>
</tr>
<tr>
<td>CSHα</td>
<td>101</td>
<td>84</td>
</tr>
<tr>
<td>AKRα</td>
<td>77</td>
<td>88</td>
</tr>
<tr>
<td>AKRβ</td>
<td>107</td>
<td>80</td>
</tr>
</tbody>
</table>

The leukemic incidences of the three AKR lines do not show any significant differences. The data are presented in Table 1.

The manifestation of leukemia in all three AKR lines is also similar, and the classification of generalized lymphocytic leukemia can be applied to all the cases. The symptoms of the disease are the visible enlargement of the superficial cervical lymph nodes, palpable enlargement of the axillary and inguinal lymph nodes, and frequently labored breathing due to the enlargement of the thymus. Animals that showed these symptoms were killed and autopsied, some of the leukemic tissues were sectioned, and diagnosis was confirmed by microscopic examination. In some cases the animals died, and diagnosis depended on either gross examination or previous records of observed lymph node enlargements. In addition to the enlargement of the subcutaneous lymph nodes the internal nodes, the liver, spleen, and thymus were usually found to be enlarged. In some cases the ovaries, kidneys, and lungs were also involved.

### OTHER TUMORS

There were a few other tumors. One AKRα female and one AKRβ female each had an adenocarcinoma of the mammary gland. Neither of these animals had leukemia. One of the AKRβ mice had a primary lung tumor in addition to leukemia.

### DISCUSSION

It has been reported by several investigators (1, 10, 12) that a slight decrease in leukemic incidence occurs in high leukemic strains of mice if they are foster-nursed by low leukemic mothers. Similarly, a lower leukemic incidence was also noted in those hybrids of reciprocal crosses between high and low leukemic strains which were born to the low leukemia females. Law (11) states that in a cross between AKR and NH strains the low leukemic NH mothers contributed to their offspring a definite resistance to spontaneous leukemia.

Furth, Cole, and Boon (6) found that, although foster nursing by low leukemic dams lowered the incidence of leukemia in the high leukemic stock, the next generation behaved as would nonfostered mice.

In our experimental animals a resistance to spontaneous leukemia contributed by low leukemic foster mothers was not evident. Neither those mice which nursed low leukemic foster mothers and those which were born from transferred ova nor their descendants showed any significant decrease in incidence of leukemia.

Gross (9) has reported that a leukemic agent is present in the AKR mice. He inoculated suckling mice of his CSH line with AKR leukemic extracts and observed that 46 per cent of the inoculated animals developed spontaneous leukemia at an average age of 5.2 months. He suggests (7) that the mouse leukemic agent is transmitted from parents to their offspring and that the transmission of the agent occurs most probably directly through the embryos. He also reports that the leukemic agent is present in normal testes and ovaries of young mice of the AK line (8).

Furth has pointed out in two of his papers (4, 5) that Gross’ experiments are vulnerable. He states that (4) “There is no virus known with properties which can be reconciled with results of the genetic and nursing studies of leukemia. Should there be such a virus, the genetic studies might mean that: (a) the virus is transmitted by both parents (sperm and ovum) to all offspring, (b) the incidence of leukemia depends on genetic resistance factors acquired from the low leukemia strain and modified by non-hereditary factors.”

The present experiments cannot prove or disprove whether a transmission of an agent occurs from parents to offspring in AKR mice. However, if such a transmission does occur it must take
place prior to the implantation of the embryo in the uterine mucosa. The results of our experiments are in accordance with genetic theories which maintain that the inherited characters are predetermined by the genic combinations of the united paternal and maternal chromosomes forming the zygote. Extrinsic factors such as the effect of nursing by low leukemic foster mothers or the combined effect of such nursing and uterine environment of low leukemic mothers did not change the leukemic incidence appreciably.

SUMMARY

From two litters of high leukemic AKR mice removed from their mothers by cesarean section and foster-nursed to low leukemic C3Hf females a line designated as AKRf has been developed. Of 77 AKRf mice, in the first four generations 83 per cent developed leukemia at an average age of 284 days.

From mice born from fertilized ova of high leukemic AKR mice transferred to the uteri of low leukemic C3Hr females, a line designated as AKRe has been developed. Of 107 AKRe mice in the first three generations 80 per cent have developed leukemia at an average age of 281 days.

These leukemic incidences do not differ significantly from that of the original AKR strain, which in 101 animals is 84 per cent at an average age of 284 days.

Extrinsic factors such as (a) the influence of nursing by low leukemic foster mothers and (b) the combined influence of such nursing and uterine environment of low leukemic mothers do not alter the incidence of leukemia. Thus, the expression of genetic tendencies has not been altered by the extrinsic factors studied.

REFERENCES

Observations on Leukemia in AKR Mice Born from Transferred Ova and Nursed by Low Leukemic Mothers

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