The Effect of Maternal Influence upon Spontaneous Leukemia of Mice*

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The effect of maternal influence upon spontaneous leukemia was first investigated by MacDowell and Richter (6). Reciprocal crosses between mice of their high (H) and low (L) leukemia stock gave the following values for spontaneous leukemia:

H/L[1]	61% leukemia	(139 mice)
L/H	42% leukemia	(106 mice)

They state that reciprocal fostering did not influence the incidence of leukemia but no figures are given.

In a similar study made in this laboratory (4) with two different stocks, reciprocal crosses yielded the following values for the incidence of spontaneous leukemia:

H/L	21.9% leukemia	(192 mice)	28.1% in ♂ 15.6% in ♀
L/H	11.6% leukemia	(173 mice)	8.8% in ♂ 14.6% in ♀

In contrast to the observations of MacDowell and Richter, fostering in experiments made in this laboratory lowered the incidence of leukemia in the high leukemia stock but did not produce leukemia in the low leukemia stock (1) as shown by the following figures:

H not fostered	60% leukemia	(432 mice)
H fostered by L	32% leukemia	(176 mice)
L not fostered	2% leukemia	(510 mice)
L fostered by H	2% leukemia	(181 mice)

These figures suggested the possibility of some maternal influence and for this reason a new series of experiments was undertaken: (a) Mice of the high leukemia stock (Ak) were crossed with mice of a low leukemia stock (C3H) which carries a strong milk influence for mammary carcinoma, thus enabling quantitative observations in the same experiments on manifestations of a known milk influence (Table I). (b) For the same purpose reciprocal fosterings were made between Ak and C3H mice (Table II).

Table I shows that the incidence of leukemia was somewhat lower when the C3H stock was used as the dam. This effect was observed for both the male and female progeny. The progeny from the C3H dam show effect of the milk factor as indicated by a much higher incidence of breast cancer. Thus all three sets of data available (4, 6, and those above) give significantly higher values for leukemia in H/L crosses than in L/H crosses.

This effect is not due to differences in age at death as indicated by comparison of Figs. 1 and 2. When the high leukemia stock was used as a dam, the peak in the incidence of leukemia occurred at 8 to 10 months, in the reciprocal cross at 12 months. A relatively large proportion of hybrid mice lived beyond 16 months of age and had sufficient opportunity to demonstrate a genetic tendency for the development of leukemia.

TABLE I: THE INCIDENCE OF LEUKEMIA AND TUMORS IN RECIPROCAL CROSSES BETWEEN AK AND C3H MICE

Mice: Stock		Number	Incidence of neoplasms, per cent: Breast	Lung	Leukemia
Ak ♀ × C3H ♂	♀ virgin	108	1	2	48
	♂	93	..	3	54
	♀ + ♂ total	201	..	2	50
C3H ♀ × Ak ♂	♀ virgin	111	14	4	39
	♂	94	..	4	28
	♀ + ♂ total	205	..	4	34

The peak of mortality from leukemia occurs at 8 to 9 months in the Ak stock. Thus in both F_1 hybrids, the peak in the leukemic mortality occurs later than in the high leukemia stock (Fig. 3), and the retardation of occurrence of the disease is greater in L/H than in H/L hybrids. The hybrid mice live on an average longer than the Ak mice.

There is a sex difference as regards incidence of leukemia in the reciprocal crosses. In the data from this laboratory the incidences of leukemia among the females of the reciprocal F_1 populations do not significantly differ. On the other hand, there is a highly

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[1] The first letter designates the dam, the second the sire.

significant difference in the incidence of leukemia between the males of the respective F_1 populations. This observation confirms our previous observations in which it was found that the differences in the incidences of leukemia among the F_1 populations were due entirely to differences in the incidence of the disease among the male populations, the female populations showing no significant difference.

The milk factor of the C3H stock dam finds expression in the development of breast cancer in 14 per cent of virgin C3H/Ak females as compared to 1 per cent in the reciprocal crosses. It is noteworthy that in our series of virgin C3H females the incidence of breast cancer was almost the same as in the C3H/Ak hybrids (15 per cent in 79 animals).

TABLE II: EFFECT OF RECIPROCAL FOSTER NURSING ON THE INCIDENCE OF LEUKEMIA AND TUMORS IN STOCK AK AND C3H

Mice			Incidence of neoplasms, per cent		
Stock		Number	Breast	Lung	Leukemia
C3H, unfostered:	♀ virgin	79	15	2	1
	♀ bred	112	53	2	0
	♂	107	..	1	0
	♀ + ♂ total	298	..	1.7	0.3
C3H, fostered by Ak:	♀ virgin	79	6	0	0
	♀ bred	24	21	0	0
	♂	112	..	4	0
	♀ + ♂ total	215	..	2	0
Ak, unfostered:	♀ virgin and bred	117 †	2 *	0	61
	♂	100	..	1	53 ‡
	♀ + ♂ total	217	..	0.5	58
Ak, fostered by C3H:	♀ virgin	90	2	0	33
	♀ bred	23	17	0	26
	♂	108	..	1	22
	♀ + ♂ total	221	..	0.5	27
Ak, parents fostered by C3H	♀ virgin	117	7	0	64
	♀ bred	15	13	0	53
	♂	84	..	0	50
	♀ + ♂ total	216	..	0	59

* These breast tumors occurred in virgin females. Previously the incidence of breast tumor in Ak mice was less than 1 in 1,000.
† Of the 117 mice, 89 were bred.
‡ Two cases of splenic tumor in mice of stock Ak have been included among the leukemias.

Table II shows that fostering C3H mice by Ak stock dams lowers the incidence of breast cancers. The relatively high per cent of breast cancer among the fostered mice may be a consequence of the technic. The exchange of suckling mice was made only twice a day and a certain number of mice must have received a small quantity of milk from their natural mothers. Experiments of Bittner (2) indicate that the quantity of milk necessary to induce breast cancer is minute.

As regards leukemia the table shows that nursing by Ak mice did not render C3H mice leukemic, as already noted by MacDowell and Richter (6) and Barnes and Cole (1).

On the contrary, fostering Ak mice by C3H dams lowers significantly the incidence of leukemia in both sexes. This confirms the previous observations of Barnes and Cole, using a different low leukemia stock and the same high leukemia stock.

This effect, unlike the Bittner factor, is not transmitted to the progeny for, as Table II shows, offspring of fostered Ak mice have as high an incidence of leukemia as nonfostered Ak stock—but the milk factor for breast cancer persists also in our experiments.

These changes in the incidence of leukemia are not due to differences in longevity, as indicated by comparison of Figs. 5 and 7, and Figs. 6 and 8. With respect to the female populations the progeny of the fostered Ak mice showed the typical curve for mortality from leukemia, as well as from other causes. The fostered mice showed a much lower incidence of leukemia and a marked tendency for a majority of the mice to live well beyond the usual peak of mortality from leukemia. A similar trend was noted for the two male populations, as shown in Figs. 6 to 8.

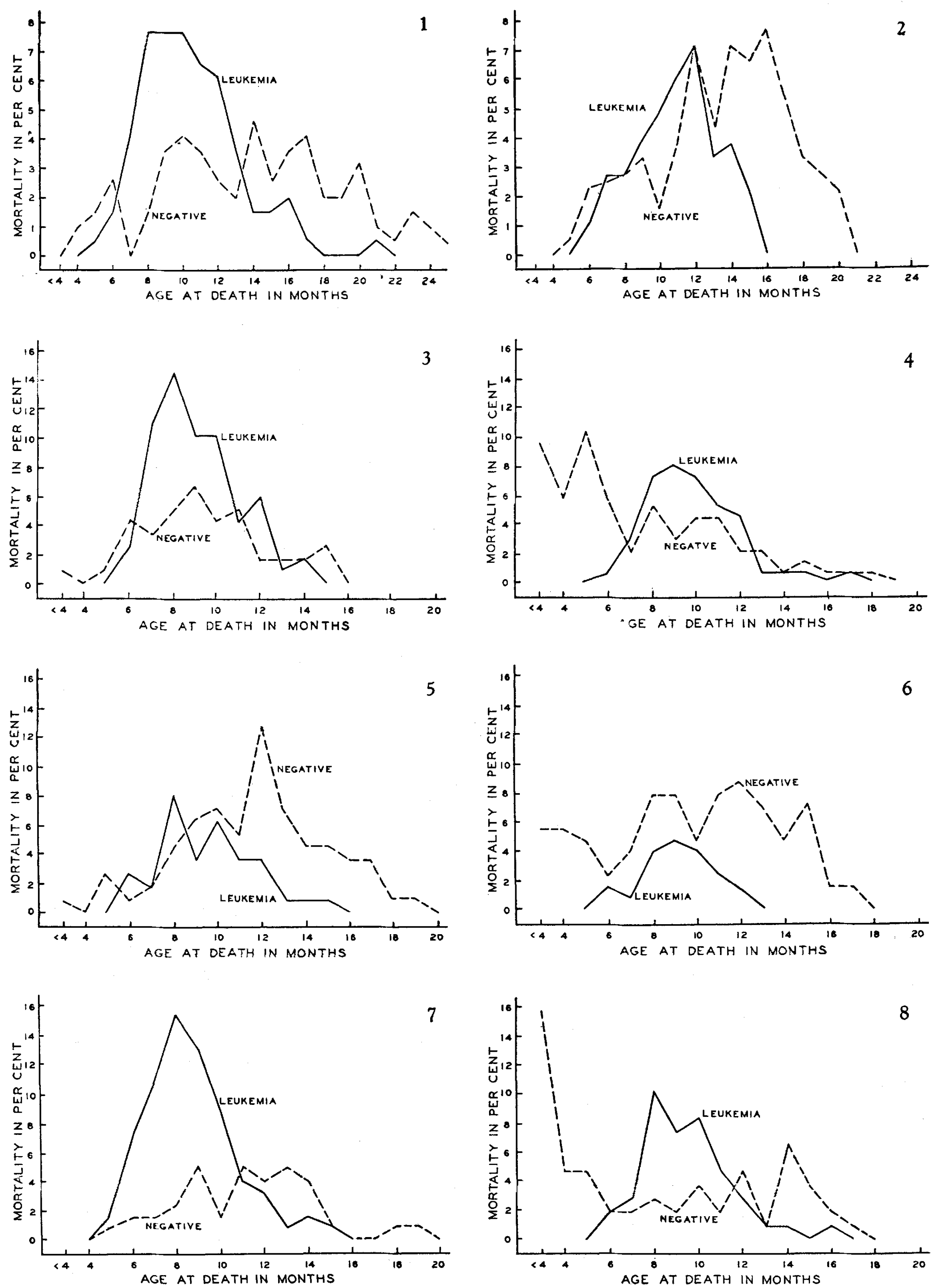
The incidence of lung tumor in the stock studied was low and the data are not sufficient for analysis.

DISCUSSION

The data from three sources, MacDowell and Richter (6), Cole and Furth (4), and those here given, indicate the existence of a maternal influence demonstrable by reciprocal crosses; our data also show this effect by foster nursing (Barnes and Cole and current experiments), while MacDowell and Richter found no evidence of a nursing influence. Unlike the milk factor producing breast cancer, described by Bittner (2, 3), the maternal influence for leukemia is not transmitted to the next generation.

This maternal influence is strong in male mice but slight in female mice. Differences in longevity do not account for this difference in incidence of leukemia as shown by comparison of the corresponding figures.

These observations can be explained in two different ways: 1. The maternal influence is similar to that described by Bittner for breast carcinoma but it is not strong enough to render the mice of the two different stocks tested (Rf and C3H) leukemic. Diminution of this leukemia influence by foster nursing will, however, lower the incidence of leukemia in susceptible mice. Some stocks may be resistant to milk influence and it will be desirable to foster hybrids with low incidence of leukemia but high percentage of Ak inheritance by Ak mice. These hybrids are expected to show a greater susceptibility to the hypothetical


1
LEUKEMIA
NEGATIVE
MORTALITY IN PER CENT
AGE AT DEATH IN MONTHS
2
LEUKEMIA
NEGATIVE
MORTALITY IN PER CENT
AGE AT DEATH IN MONTHS
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7
LEUKEMIA
NEGATIVE
MORTALITY IN PER CENT
AGE AT DEATH IN MONTHS
8
LEUKEMIA
NEGATIVE
MORTALITY IN PER CENT
AGE AT DEATH IN MONTHS

FIGS. 1-8

milk factor of Ak stock than pure C3H mice. The absence of the maternal influence in the second generation suggests that this influence is different from that of the breast cancer influence.

2. It is possible that there exists an inhibitory factor in the low leukemia stock, transferable by foster nursing. The hybridization of the high leukemia stock Ak to two different low leukemia stocks (Rf and C3H) indicates a factor of resistance greater in Rf than in C3H mice as indicated by the following figures:

	Pure stocks			F_1 hybrids			
	Ak	Rf	C3H	Ak/Rf	Rf/Ak	Ak/C3H	C3H/Ak
Per cent leukemia	70	2	1	21.9	11.6	54	36

The fostering experiments do not show this difference, the Rf foster dams reducing the incidence of leukemia in Ak stock mice to 32 per cent, the C3H dams to 33 per cent.

The difference in the behavior of the sexes, one showing a high susceptibility and the other a low susceptibility to the milk factor, requires further elucidation. One observation may be of significance; namely, that in the first few months of adult life mortality is high among the male mice as a result of fighting. It is possible, though not probable, that this may eliminate a larger portion of mice in the preleukemic state.

Transmission experiments of leukemias into these three different stocks of mice (5, 7, and unpublished data) indicate a resistance factor in Rf mice which is almost absent in C3H mice. Spontaneous leukemia arising in Ak mice can be grafted to a high percentage of C3H mice but not at all to Rf mice. The mechanism of tumor transmission is different from that of spontaneous development of neoplasms yet in this instance a relation exists which deserves further study.

Differences in intensity of the milk influence are indicated by foster nursing of low breast cancer mice, Ak, to high breast cancer mice, Af and C3H. The incidence of breast cancer in Af and C3H mice was approximately the same, but the former failed to render Ak mice cancerous while the latter did.

SUMMARY

Reciprocal crosses and reciprocal foster nursings were made between a high leukemia stock, Ak, and a low leukemia, high breast cancer stock, C3H. The incidence of leukemia in the C3H/Ak hybrids was significantly lower than in the reciprocal F_1 generation and the difference was greater between the males.

Foster nursing by low leukemia dams significantly lowered the incidence of leukemia in the high leukemia stock but the next generation behaved as nonfostered mice. Thus this nursing influence is not transmitted to the offspring.

The reciprocal nursing failed to be productive of leukemia in the C3H mice.

Leukemia tends to occur at a later age in F_1 hybrids than in the pure high leukemia stock mice.

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DESCRIPTION OF FIGURES 1 TO 8

Graphs showing comparison of mortality from leukemia and from causes other than leukemia. Mortality is given in per cent of the total number of mice included in each group. Age at death is given as the nearest month.

Fig. 1.—Mortality curve in Ak ♀/C3H ♂ mice, including both sexes.

Fig. 2.—Mortality curve in C3H ♀/Ak ♂ mice, including both sexes.

Fig. 3.—Mortality curve in unfostered Ak ♀ mice.

Fig. 4.—Mortality curve in unfostered Ak ♂ mice.

Fig. 5.—Mortality curve in Ak ♀ mice fostered by C3H mice.

Fig. 6.—Mortality curve in Ak ♂ mice fostered by C3H mice.

Fig. 7.—Mortality curve in Ak ♀ mice whose parents were fostered by C3H mice.

Fig. 8.—Mortality curve in Ak ♂ mice whose parents were fostered by C3H mice.