# SPECIAL ARTICLES

## ENHANCEMENT OF LEUKEMOGENIC ACTION OF METHYLCHOLANTHRENE BY PRE-IRRADIATION WITH X-RAYS[1]

LEUKEMOGENIC agents to which man is exposed are numerous, and it is of great interest to find out if one such agent can prepare the soil for or enhance the action of another.

X-rays are mildly leukemogenic.[2, 3] Moderate and large doses rapidly destroy blood-forming organs, but if x-ray action is discontinued, regeneration follows within a few days, and during this phase mitotic figures are seen in abundance in sections of blood-forming organs. It seems probable that during this phase blood-forming organs would be particularly susceptible to leukemogenic irritants.

To test this possibility, thirty-six mice of four to six weeks of age were irradiated with 175 r over the entire body. These mice were painted with methylcholanthrene, beginning the day following the irradiation. The technic of irradiation of treatment with methylcholanthrene has been described.[4] In addition, thirty-seven mice were painted but not irradiated, and eighteen mice were irradiated but not painted. The results are given in Table 1.

The figures indicate that pre-irradiation greatly enhances the susceptibility of mice to the leukemogenic action of methylcholanthrene. In addition, pre-irradiation hastens the onset of leukemia, as shown in Fig. 1.

According to more extensive, earlier work,[5] spontaneous leukemia occurs in about 11.6 per cent. of this genetically uniform stock (Rf/Ak), but the onset of illness is seldom if ever noted before the age of seven months. Preceding the current experiments the incidence of leukemia was again determined in both irradiated and non-irradiated mice of this stock (Table 2).

In this test the incidence of spontaneous leukemia in the stock used (Rf/Ak) was even slightly lower than noted before, but that among the x-rayed mice was fairly high. However, in this experiment 300 r of x-rays were used, while in that recorded in Table 1, 175 r were used. Moreover, the disease in these mice occurred at a later period than in those exposed to methylcholanthrene. The two control mice died of leukemia at twenty-one months of age, one of the x-rayed mice at five, the others at eight to seventeen months of age.

TABLE 1

INCIDENCE OF LEUKEMIA IN MICE TREATED WITH METHYLCHOLANTHRENE OR X-RAYS OR BOTH

| Treatment of mice | Experiment 1 | | | Experiment 2 | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. used | No. + | No. alive at 10–16 mo. | No. used | No. + | No. alive at 10–16 mo. | No. used | No. + | Per cent. + | No. alive at 10–16 mo. |
| X-ray, 175 r | 18 | 1 | 16 | .. | .. | .. | 18 | 1 | 6 | 16 |
| Painting with methylcholanthrene | 21 | 5 | 7 | 16 | 1 | 7 | 37 | 6 | 16 | 14 |
| X-ray and painting with methylcholanthrene | 19 | 11 | 5 | 17 | 12 | 5 | 36 | 23 | 64 | 10 |

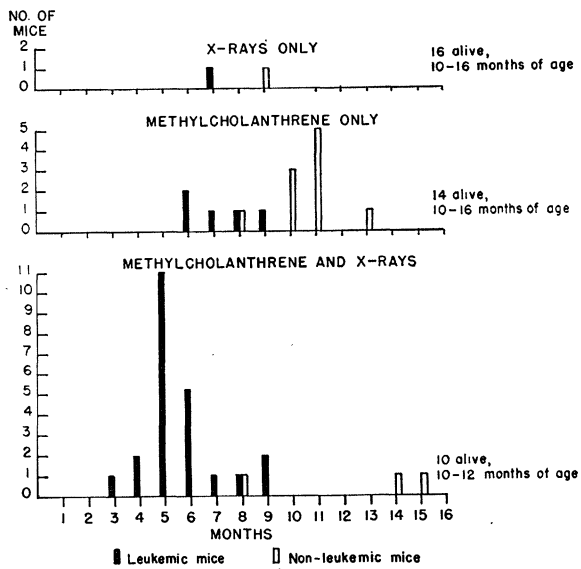


FIG. 1. Time of occurrence and frequency of leukemia in mice treated with methylcholanthrene or x-rays or both.

TABLE 2

| | No. in group | No. + | Per cent. + |
|---|---|---|---|
| Irradiated mice (300 r) .. | 17 | 10 | 59 |
| Non-irradiated control .... | 25 | 2 | 8 |

These findings can be explained in several ways. According to the supposition that seems most probable, the neo-plastic transformation of lymphoid cells is brought about by methylcholanthrene, while the derangement that follows irradiation prepares (sensitizes) them for the action of methylcholanthrene.

[1] This study has been supported by the Jane Coffin Childs Memorial Fund for Medical Research, the International Cancer Research Foundation, the Lady Tata Memorial Trust and the Anna Fuller Fund.

[2] C. Krebs, H. C. Rask-Nielsen and A. Wagner, *Acta Radiol. Suppl.*, 10: 1, 1930.

[3] J. Furth and O. B. Furth, *Am. Jour. Cancer*, 28: 54, 1936.

[4] D. P. McEndy, M. C. Boon and J. Furth, *Jour. Nat. Cancer Inst.*, 3: 227, 1942.

[5] R. K. Cole and J. Furth, *Cancer Res.*, 1: 957, 1941.

Results similar to those described above have already been noted in experimental studies on the production of skin tumors. Mottram[6] found that painting mice with 3:4 benzpyrene and irradiating them on the sixtieth day with a dose of 176 to 1,584 r gamma radiation produced both benign and malignant tumors of the skin. No tumors followed painting for the same period without irradiation. Similar results were obtained by Mayneord and Parsons[7] by the combined application of x-rays and a different carcinogen. They observed that irradiated and painted mice developed sarcomas at an earlier date and in greater numbers than the non-irradiated mice. Gilmour[8] obtained similar results by the combined application of estrone and 3:4 benzpyrene. The follicular sex hormone alone did not produce cutaneous tumors.

These observations indicate that subthreshold doses of different carcinogens may summate, or that one may sensitize tissues for the action of the other. The essential similarity of leukemia and accepted types of cancers is again emphasized by these experiments. The same agents differently spaced and dosed may produce either predominantly leukemia or the more accepted types of cancers. The mechanism of summation of carcinogenic stimuli deserves further experimental study.

### CONCLUSION

Both x-rays and methylcholanthrene are leukemogenic. The leukemogenic action of small doses of methylcholanthrene is greatly enhanced by pre-irradiation with doses of x-rays which alone rarely produce leukemia. The leukemogenic action of x-rays is milder than that of methylcholanthrene and affects a smaller number of mice after a longer period of latency.

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## THE COMPARATIVE NUTRITIVE VALUE OF BUTTER AND SOME VEGETABLE FATS[1]

IT has been generally accepted by nutritionists that, aside from differences in vitamin potencies, all fats have essentially the same nutritive value. An exception to this is the specific rôle played by those fats which contain certain unsaturated fatty acids.[2] Schantz *et al.*[3] have recently postulated that butter is more effective than vegetable oils in producing growth in weanling rats presumably due to long chain saturated fatty acids, although in a recent report the superiority of butter over corn oil was observed only when the dietary carbohydrate was lactose while conditions were reversed when carbohydrates other than lactose constituted the carbohydrate portion of the diet.[4]

We have followed the rate of growth of 21-day weanling rats for six or 12 weeks on diets composed of 68 per cent. of mineralized skim milk powder and 32 per cent. of the fat under study with supplements of vitamins A (as carotene and A), D and E added to the fats. Corn, cottonseed, olive, peanut and soybean oils were tested as well as butter and vegetable margarine fat. In one series where vegetable margarine fat and butter fat only were compared over a six-week period no differences in growth rate were noted. A total of 46 male rats and 89 female rats were used in these tests. In series II, where groups of approximately 15 male and 15 female rats were fed for 12 weeks diets containing each of the seven fats listed above, no differences were found in the growth at three or six weeks or with the males at 12 weeks. The female rats receiving the butter diet weighed slightly more at 12 weeks, but the difference was not significant statistically. However, in series III where diacetyl was added to the vegetable fats in an amount of 4 parts per million, no differences of weight were noted at any interval either in the males or females. The same number of rats was used as in series II. Not only was the growth rate identical as demonstrated by body weight but bone growth was also equal as found by x-ray measurements of tibia length at the end of three and six weeks on the respective diets. Also no significant differences were obtained in the water, protin, lipid, ash and calcium content of the rats which had received the various diets for 12 weeks. This would prove that the equal growth was actually due to similar tissue growth.

One explanation for the discrepancies between our results and some of those where *ad lib.* feeding is employed[3] is in all probability to be traced to the fact that weanling rats prefer a butter flavor and will eat more of such a diet. In experiments where the rats had a choice of a diet containing margarine fat or peanut oil with or without diacetyl, the rats ate more of the diacetyl-containing diets 18 times and of the unflavored diets in only one instance. Also in tests on twelve weanling rats carried out over 12 weeks, where both an unflavored peanut oil diet and one containing commercial butter flavor[5] were offered the rats, a decided preference was invariably shown for the

[6] J. C. Mottram, *Am. Jour. Cancer*, 30: 746, 1937.
[7] W. V. Mayneord, L. D. Parsons, *Jour. Path. and Bact.*, 45: 35, 1937.
[8] M. D. Gilmour, *Jour. Path. and Bact.*, 45: 179, 1937.
[1] This work was carried out under a research grant from The Best Foods, Inc.
[2] G. O. Burr and M. M. Burr, *Jour. Biol. Chem.*, 82: 345, 1929; 86: 618, 1930.
[3] E. J. Schantz, C. A. Elvehjem and E. B. Hart, *Jour. Dairy Sci.*, 23: 181, 1940.
[4] R. K. Boutwell, R. P. Geyer, C. A. Elvehjem and E. B. Hart, *Jour. Dairy Sci.*, 26: 429, 1943.
[5] Verley "B F A."