The Effect of Visible Light on the Development in Mice of Skin Tumors and Leukemia Induced by Carcinogens

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The absence of light enhances epidermal carcinogenesis in Swiss albino (9) and C57 black (10) strains of mice painted with a solution of 3,4-benzpyrene. It now appears that the presence or absence of light affects the response of mice of the dilute brown (DBA) strain to percutaneous administration of either 3,4-benzpyrene or 20-methylcholanthrene by altering the incidence of not only skin carcinomas but leukemias as well. These mice are peculiarly susceptible to the leukemogenic action of several carcinogenic hydrocarbons, although the incidence of spontaneous leukemia in the strain is low (2, 4–6, 11).

EXPERIMENTAL PROCEDURE

Mice of the dilute brown strain obtained from the Biological Station of the Roswell Park Memorial Institute, through the courtesy of Dr. W. S. Murray and Dr. S. G. Warner, were divided into groups of 50. The sexes were equally distributed among the groups but were segregated to prevent breeding. The mice were housed in wire mesh cages in specially constructed rooms, the details of which have been described (3). No light was admitted to the dark room, while the light room was illuminated for 12 hours each day by fluorescent lamps, as in the experiments reported earlier (9, 10). The diet consisted of unlimited quantities of Purina Dog Chow and water. The mice were 6–7 weeks old at the first painting.

The first experiment was conducted between December, 1941, and July, 1942. Forty mice from each group were painted twice weekly with a 0.5 per cent solution of 3,4-benzpyrene in benzene, applied to the interscapular region with a No. 8 camel's hair brush. Thirty-five such paintings were given over a period of 17 weeks. The mice were observed for an additional 60 days after cessation of the applications. Ten untreated mice of each group served as controls.

The second experiment, conducted between January and July, 1949, was performed with 40 treated mice and 10 untreated controls in each group. Litter-mates were distributed equally between those in the light and dark rooms. Each of the treated mice was painted twice weekly with a 0.5 per cent solution of 20-methylcholanthrene in benzene. The solution was applied to nine successive sites in rotation as previously described (6). Paintings were continued until most of the mice had developed either leukemia or epidermoid carcinomas.

All animals were allowed to die or were sacrificed when they appeared moribund. Autopsies were performed and appropriate specimens were examined histologically.

The experimental design provided a relatively potent stimulus for epidermal carcinogenesis in the first experiment and a relatively strong leukemogenic stimulus in the second experiment.

RESULTS

One mouse died from no ascertainable cause in each of the experimental groups before the first neoplasm appeared in any member of the group. Each group, then, contained 39 treated mice. The untreated control mice were sacrificed at termination of the experiments. None of them developed a neoplasm.

Topical application of 3,4-benzpyrene solution to the mice in the first experiment produced epilation of the interscapular region, followed by growth of hair, particularly among those mice kept in the dark. No light was admitted to the dark room, while the light room was illuminated for 12 hours each day by fluorescent lamps, as in the experiments reported earlier (9, 10). The diet consisted of unlimited quantities of Purina Dog Chow and water. The mice were 6–7 weeks old at the first painting.

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Topical application of 3,4-benzpyrene solution to the mice in the first experiment produced epilation of the interscapular region, followed by growth of hair, particularly among those mice kept in the dark. No difference in hair growth was observed after the nineteenth painting, but all the mice in the light room always seemed more excitable and difficult to handle. Dermatitis comparable to that found in C57 black mice painted with a benzpyrene solution (10) was not observed.

Mortality curves for the mice in the first experiment are depicted in Chart 1, and the incidence of epidermoid carcinoma and leukemias is presented in Table 1. Some mice had both lesions. The difference in incidence of the two anatomical types of neoplasia between the light and dark room mice is
statistically significant, for P is far less than 0.01 when the data are analyzed by the \( \chi^2 \) method. The more rapid mortality among the mice housed in the light room probably reflects the highly lethal characteristics of hydrocarbon-induced leukemia in mice as compared to the more chronic course of epidermoid carcinoma.

The mortality curves for the second experiment (Chart 2) again reveal that the mice exposed to light died more rapidly than did those kept in the dark room. The incidence of leukemias and epidermoid cancers is listed in Table 2. Differences in the distribution of leukemias between the two groups are significant at a level of 0.03. The difference in distribution of epidermoid carcinomas is not statistically significant. The higher incidence of leukemia (Table 2) in this experiment produces a marked decrease in survival time for both groups as contrasted with the mice in the first experiment. Hyperexcitability of the mice exposed to light was readily apparent, but no difference in epilation could be noted in the two groups.

The leukemias observed were identical in all respects with the mediastinal lymphoma and generalized lymphomatosis that follow percutaneous application of carcinogenic hydrocarbons in mice of the dilute brown strain, as reported previously (6). The disseminated type of disease was found far more commonly than the localized mediastinal lesion. The diagnosis of epidermoid carcinoma required that neoplastic cells infiltrate the panniculus carnosus.

**DISCUSSION**

Epidermal carcinogenesis by 3,4-benzpyrene is strongly influenced by the presence or absence of light in at least three different strains of mice. Ultraviolet irradiations cannot be incriminated in this reaction, since they were not present in the radiations used in our experiments. Doniach and Mottram (1), however, showed that fewer skin cancers occurred among mice treated with 3,4-benzpyrene and exposed to direct sunlight than among those which received no ultraviolet irradiation. They thought that strong sunlight reduced
tumor production by increasing dermatitis caused by the photodynamic properties of the carcinogen. Light produced no significant dermatitis in two of the three strains of mice studied in our experiments, but the effect on epidermal carcinogenesis was similar in all. Therefore, dermatitis does not appear to be a major factor in producing the different responses to 3,4-benzpyrene in the light and in the dark.

The nutritional state of the subject may affect its response to a carcinogenic agent. Failure to demonstrate any difference in weight between the mice kept in the light and those in the dark rooms eliminates pronounced difference in nutritional status as a major influence in eliciting the different reactions observed.

Strong circumstantial evidence implicates the formation of protein-carcinogen complexes as an important factor in the pathogenesis of hepatic tumors produced by azo dyes (8). An analogous situation is suggested in the production of carcinoma of the skin. E. C. Miller (7) found that the application of 3,4-benzpyrene to the skin of mice produced protein-bound fluorescent substances only in the epidermis. Exposure of the mice to sunlight or to light from incandescent bulbs reduced the levels of epidermal protein-bound derivatives significantly, as compared to the concentrations attained by mice kept in the dark. The direction of the change parallels the light effect on epidermal carcinogenesis.

Miller suggested that the diminished levels of 3,4-benzpyrene derivatives and the lower skin tumor incidence in the presence of light might result from partial photo-oxidation of the carcinogen, thereby decreasing the effective dose of the agent. If this is the case, metabolites of 3,4-benzpyrene or 20-methylcholanthrene, rather than the parent substances themselves, must be leukemogenic. Weigert, Calcutt, and Powell have discovered only one metabolite of 3,4-benzpyrene in painted mouse skin, but its chemical nature and biologic properties have not been established (12). Other metabolites are known to be formed during passage of the carcinogen through the body (13). The reciprocal relationship between the incidence of skin cancer and leukemia in our experiments might be interpreted to suggest that light facilitates absorption through the skin of unchanged carcinogen or a leukemogenic derivative, permitting it to act upon the lymphoid tissue.

The second experiment, using 20-methylcholanthrene, provides a relatively great stimulus for leukemogenesis. The reciprocal relationship between skin cancer and leukemia production in the light and dark is similar to that observed among the mice treated with 3,4-benzpyrene. The reduction in statistical significance of the differences observed agrees with the general principle that physiologic influences in tumor production may be masked by overwhelming carcinogenic stimuli.

A full explanation of the effects of the radiations used on tumorigenesis must await further experiment.

SUMMARY

Mice of the dilute brown (DBA) strain kept in an environment of visible light for 12 hours daily or in complete darkness were painted with solutions of 3,4-benzpyrene or 20-methylcholanthrene. The incidence of leukemia among the mice exposed to light was significantly higher than in those kept in the dark. Fewer animals exposed to light developed skin carcinomas.

REFERENCES
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