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Inhibitory Influence of a Normally Occurring Pyrimidine Precursor upon Methylcholanthrene Carcinogenesis.* (23508)

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In studies of the mechanism of action of urethane in initiating pulmonary adenomas in the lungs of mice, orotic acid, a naturally occurring pyrimidine(1) known to play a large part in nucleic acid synthesis(2) was found to be one of the most potent inhibitors of the sequential metabolic processes originally set off by the carcinogen(3). The following experiments were carried out to determine whether it might influence the carcinogenic effect of methylcholanthrene, a polynuclear hydrocarbon. The fact that polynuclear hydrocarbons exert their effect over a long period of time necessitated, however, the use of a different technic from that carried out in the studies of the short acting carcinogens (3,4).

Materials and method. Mice of the Swiss and "C" strains, raised in this laboratory and procured originally from the stock of the Rockefeller Institute for Medical Research, New York City, and mice of the "A" strain procured from Bar Harbor, Maine, were used. The Swiss and "A" strain animals develop large numbers of pulmonary tumors following administration of a variety of carcinogens. In the "C" strain the tumors are much less numerous. In each experiment the animals used were of the same sex and matched as to age and weight. They were all kept on a stock diet (Laboratory Mouse Chow, made by Dietrich and Gambrill, Frederick, Md.) This was

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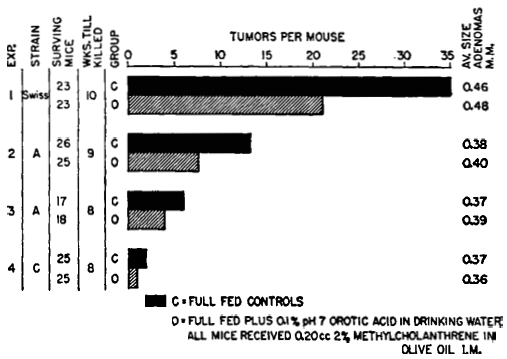

CHART 1. Inhibition of methylcholanthrene carcinogenesis by increasing dietary orotic acid.

supplemented twice weekly with whole wheat bread and milk. All mice were injected with 0.2 cc of 2% methylcholanthrene (Eastman Kodak Laboratories, Rochester, N. Y.) in olive oil intramuscularly in the right thigh. Two to 5 days prior to the methylcholanthrene injection half the animals were given 0.1% pH 7 orotic acid (Nutritional Biochemicals Corp., Cleveland, O.) in tap water as their normal water supply. The control animals received only tap water. The mice receiving orotic acid in Exp. 1 and 4 received it for the duration of the experiment. Those of Exp. 2 and 3 were given tap water for the last 4 weeks of the experiment. There was no difference in the relative fluid intake of experimental and control groups. The weights and general condition of the animals were followed closely because these factors significantly influence the number of tumors occurring following exposure to carcinogens(5). Animals which developed intercurrent disease or deviated in weight from the mean as much as 2 g were discarded. The mice were killed by decapitation in each experiment at the interval indicated in the Chart and their lungs examined for tumors. Only tumors on the surface of the lungs were measured and counted, and among these only those one-third mm in diameter and over figured in the results.

Results. In the accompanying chart it is evident that the mice receiving supplementary orotic acid developed significantly fewer tumors than did the controls. Since the weight curves of the compared groups were held constant by discarding deviates they are not included in this report. The constancy of the weights of the 2 groups under these experimental conditions is indicated by the fact that the number of surviving animals in the groups is essentially equal. This together with the equality in average size of adenomas from group to compared group makes it clear that non-specific growth effects could not account for the reduction in the number of tumors in the animals receiving orotic acid and further that the inhibitory influence of orotate is upon the initiation and not the subsequent growth of the tumors(6). The tumors produced in the lungs were all of the general class variously categorized as pulmonary adenomas or adenocarcinomas. The infrequency of the appearance of sarcomas at the site of injection of the carcinogen in these experiments does not permit the use of this feature in making a comparison of the response of the two groups of animals.

Summary. The carcinogenic influence of methylcholanthrene may be considerably reduced by increasing the intake of a normal dietary constituent, orotic acid, a substance well known to be of great importance to the synthesis of nucleic acid pyrimidines. The absence of influence of this substance upon the condition of the mice or the size of the tumors indicates that it is acting at the level of initiation of the pulmonary tumors rather than upon their subsequent growth. This fact suggests that the metabolic mechanisms through which methylcholanthrene initiates neoplastic change is, like urethane(3), closely related to the synthesis of nucleic acid.

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