Oral Griseofulvin: A Cocarcinogenic Agent to Methylcholanthrene-induced Cutaneous Tumors*

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SUMMARY

Since certain antitumor drugs also arrest mitosis in metaphase, an attempt was made to determine the effect of oral griseofulvin on methylcholanthrene-induced cutaneous tumors in mice. Contrary to expectations, mice on large doses (1000-1500 mg/kg) of griseofulvin subjected to methylcholanthrene applications had a shorter tumor lag period and developed more and larger tumors than did mice not receiving griseofulvin but receiving similar amounts of methylcholanthrene. A cocarcinogenic effect was also noted in mice that received lower doses (10-15 mg/kg) of griseofulvin for 6 weeks prior to, during, and subsequent to methylcholanthrene applications, but not in mice that received this dosage for 4 weeks prior to, during, and subsequent to methylcholanthrene application.

Griseofulvin is an antibiotic isolated in 1939 by Oxford et al. (4) from a Penicillium mold. Gentles (2) in 1958 used it on experimental dermatophytosis in guinea pigs. In 1958, Paget and Walker (5) noted the cytotoxic effect of large intravenous doses of griseofulvin in rats, resulting in arrest of mitosis in metaphase in certain organs—e.g., bone marrow, seminal and intestinal epithelium. Schwarz and Loutzenhizer (7) have shown that prolonged high oral doses of griseofulvin can cause atrophy of mouse testes. Roth and Blank (6) have discussed the oral administration of griseofulvin and its subsequent incorporation into the keratinized tissues of the skin, hair, and nails.

Many of the currently used antitumor drugs arrest mitosis in metaphase, and it was hoped that griseofulvin might have an antitumor effect when the carcinogenic agent methylcholanthrene was applied to the epidermis of mice. A pilot experiment was performed, and preliminary findings are reported (1). Contrary to this expectation, it was found that excessively large oral doses of griseofulvin had a tumor-promoting effect upon methylcholanthrene-induced tumors (1). The following experiments confirm this.

MATERIALS AND METHODS

Swiss-Webster strain male mice from Huntingdon Farms in Philadelphia, weighing 17-23 gm. prior to being placed on their respective diets, were used. Rockland Rat Diet, produced by the A. E. Staley Manufacturing Co., Decatur, Ill., was used; griseofulvin was supplied by the Schering Corporation; 3-methylcholanthrene was obtained from Mann Research Laboratories.

Two levels of griseofulvin were given. Mice on a 1 per cent griseofulvin mouse food mixture would be in a dosage range of 1000-1500 mg/kg/day depending upon their size and food consumption. Mice on a 0.01 per cent griseofulvin mouse food mixture would be in a dosage range of 10-15 mg/kg/day and would correspond to customary human dosage. Another group of mice received only a regular mouse food diet. All mice had the hair of the lower back clipped with an electric clipper a few days prior to the start of methylcholanthrene application.

Mice in Experiment 1 received their respective diets for 4 weeks prior to, during, and subsequent
to being placed on twice-weekly applications of 0.05 cc. of 0.5 per cent methylcholanthrene in acetone solution, for a total of eight applications, to the epidermis of the lower back.

Mice in Experiment 2 received their respective diets for 6 weeks prior to, during, and subsequent to being placed on twice-weekly applications of 0.05 cc. of 0.5 per cent methylcholanthrene in acetone solution, for a total of seven applications, to the epidermis of the lower back.

Mice in Experiment 3 received their respective diets for 6 weeks prior to, during, and subsequent to being placed on twice-weekly applications of 0.04 cc. of 0.5 per cent methylcholanthrene in acetone solution, for a total of seven applications, to the epidermis of the lower back.

Results and Discussion

The results are summarized in Table 1. All three experiments showed that the mice on 1 per cent griseofulvin had the shortest tumor latent period, largest percentage of mice developing tumors, most tumors per mouse, and largest tumors (Fig. 1). If the mice had been on a 0.01 per cent griseofulvin diet for 6 weeks before methylcholanthrene applications, as in Experiments 2 and 3, there is evidence that griseofulvin had tumor-promoting properties at this very important dosage level. These 0.01 per cent griseofulvin groups in Experiments 2 and 3 had a shorter tumor latent period, larger percentage of mice developing tumors, more tumors per mouse, and larger tumors than did control animals not receiving griseofulvin. However, mice on 0.01 per cent griseofulvin diet for only 4 weeks before the methylcholanthrene application, as in Experiment 1, did not exhibit enhancement of tumor growth.

In our control group not receiving methylcholanthrene, there are 37 mice on 1 per cent griseofulvin, 27 on 0.01 per cent griseofulvin, and 25 on regular mouse food. These mice have been on their respective diets for 92 days, and not a single spontaneous tumor has appeared. These mice had the hair of the lower back clipped with an electric clipper. It is too early to be certain, but it appears that the mice on the 1 per cent griseofulvin diet do

![Figure 1](https://example.com/fig1.png)

**FIG. 1.**—Figure 1 shows the difference in size and number of typical tumor formations in mice receiving 1 per cent and in mice not receiving griseofulvin 80 days after the start of methylcholanthrene applications in Experiment 1. The mouse on 1 per cent griseofulvin had at least twenty individual tumors that, upon growing, became one huge, confluent tumor mass. Microscopic sections of the tumors on these two mice show hyperkeratinomatous papillomas.

**TABLE 1**

<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>DAYS AFTER START OF METHYLCHOLANTHRENE APPLICATION</th>
<th>NO GRISEOFULVIN</th>
<th>0.01 PER CENT GRISEOFULVIN</th>
<th>1.0 PER CENT GRISEOFULVIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. mice with pap. / total no. mice</td>
<td>Per cent mice with pap.</td>
<td>Total no. pap.</td>
<td>No. mice with pap. / total no. mice</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>0/20</td>
<td>0</td>
<td>1/20</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
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<td>0</td>
<td>0/17</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>0/20</td>
<td>0</td>
<td>0/17</td>
</tr>
</tbody>
</table>

*N.D. = not determined.

Mice in Experiment 1 had their respective diets for 4 weeks prior to, during, and subsequent to eight applications of 0.05 cc. of 0.5 per cent methylcholanthrene. Mice in Experiment 2 had their respective diets for 6 weeks prior to, during, and subsequent to seven applications of 0.05 cc. of 0.5 per cent methylcholanthrene. Mice in Experiment 3 had their respective diets for 6 weeks prior to, during, and subsequent to seven applications of 0.04 cc. of 0.5 per cent methylcholanthrene.
not have their hair growing back as rapidly as do the mice on regular food; apparently the hair's anagen phase is affected.

Tumors in the 1 per cent griseofulvin group receiving methylcholanthrene were more prone to develop in mice that had very little of their hair regrown after being clipped. A speculation would be that hair, which is a very active area of mitosis, will have its mitotic pattern arrested by griseofulvin and enters a telogen phase. Methylcholanthrene enters via the hair follicle, and perhaps the hair is not growing to carry the carcinogenic agent outward, and there is an accumulation of the carcinogen in the hair follicle. Wolbach (8) states that carcinogenic agents develop papillomas from arrested hair papillae and that cancers develop only from these papillomas. Hair in the anagen phase has a protective effect against tumor induction by chemical carcinogens.

There were many more fights, bites, and pyodermas in the group not receiving griseofulvin; and when they developed tumors it was usually at the sites of skin breakage. We have found that mice in cages not receiving griseofulvin and not having skin breakage will have no or only very small tumors.

Previous experience (1) shows that at about 9 weeks after methylcholanthrene applications, squamous-cell carcinomas can develop in the 1 per cent griseofulvin group.

Wolf (9) defines a cocarcinogen as a substance which, though not in itself carcinogenic, can enhance tumor incidence and shorten the latent period when applied together with or shortly after the carcinogen. Large oral doses of griseofulvin, which eventually find their way to the skin, act as tumor-promoters when methylcholanthrene is applied to the epidermis of mice. McNall (3) suspects that griseofulvin exerts a direct interference with the synthesis of nucleic acids. Possibly griseofulvin, in affecting the mitosis of the cell and the nucleic acids, has done something to make the cell more vulnerable to a carcinogenic agent.

REFERENCES

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