Griseofulvin: Immunosuppressive Action (37277)

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Griseofulvin is a fungal antibiotic, used extensively for certain dermatological conditions by oral intake in high dosages under chronic conditions (1). Thus, reports that griseofulvin induced liver tumors in mice (2–5), and potentiated the carcinogenic effect of polycyclic aromatic hydrocarbons applied cutaneously (6) to mice led to concern relative to the safety of the clinical application of this drug, especially as regards use in young people, and indeed on a prophylactic basis in individuals without overt disease.

Recent studies have indicated that cellular immunity may play a role in skin tumor induction in mice (7). Specifically, in experiments involving cutaneous application of carcinogenic hydrocarbons, immunosuppression has led to enhancement, almost like that seen in the tests in which griseofulvin potentiated the carcinogenic effect. Thus, we thought that the question whether griseofulvin might appear to exhibit carcinogenicity or cocarcinogenicity perhaps via immunosuppression was worthy of investigation.

This paper records our findings that griseofulvin does seem to affect cellular immunity, as measured by mortality of mice upon injection of *Listeria monocytogenes* (8) and also quantitated by the number of such organisms in the spleen of treated mice.

Materials and Methods. Female Balb/C mice (NIH Animal Production), 6 weeks old, were fed a diet of ground Wayne Laboratory meal containing 1% microfine griseofulvin (a gift of Schering Corporation, Bloomfield, NJ) mixed in a V-blender. Control mice were given Wayne meal only. After 4 weeks, all mice were injected iv with 6.4×10^3 (LD_5) *L. monocytogenes* (obtained through the courtesy of Dr. G. Mackaness, Trudeau Institute, Saranac Lake, NY) and maintained on their respective diets. Mortality in the experimental group treated with griseofulvin and the control group was determined over the next 10 days.

A second group of 25 mice was placed on similar 1% griseofulvin regimen, as were 25 simultaneous controls. After 6 weeks of feeding, groups of 5 mice from each group were killed after 1, 2, 3, 4, and 9 days after the iv injection of 3.2×10^3 *L. monocytogenes*. The spleen from each mouse was removed, homogenized in 0.85% saline solution and the homogenate was subdiluted. Dilutions were placed dropwise on Trypticase soy agar plates and incubated at 37° for 24 hr. A colony count reflected the number of *L. monocytogenes* organisms in each spleen at each time period.

Results. Mice injected with *L. monocytogenes* exhibited high mortality after 4 weeks on the griseofulvin diet (Table I). Only 1 of 35 mice survived 10 days after injection of the organisms. Most of the deaths occurred on Days 3 and 4. In contrast, on control diet, 33 of 35 mice injected likewise with *L.*

TABLE I. Mortality of Mice Prefed 1% Griseofulvin and Injected iv with *Listeria monocytogenes*.[a]

	No. of mice dead on day									
	1	2	3	4	5	6	7	8	9	10
Griseofulvin	0	0	15	14	2	1	0	1	1	0
Control	0	0	0	0	1	0	1	0	0	0

[a] A group of 35 mice was fed 1% griseofulvin for 4 weeks and a similar group control Wayne Laboratory meal. Both groups were injected iv with a predetermined LD_5 dose of 6.4×10^3 *Listeria monocytogenes*, and the mortality recorded.

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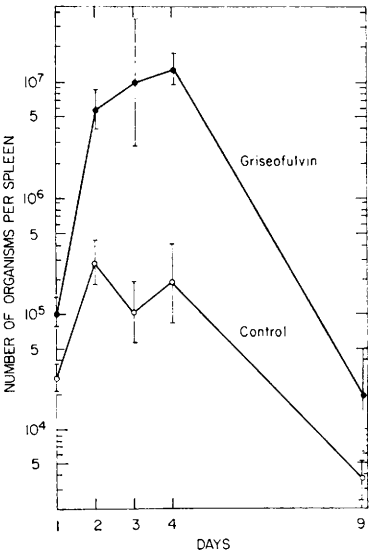

FIG. 1. Average counts of *Listeria monocytogenes* in the spleen of mice as a function of time after iv injection of the organism. Bars show standard error of the mean on counts from 5 mice, at each point, prefed 1% griseofulvin for 6 weeks.

monocytogenes lived.

Figure 1 records the number of organisms in the spleen as a function of time after injection of *Listeria*. The spleens of the control group had a significantly lower count of organisms at several time periods than the spleens of mice pretreated with griseofulvin for 6 weeks.

Thus, the combined data, increased number of organisms in spleen, as well as paucity of survivors upon injection with *Listeria* indicate that griseofulvin may suppress cellular immunity (8).

Discussion. Griseofulvin has an unquestioned carcinogenic effect in mice of several strains, where it leads to liver tumor formation. In rats, it appears to be either negative or only very weakly active. Thus far, there has been no long-term study where mice were placed continuously on a more classical immunosuppressive treatment to determine whether this alone could lead to the production of liver tumors. Immunosuppression in the clinic has led to new primary or secondary cancers (cf. 9, 10). Also, the effect of oral griseofulvin in potentiating skin tumor formation in mice induced by polycyclic aromatic hydrocarbons (6) has an exact parallel in the reported cocarcinogenic effect of immunosuppressive treatment (cf. 7). Furthermore, Hurst and Paget (2) thought their mice on griseofulvin were "unduly susceptible to infection," possibly reflecting immunosuppression.

Thus, our results bear on the reported carcinogenicity of griseofulvin in mice. If this effect stems from the possibly specific immunosuppressive action, which requires further detailed study as to the underlying mechanism, it would seem that griseofulvin may exert a sort of special cocarcinogenic effect. In the absence of primary carcinogens, there may be reduced risk of tumor development, a point which may aid in determining the risk of administering this drug to man. More fundamental relationships between carcinogenesis, immunosuppression, and porphyria induction (11) in various species need to be established.

Summary. Mice fed 1% griseofulvin in the diet for 4–6 weeks exhibited considerable mortality upon injection of *Listeria monocytogenes,* and had a significantly higher count of organism in the spleen than controls. The data are interpreted as signifying a select depressing effect of griseofulvin on cellular immune response in mice, which may thus account for some aspects of the carcinogenic and cocarcinogenic effect of griseofulvin in mice.

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