Failure of treatment in chronic dermatophyte infections

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Summary
A proportion of dermatophyte infections fail to respond to normally adequate courses of griseofulvin and tropical antifungal therapy. The organism Trichophyton rubrum was isolated from 96% of 50 patients studied, but no instances of in vitro resistance were seen. Of these patients, 57% had an underlying condition, commonly hay fever/asthma, atopic eczema, collagen disease or ichthyosis. Defective delayed type hypersensitivity responses and leucocyte migration inhibition to the specific antigen, trichophytin, were demonstrated. Immediate type hypersensitivity was seen in 58% and this was partially suppressible with chlorpheniramine and cimetidine. The relationship between these abnormalities and failure of treatment is discussed.

Introduction
It is a common experience amongst dermatologists that certain types of dermatophyte infection fail to respond to a normally adequate course of the drug griseofulvin given in a dose of one g daily for at least 3 months. This occurs even where the influence of nail involvement, which is notoriously slow to respond, is excluded.

Griseofulvin is a metabolic by-product of several species of the mould Penicillium, e.g. P. griseofulvum, and the discovery that it was active against dermatophyte fungi in vivo was a therapeutic advance of great importance (Gentles, 1958). It is absorbed in adequate amounts after oral administration, the serum levels depending on a number of variables including the size of the griseofulvin particles, e.g. microcrystalline form (Crounse 1963), and the timing of the dose in relation to a meal. However, there are 2 findings of particular relevance here. Firstly, griseofulvin has been shown to be selectively accumulated in the stratum corneum where the fungal invasion occurs (Epstein, Shah and Riegelman, 1972). Drug levels in this layer may be several times greater than in serum and follow excretion of the drug in the sweat. Secondly, it was observed that in vitro high levels of griseofulvin (up to 30 μg/ml) failed to kill pellets of dermatophytes and the drug was limited in its effect in this system to fungistasis (Roth, Sallman and Blank, 1959). It seems, therefore, that the effectiveness of griseofulvin is dependent on host factors such as the immune response and a normal turnover of epidermis which tends to shed the organism into the environment.

Griseofulvin remains a useful drug, surprisingly free of side effects in the doses normally used (Livingood et al., 1960). Gastric intolerance, headaches, urticaria and rashes, and leucopenia have been described.

The patients described here had chronic dermatophyte infections, often of many years’ standing. The clinical presentation was remarkably constant and the very rare variants, dermatophyte mycetoma and systemic dermatophytosis, were not seen. The clinical, immunological and pharmacological data are presented and their relevance to treatment failure is discussed.

Materials and methods
Fifty patients were seen in the out-patient department of St John’s Hospital for Diseases of the Skin, London. A full clinical assessment was made and laboratory isolation of the causative organism carried out. Minimal inhibitory concentrations of griseofulvin were measured by comparing the growth of the organisms in serial dilutions of the drug. Skin tests were performed on all patients using trichophytin (Bencard Ltd, Middlesex) and in appropriate cases the immediate reaction was suppressed using either an equal volume of chlorpheniramine maleate (Piriton injection, 10 mg/ml) given concurrently with the intradermal antigen or cimetidine (Tagamet) 200 mg 4 times daily by mouth for 2 days before the skin test.

The method used in the leucocyte migration inhibition test has already been described (Hay and Brostoff, 1977). The test was carried out in sterile plastic chambers and peripheral blood leucocytes were used. Griseofulvin levels were kindly measured by Glaxo Laboratories Ltd.

Results
In 48 patients the organism isolated was Trichophyton rubrum. One patient, with tylosis, was in-
fected with *Epidermophyton floccosum* and one other, with chronic mucocutaneous candidiasis, with *Microsporum canis*.

In 10 organisms isolated from patients and studied for resistance to griseofulvin, the minimum inhibitory concentrations ranged from 1.5 to 6.3 mg/l. These values did not differ significantly from control values.

Out of 50 patients studied 34 were male and 16 female, with a mean age of 44 years (range 17-76 years). In 41 patients, the infection was of the dry non-inflammatory variety with moccasin distribution and involvement of at least 2 of the following sites: palms, soles, toewebs, finger- or toe-nails, and groins. Four patients had bullae either between toes or on the soles. Four had isolated tinea corporis and one had tinea capitis.

In the group, 28 (57%) had an underlying condition. The commonest was asthma or asthma/hay fever or atopic eczema of varying severity (16 patients); collagen disease or rheumatoid arthritis was seen in 2 and another patient was on systemic corticosteroid therapy; 5 patients had an epidermal disorder such as tylosis or non-bullous ichthyosiform erythroderma and 2 more were found to have severe intermittent claudiation. The associated clinical conditions can therefore be broadly grouped into diseases associated with immune defects and disorders of keratinization or circulation. Of 8 patients with persistent tinea corporis, 6 (75%) had an underlying condition – chronic mucocutaneous candidiasis (1), systemic lupus erythematosus (1), ichthyosis (1), atopic eczema (2), mycosis fungoides (1), 2 were normal (both Chinese). In Caucasian patients with persistent tinea corporis it may be advisable to search for an underlying disease.

No abnormalities were found in serum biochemistry apart from raised circulating IgE levels in 4 patients.

The reasons for the repeated failure to detect specific circulating antibodies to dermatophytes by all available methods, e.g. immunodiffusion, complement fixation, and immunofluorescence, have been reviewed recently (Grappel, Bishop and Blank, 1974). However, the affinity of antibodies present in dermatophyte infections for epithelial tissue has been demonstrated (Hopfer, Grappel and Blank, 1975), and this aspect is currently under investigation. It is possible that this accounts for the absence of demonstrable circulating antibodies. Several workers have emphasized defective cellular immune responses in some of these patients (Hanifin, Ray and Lobitz, 1974; Jones, Reinhardt and Rinaldi, 1974).

Within the group studied only 12% showed delayed hypersensitivity (DTH) to intradermal trichophy tin, whereas 58% had immediate responses. This contrasts with the responses in patients with other dermatophyte infections, usually *T. mentagrophytes*, where 75% showed DTH. Of the patients with chronic dermatophyte infections tested 85% (total 19) showed poor leucocyte-migration inhibition, i.e. a migration index < 0.8. This poor response suggests a defect in the production of migratory inhibitory factor (MIF) in response to trichophy tin. In contrast, the control group of patients with other dermatophyte infections had good responses, 95% with a migration index < 0.8.

The ability to suppress the immediate type response to intradermal trichophy tin with cimetidine or chlorpheniramine is shown in Table 1. Although there is partial suppression no delayed reactions were uncovered.

| Table 1. Effect of histamine blocking agents on trichophy tin test (immediate reaction) |
|-------------------------------------------|-----------------|
| **Weal** | **Flare** |
| Nil | 48 ± 21 170 ± 42 |
| Chlorpheniramine | 28 ± 20 113 ± 46 |
| Cimetidine | 34 ± 19 62 ± 26 |
| Chlorpheniramine + cimetidine | 17 ± 9 43 ± 22 |

* Mean (10 patients) radii² (mm²)

In all but 2 patients whose serum griseofulvin levels were studied, adequate values were obtained. Both patients subsequently admitted failing to take the tablets. In one patient, with non-bullous ichthyosiform erythroderma, levels of griseofulvin in stratum corneum were found to be at least 5 times the serum concentration.

**Discussion**

The outcome of treatment in a dermatophyte infection depends on the ability of the drug to inhibit the fungus coupled with the ability of the host to destroy it, set against the organism’s resistance. From this study it does not appear that drug resistance is an important factor. The serum levels of griseofulvin were also adequate, although the presence of conditions, such as ichthyosis, where epidermal turnover is abnormal, amongst the predisposing diseases might suggest that defective distribution of the drug could be important.

However, epidermal turnover as well as cellular immunity are important host responses to infections. Increased epidermal labelling has been demonstrated in the vicinity of dermatophyte infections using autoradiography (Berk, Penneys and Weinstein, 1976). A defect in epidermal growth would be important in determining chronicity of an infection. Likewise, the defect of cellular immunity reported here and elsewhere (Hay and Brostoff, 1977) may also be relevant. The mechanisms underlying the defective cellular responses in this system are complex and speculative and include the disruption
of normal T-lymphocyte recirculation, the development of clones of suppressor cells or factors relating to the antigenicity of the organism. It has been shown in hay fever that suppression of an immediate skin test by, for instance, chlorpheniramine may uncover a delayed type hypersensitivity reaction previously absent (Brostoff and Roitt, 1969). The mechanism is unknown but there is evidence that an H2-receptor blocker for histamine is present on certain T lymphocytes and that histamine may modulate cell-mediated responses (Wang and Zweiman, 1978). In this system neither the use of the H2-receptor blocker cimetidine nor the H1-blocker chlorpheniramine was able to ‘uncover’ delayed type hypersensitivity to trichophyitin. However, this in vivo experiment does not entirely exclude a role of histamine in inhibiting cellular immune responses.

In conclusion there are demonstrable deficiencies in host defence mechanisms which may adversely affect the ability of an individual to overcome a dermatophyte infection. It seems unlikely that drug resistance or defective absorption of griseofulvin play a major role in treatment failure, although in individual examples they may be important. However, the interaction between host immunity and the organism remains largely unexplored. In particular, it is not known whether T. rubrum differs from other organisms in its ability to evade immune surveillance and host defences. More work is needed in this area, in particular, before an adequate picture of the complex balance between drug, host and organism can be established.

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References
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