casts of the capillaries and at times, therefore, appear in the peripheral blood as long platelets.

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PATHOLOGY

Absence of Local Cytotoxic Change in Man from Griseofulvin

With the importance of griseofulvin in the treatment of superficial fungous infections, it is imperative to know more about the toxic reactions especially if treatment is prolonged. Since the significant studies of Paget and Walpole[1] on the interference with mitosis under massive parenteral administration of griseofulvin in rats, there has been continued interest in investigations of this phase of reaction in man. Our purpose was to develop a technique for studying possible local cytotoxic reactions in man from locally deposited griseofulvin.

Supersaturated solutions of microcrystalline griseofulvin were prepared in saline, sterilized by autoclaving, and after vigorous agitation, 0·1–0·2 ml. was injected into 14 patients into areas of normal skin of the back and arm and into the scalp in the occiput area. In many instances the injection site was tatooed with indian ink to localize the crystal mass. Controls had been done previously with indian ink particles. In addition, in 6 patients, griseofulvin was injected into three basal cell tumours, one squamous malignancy, one melanoma and one malignant lymphoma. In four additional subjects, a lotion containing 1 per cent griseofulvin was rubbed daily for three weeks into basal cell carcinoma, squamous cell carcinoma, and into the so-called precancerous senile keratosis. To detect any anti-inflammatory activity of griseofulvin, saline suspensions of griseofulvin were injected repeatedly into spots of psoriasis, and neurodermatitis.

No local anti-inflammatory property could be detected. In normal skin, the biopsies were taken at intervals ranging from 1 hr. to three months after local injection and were studied in frozen section and in prepared sections with routine hæmatoxylin–eosin, toluidine blue *p*H 6, periodic acid–Schiff, Feulgen stains. The frozen sections were examined under the polarizing microscope to detect the depots in the dermis of the insoluble crystals. After a period of several days, crystals could not be detected under the polarizing microscope. In three instances, a bioassay of the skin extract was performed to detect antifungal activity of the tissue. In all these experiments, there were no spectrofluorometric determinations for griseofulvin in extracts of the injected skin. A total of 30 injections of griseofulvin was given.

In brief, there was only occasionally a mild foreign-body reaction of non-specific type about the depot of crystals. This subsided rapidly, usually within three or four days, and then no demonstrable inflammatory activity could be detected except occasional perivascular lymphocytic infiltrate. In one patient, after three weeks there were still a few histiocytes and foreign-body giant cells. There was no change in mitosis in any portion of the epidermis surrounding this, or in any portion of the adjacent hair follicle. In only one experiment, vacuolization of the cells in the adjacent portion of the hair follicle was found. In one instance, three months after injection, no change was found. In all the human tumour experiments there was no effect in either retardation or acceleration of the tumour growth, nor any demonstrable local effect on the individual tumour cell. In clinical observation[2] of a year's experience with oral griseofulvin in fungous therapy programme on more than 400 patients, there has been no evidence of any effect upon associated skin tumours, including basal cell, squamous cell and melanomas. In two patients with melanomas, griseofulvin was given in dosages of 2–4 gm. There is no information available on the effect on any associated internal visceral tumours other than the melanomas.

To amplify this study in the Department, the effect of griseofulvin in animal tumour experiments was initiated.

Griseofulvin crystals were furnished by Dr. G. Kenneth Hawkins, Clinical Research Division, Schering Corporation, Bloomfield, New Jersey.

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Tumour-promoting Effect of Excessively Large Doses of Oral Griseofulvin on Tumours induced in Mice by Methylcholanthrene

Large intravenous doses of griseofulvin in rats have been found to arrest mitosis in metaphase in certain organs, for example, bone marrow, seminal epithelium and intestinal epithelium. We postulated that since griseofulvin taken orally is soon found in the keratin layer of the skin, there might be an antimitotic effect with a delay in the production, and a reduction in the number, of tumours that would be produced by applications of methylcholanthrene to the epidermis of mice. A pilot experiment was performed which gave quite unexpected results.

White Swiss male mice of 24–28 gm. per mouse were divided into five groups. One drop of 0·5 per cent 3-methylcholanthrene in acetone was applied twice weekly for 4 weeks to the lower back of the mice of groups 1, 2 and 3.

Group 1 consisted of 20 mice receiving standard mouse food and having applications of methylcholanthrene. None of the 20 mice had any tumours formed as late as 12 weeks after the start of methylcholanthrene applications.

Group 2 consisted of 10 mice receiving a 1 per cent griseofulvin mouse food mixture for 6 weeks prior to, during and after the applications of methylcholanthrene. This group showed 5 of the 10 mice to have papillomas formed at the end of the first month of applications of methylcholanthrene. By the end of the second month of the experiment, 6 of