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Flavofungin, a New Crystalline Antifungal Antibiotic: Origin and Biological Properties

During the systematic study of actinomycetes antagonizing fungi pathogenic in man, a species of *Streptomyces* (*SA*-IX/1) was found from desert sand that markedly inhibits growth of *Cryptococcus neoformans* and *Trichophyton mentagrophytes* used for screening[1]. In laboratory deep fermentation, besides the antifungal antibiotic, an antibacterial one was produced also by this species. A natural stable variant (*SA*-IX/3) differing morphologically from the original strain isolated was selected that is capable of producing increased quantities of the antifungal and decreased quantities of the antibacterial agent. This proved to be a new species and has been named *Streptomyces flavofungini*./ The antifungal, crystalline antibiotic (Fig. 1) was isolated as a uniform product from the mycelium and fermentation fluid of this asporogenic, chromogenic variant. From its colour and effects, the new antifungal agent has been called 'flavofungin'.

Pure flavofungin has no influence upon growth of *Streptomycetes* and common bacteria; but the growth of *B. subtilis* and of a few strains of *M. pyogenes* var. *aureus* is inhibited by relatively high concentrations of more than 100 μgm./ml. Marked inhibition is exerted *in vitro* upon the growth of pathogenic and non-pathogenic yeasts and yeast-like fungi, dermatophytes, and also of saprophytic and plant pathogenic fungi; inhibitory concentrations are shown in Table 1. Assays were carried out by serial dilutions in Czapek–Dox, Sabouraud, Jensen and mush media. Its diffusion into agar is rather slow.

In aqueous suspension, given *per os* or subcutaneously, in dosages up to 250 mgm./kgm., to the mouse,

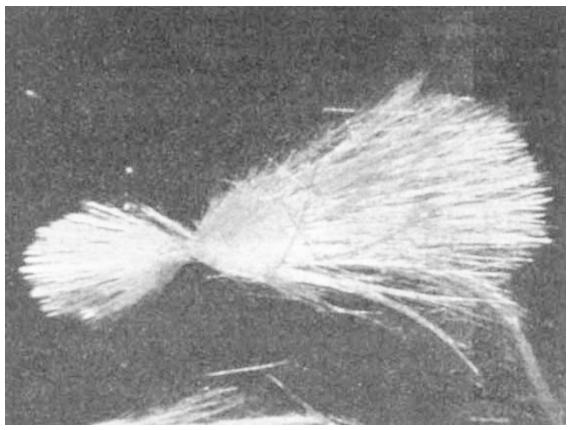

Fig. 1. Flavofungin crystals

Table 1

Micro-organism	Inhibitory conc. (μgm./ml.)
Fungi	
Aspergillus clavatus	15
Penicillium chrysogenum	8
Penicillium novum hybrid	8
Penicillium sp. (two strains)	10–20
Scopulariopsis sp.	15
Cephalosporium sp.	15
Monosporium apiospermum	15
Helminthosporium sp.	10
Trichotecium roseum	15
Mastigocladium sp.	10
Yeasts and yeast-like fungi	
Candida albicans (three strains)	4–5
Candida krusei	6
Candida tropicalis	15
Saccharomyces cerevisiae (three strains)	3–20
Saccharomyces niger	2
Cryptococcus neoformans	2
Torula utilis	10
Hansenula anomala	10
Rhodotorula sp.	2
Torulopsis pulcherrima	2
Pathogenic fungi	
Trichophyton mentagrophytes	20
Trichophyton tonsurans (two strains)	8–30
Trichophyton rubrum (two strains)	10
Trichophyton gypseum (two strains)	20
Trichophyton sulfureum	8
Epidermophyton kaufmann-wolf (three strains)	15–20
Epidermophyton inguinale	10
Microsporum canis	8
Microsporum gypseum	8
Achorion quinckeanum	8
Ceratinomyces	10
Phialophora verrucosa	20
Histoplasma capsulatum	10
Sporotrichum schenkii	10
Hormodendrum compactum	8
Nocardia asteroides	20
Geotrichum sp.	20

no acute or late symptoms were evoked; *LD*50 is 25 mgm./kgm. in aqueous suspension given by the intraperitoneal route.

In the fæces of mice fed with *Candida albicans*, no colonies, or only a few, can be demonstrated after having received flavofungin *per os*, in marked contrast to untreated controls.

Flavofungin is strongly bound to serum proteins, but can be liberated.

According to its chemical, physical and biological properties, flavofungin is not identical with formerly known antifungal antibiotics[2]. Its isolation and chemical properties will be described in detail elsewhere.

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Effect of Heparin on Pathologically Decreased Serum Esterase in Carcinoma

Plasma and serum esterolytic activity may be considerably decreased in pathological conditions. The substrates most often used for the determination of esterolytic activity are acetylcholine[1], tributyrine[2] and procaine[3]. Decreased activity is found most often in cirrhosis of the liver and carcinoma. In our work ethyl butyrate was used as the substrate and esterase activity was determined by the titrimetric method[4]. The values are given in ml. of 0·05 *N* sodium hydroxide required to neutralize the acid liberated in 24 hr. In agreement with other workers we found low values, especially in some forms of carcinoma and cirrhosis. These low values are in sharp contrast to the increase in esterase activity