# Section of Pathology

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[*February* 4, 1958]

## The Role of Fungi as Human Pathogens

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ONLY very few species of fungi occurring in nature as saprophytes have the ability to produce infection in man and animals; greater numbers have the ability to evoke allergic reactions in hypersensitive subjects. There are a few fungi like *Malassezia furfur*, causing pityriasis versicolor, and *Blastomyces dermatitidis*, responsible for blastomycosis, which have not been found other than in association with infections of man and animals, but the majority of pathogenic fungi may exist as saprophytes in nature. One of the more recent to be demonstrated in the soil is a ringworm fungus, *Microsporum gypseum*. In the case of the filamentous fungus, *Aspergillus fumigatus*, there is no difference in structure between the saprophytic and parasitic forms of the organism, but in most other pathogenic fungi these forms are dissimilar. In some, such as the fungi causing ringworm, Madura disease and chromoblastomycosis, the parasitic growth represents a restricted or dysgonic form. In others, like *Sporotrichum schencki* and *Histoplasma capsulatum* producing sporotrichosis and histoplasmosis respectively, the parasitic form is entirely different from the saprophytic, and, in consequence, they are termed "dimorphic". The filamentous fungi, therefore, exhibit a range of structural adaptations to parasitic existence; the more adaptable they are the greater is their ability to invade. Some can persist as filamentous organisms in exudates and in non-viable tissues as is the case with *Aspergillus fumigatus* and the dermatophytes or ringworm fungi. At the other extreme, the filamentous form of fungi causing systemic infections is incompatible with parasitism and a change to a unicellular fungal form results (e.g. *H. capsulatum*). A fungus like *Cryptococcus neoformans*, causing torulosis, which exists entirely in a yeast form, is structurally similar in its role as a human pathogen (Fig. 1) and as a saprophyte grown from the soil.

Like all parasites, there is great variability in the amount of injury which fungi inflict on their human or animal hosts. Certain anthropophilic ringworm organisms (e.g. *Epidermophyton floccosum*) growing on the skin surface may remain unnoticed by the host and behave as little more than saprophytes in keratin. Some would query whether the presence of fungus in skin is compatible with normal appearances, but there is no doubt that only the slightest degree of hyperkeratosis may be evoked. In other instances, however, as frequently occurs with the zoophilic ringworm species, the host tissues are injured greatly leading to suppuration and even permanent scarring. Though there tends to be a typical response to infection by various ringworm species, unusual reactions not infrequently occur (Partridge, 1952). It should be stressed that whether or not the host is injured the zone of dermatophyte invasion is always limited to the keratin layer. Living tissues are not attacked by the dermatophyte fungi. Similarly, the wall of a pulmonary cavity or an infected pleural space may be temporarily invaded by *A. fumigatus* without causing apparent harm. On the other hand, an infection of this kind may, in other instances, materially delay healing and give rise to signs and symptoms of toxæmia. Here again, histological examination of the infected areas shows no evidence of fungal invasion of living tissues.

In ringworm and in *A. fumigatus* infections of man, the products of fungi growing in non-viable tissues must be assumed to diffuse into living tissues in the environment, there to

evoke an inflammatory reaction of greater or lesser degree or to bring about tissue degeneration. In some instances it appears that the damage produced in the tissues by fungus "toxins" may pave the way to further fungus invasion; this seems to be the case in aspergillosis, particularly in avian disease. The nature of the toxic products from fungi which produce the changes typifying these various infections has received little study. Henrici (1939) produced evidence for the existence of a thermolabile endotoxin from *A. fumigatus*, and Winner (1956) of a toxin responsible for the pathogenicity of *Candida albicans*. Histologically the lesions of coccidioidomycosis and tuberculosis are closely similar and it is obvious that *Coccidioides immitis* possesses chemical components which evoke caseation in the tissues like that produced by *Myco. tuberculosis*, but these have not been characterized.

As in many other diseases, the factors predisposing to fungal infections are not understood. Obvious causes such as maceration in ringworm infection, and diabetes and antibiotic therapy in moniliasis, are well recognized. Where such factors are absent, as is usually the case, more fundamental reasons for predisposition to infection remain unrecognized. These are particularly pertinent in *Trichophyton rubrum* infections where individual susceptibility to fungal infection, and indeed regional susceptibility too, is very prominent. Differences in host species behaviour are evident in aspergillosis, in which tissue damage from infective, neoplastic or vascular causes is apparently a pre-requisite for human disease, whereas in birds primary infection of healthy tissues may occur. Once infection is established, it is possible that changes occurring in the tissues may promote further fungus invasion. This would seem to be the case in avian aspergillosis where the growth of *A. fumigatus* is intimately associated with an extending area of necrosis (Fig. 2). To a lesser degree this also appears to occur in man, and the extensive invasion of infarcted areas of lung by *A. fumigatus* is evidence of the suitability of non-viable tissues for growth of this fungus.

Of the many aspergillus species only *A. fumigatus* possesses any definite pathogenicity for human tissues, and *C. albicans* is also alone in this respect amongst the numerous candida species (Dawkins *et al.*, 1953). Pathogenicity is, therefore, in these species related to special products of fungal metabolism rather than to structure. All species of microsporum, trichophyton and epidermophyton have the ability to invade keratin, a property dependent on possession of one or more keratinolytic enzymes. The properties of such enzymes remain undiscovered. Within these genera, species differ in their potentialities for attacking keratin of nail and of hair, and in the case of hair such differences may be demonstrated *in vitro* (Fig. 3). Though it is possible to exemplify keratinolysis of hair *in vitro*, the manner in which hair is invaded in such tests is quite different from that which occurs *in vivo*. In natural disease, longitudinal tunnelling of hair occurs always in the direction of the hair bulb. This chemotactic attraction in the direction of germinal cells is obvious, not only in hairs where the advancing line of fungal filaments has long been recognized as Adamson's fringe, but also in skin where dermatophyte hyphæ are seen near to the stratum granulosum of the epidermis (Fig. 4). This invasion of the deeper keratin layers occurring in subjects in whom little tissue response is provoked results in persistence of infection. Under such conditions keratin is attacked as fast as it matures in a zone which is inaccessible to any fungicidal agents known at present.

As in all infections, establishment of mycotic disease depends on the susceptibility of the host and on the infectiveness and virulence of the causative fungus. In torulosis, the fact that laboratory infections are unknown indicates that *C. neoformans* has a low degree of infectivity; torulosis is, furthermore, an uncommon sporadic disease widely distributed throughout the world. Individual proneness to respiratory infection by inhalation would seem to be the all-important factor in this disease. Once established, the fungus may remain localized to lungs or may disseminate when it is usually lethal. As far as can be assessed at present, benign infection is more rare than systemic disease. In coccidioidomycosis and histoplasmosis, on the other hand, infectiveness of the causative fungi is very high, but human susceptibility is such that disease is usually benign and limited to the lungs, only very rarely disseminating.

The fungi pathogenic for man which parasitize in the filamentous form are almost invariably only locally invasive. Some, like *M. audouini* and *T. rubrum*, are usually ideal parasites since they cause negligible harm to the host and are difficult to eradicate. Others, like *T. verrucosum*, are usually unsuccessful parasites in that they evoke a tissue reaction which rapidly brings to an end their existence in keratin. Even less successful parasites are the fungi causing systemic mycoses, for these produce a short-lasting benign infection in which the fungus is destroyed, or more rarely a disseminated infection in which the host perishes. *Aspergillus fumigatus* is dependent on previous lung damage before it can be established in human tissues but it may be responsible for pathological changes at present unassessed. Greater understanding of these infections requires research into the properties of metabolic products of fungal growth and more critical studies of the relationship of various fungus

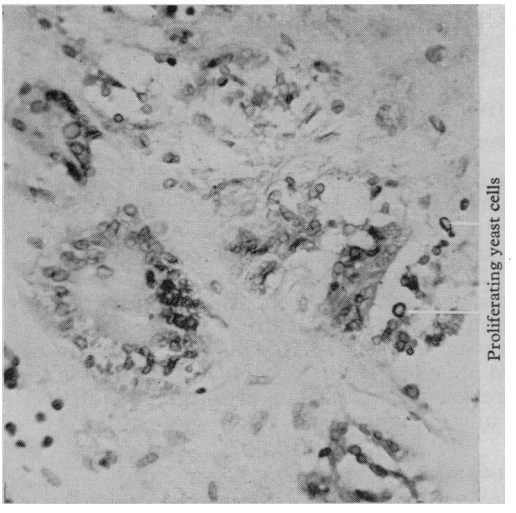


FIG. 1.—Torulosis of brain. Section showing proliferating *Cryptococcus neoformans* cells producing giant-cell reaction. (Stained periodic acid Schiff and haematoxylin. ×256.)

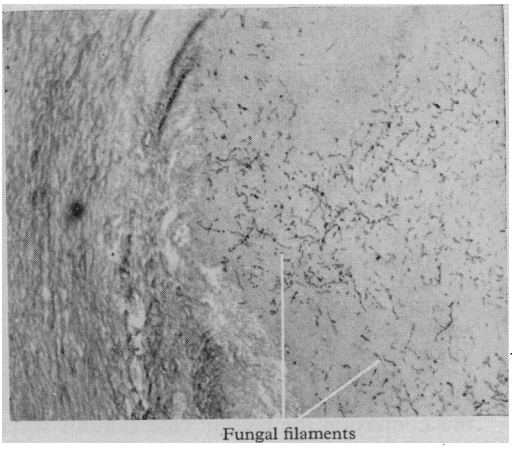


FIG. 2.—Aspergillosis of avian lung. *Aspergillus fumigatus* filaments in periphery of area of caseation. (Stained periodic acid Schiff. ×109.)

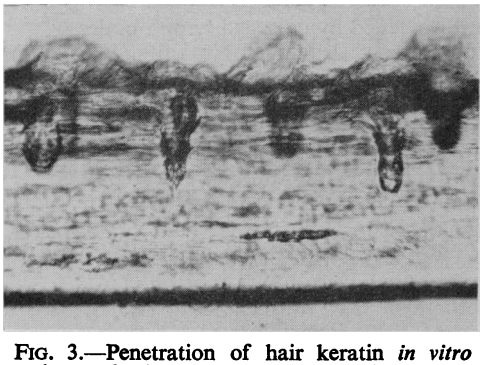

FIG. 3.—Penetration of hair keratin *in vitro* by *Trichophyton mentagrophytes*. (×107).

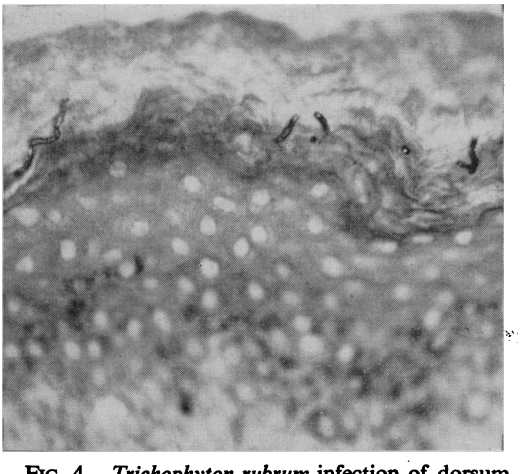

FIG. 4.—*Trichophyton rubrum* infection of dorsum of foot. Section showing fungus filaments deep in keratin near stratum granulosum. (Stained periodic acid Schiff. ×244.)

species to human disease processes. In Britain, where the more virulent types of pathogenic fungi are rarely met with, the role of the potential pathogen is of main importance.

I wish to acknowledge with thanks the help of Mr. R. J. Lunnon, Institute of Dermatology, for the photographs and of Miss Y. M. Clayton and Dr. C. D. Calnan for providing the material shown in Figs. 3 and 4 respectively.

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