CONTINUING MEDICAL EDUCATION

FUNGI, FRAGILE, FASTIDIOUS, FASCINATING

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Fungal infections can be fragile in that they are amenable to treatment; some of them are fastidious in that they are resistant to therapy, but on the whole the subject of mycology is indeed a fascinating one.

It was Ajello who said in 1970,

"More than a decade has passed since mycoses have been likened to an iceberg with its vast bulk....submerged in the murky sea of ignorance."

However, the veritable avalanche in our knowledge of these mycoses has reduced the size of the iceberg, as we know more and more of these diseases. Besides, with the increase in our armamentarium to combat them, the overall picture in mycology is one of optimism.

In this presentation, an overall perspective of the fungal flora as encountered in India is presented.

1. Superficial mycoses

The infection is limited to the outermost layer of the skin and cellular response from the host is minimal. In this group, pityriasis versicolor, tinea nigra and piedra are included.

Pityriasis versicolor : It is caused by a lipophilic fungus *Pityrosporum orbiculare*. It is seen more in warm humid climates. Sweating plays an important role in host susceptibility.[1] The incidence of pityriasis versicolor in public hospitals in India is—BYL Nair Hospital 1.4% of all dermatomycoses; KEM Hospital 8.3% of all dermatomycoses; Sasoon Hospital 1.75%; Madras 17.5%; Baroda 1.5% of patients attending the Skin OPD and at Madras 2.9% of all patients attending the Skin OPD.[2]

It is characterised by maculo-squamous lesions of varied colour, hypopigmentation being more frequent than hyperpigmentation. *P. orbiculare* produces an azelaic acid compound which is an inhibitor of tyrosinase, which accounts for the hypopigmentation. Occasionally, follicular lesions may be encountered. Wood's lamp examination gives a golden yellow fluorescence due to a metabolic product of coproporphyrin. Microscopic examination shows the spaghetti and meat ball appearance of the yeast and hyphal forms. *P. orbiculare* is culturable in Sabouraud's medium with olive oil, Martin Scott with sodium thyroglycocholate, Caprilli's medium with yeast extract, with glycerol monophosphate at 30°C.[3] The colonies are grouped, friable, heaped and cream coloured. Treatment is effective in eliminating the fungi, although pigmentary changes may take a few weeks to a few months to return to normal. Recurrences occur in 30-50% patients. Older remedies include daily applications of 20% sodium hyposulfite, 3% salicylic acid, in 70% alcohol, Whitfield's ointment and sulphur ointment 2%. These are less effective than modern therapies and are messier and more tedious. Haloprogin, tolnaftate 0.5 to 1%, propylene glycol 50% in water, clotrimazole 1%, miconazole nitrate 2% and econazole 1% are equally effective. The mainstay of therapy has been 2.5% selenium sulfide shampoo used on the scalp and affected areas and kept overnight,

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Table I. Evaluation of ketoconazole in 40 cases having pityriasis versicolor.

Phase I	Duration of treatment in weeks	Number(%) of cases showing improvement		
		Subjective	Objective	Scrapings test
Ketoconazole 200 mg daily for 2-4 weeks	2	26 (65)	23 (60)	23 (60)
	3	30 (75)	28 (70)	28 (70)
	4	32 (80)	38 (90)	40 (100)

Phase II	Duration of treatment in months	Number of cases showing recurrence following treatment with	
		Ketoconazole (19 cases)	Placebo (18 cases)
Ketoconazole 200 mg daily for 3 days in a month for 3 months.	1	Nil	Nil
	2	Nil	1
	3	Nil	5
	Total	Nil	6 (30%) recurrence

with morning bathing. The therapy is repeated after one week and then once every three months to diminish recurrences. Recently, ketoconazole 200 mg given orally has been reported effective in extensive pityriasis versicolor in reducing the incidence of recurrences.[4]

In our study all the 40 (100%) cases of pityriasis versicolor given ketoconazole 200 mg daily for 2-4 weeks showed negative scrapings after 4 weeks (Table I). In the next double blind study, ketoconazole was given for 3 consecutive days in a month for three months. There was no recurrence in the 19 cases, while 6 of the 18 cases receiving placebo treatment showed recurrences.

Tinea nigra : It is caused by the fungus *Exophiala wernecki*. It is seen more in the tropics; the organism being found in the soil compost and sewage. In India, Dasgupta et al[5] from south India and Hemashettar et al[6] have reported cases. It is characterised by pigmented macular lesions with an advancing periphery. Macules may coalesce into polycyclic patterns without scales or vesicles.

Scrapings show the dematiacious hyphae. The culture shows greenish black colony. Salicylic acid and imidazoles topically are highly effective. Griseofulvin is ineffective.

Piedra : This is a superficial fungal infection characterised by dark gritty or soft nodules on the hair shaft. There are two varieties :

(a) White piedra

The causative organism is *Trichosporum cutaneum*. It is seen in tropical and temperate areas of Europe and Asia. In India, at Madras the reported incidence was 0.1%.[7,8] At BYL Nair Hospital we reported a single case. Multiple, whitish to light brown, firm nodules are found on the coarse hairs of the body, beard, eye-brows, eyelashes, scalp and pubic region; associated with mild pruritus. Microscopically, hyphae and spores surround and invade the hair shaft, the hyaline hyphae and oval arthrospores are held together in a cement matrix. Culture shows a creamy colony. Shaving or clipping of the affected hair along with topical therapy is needed. Topical bichloride of mercury (1 : 2000), ammoniated mercury 3%, formalin 2%, sulphur 2%, clotrimazole and amphotericin B lotion are also effective.

(b) Black piedra

The causative agent is *Piedraia hortai*. A high incidence is seen in hot humid tropical areas of Africa, Asia and Latin America. In India, it was reported from Varanasi[9] and also by us at Nair Hospital. It is quite common in Kerala. In Malaysia, it is considered a mark

of beauty and called "rambat-barbuah" meaning "fruit bearing". Natives stop using oil and sleep with their heads depressed in the soil to encourage growth of the fungi. The hard, gritty nodules on the hair shaft of the scalp, beard or moustache are produced by masses of tightly packed hyphae with oval asci-containing ascospores. Culture shows a black colony with brownish filaments at the periphery. Therapy is identical as for white piedra.

2. Cutaneous mycoses—dermatophytoses

In this group, clinically apparent signs of host response can be observed. These infections are the most prevalent medical conditions in all humans regardless of race, age, economic status, sex or geographic origin. These are caused by fungi of the genera *Microsporum, Trichophyton and Epidermophyton.*

At present 39 species of dermatophytes are recognised though most infections are caused by 11 species.[10] In India, the list is pared to 8 (*T. rubrum, T. mentagrophytes, T. tonsurans, T. violaceum, T. verrucosum, T. schoenleinii, Microsporum* species and *E. floccosum*).

Table II shows an all India perspective of the clinical types of dermatophytoses. The commonest sites being tinea corporis, cruris, pedis, capitis and barbae, unguium and manum in descending order of frequeny.[11-22]

Table III shows the mycological species isolated in India. The commonest species being *T. rubrum, T. mentagrophytes, T. tonsurans, T. violaceum, E. floccosum and Microsporum* on the skin, and on the scalp the commonest species being *T. violaceum, T. tonsurans, T. schoenleinii and Microsporum.*[11-30]

Table II. Percentages of cases of different clinical types in the four zones of India.

Zone	Corporis	Cruris	Pedis	Manum	Capitis	Barbae	Unguium
North	41.52%	36.01%	6.02%	0.35%	3.09%	—	1.51%
West	45.65%	37.91%	2.61%	0.74%	4.75%	3.02%	3.39%
South	38.32%	33.64%	5.53%	2.78%	3.55%	0.84%	2.46%
East	50.20%	37.00%	7.40%	0.70%	2.10%	0.70%	2.10%

Table III. Percentage of dermatophyte species isolated from the patients in the four zones of India.

zone	*T. rubrum*	*T. mentagro-phytes*	*T. tonsurans*	*T. violaceum*	*T. verrucosum*	*E. floccosum*	*M. canis*	*M. gypseum*
North	72.44%	8.58%	4.74%	2.88%	0.13%	3.76%	0.57%	0.15%
West	77.81%	8.75%	6.68%	3.91%	—	4.94%	0.22%	0.51%
South	59.71%	8.64%	6.34%	3.83%	—	11.40%	—	0.78%
East	54.55%	18.98%	5.75%	1.72%	0.77%	13.31%	0.19%	0.38%

Dermatophyte species isolated in tinea capitis

	T. violaceum	*T. rubrum*	*T. menta-grophytes*	*T. tonsurans*	*T. verrucosum*	*T. schoenleinii*	*M. gypseum*	*M. canis*	*M. audouinii*
Overall incidence	74.8%	18.9%	15.55%	1.86%	0.60%	0.87%	5.5%	0.66%	0.56%

Conventional classification of dermatophytoses according to their regional distribution on the body, though useful clinically, disregards the lesions themselves. The anatomo-clinical classification of dermatophytoses of Lachapelle and Armijo,[31] underlies the host-parasite interrelationship and gives a clue to logical therapy. The main groups are as follows :

A. Dermatophytoses limited to keratinous structures

(a) Tinea of glabrous skin

In scaly lesions, the stratum corneum is thickened, hyper and ortho keratotic and hyphae lie parallel to the epidermis. The dermis shows a lympho-histiocytic infiltrate around the blood vessels.

In vesicular lesions the immunological response is more pronounced. Focal spongiosis (spongiotic dermatophytosis), intraepidermal vesiculation and a dense peri-vascular infiltrate extends to the superficial dermis.

(b) Tinea of palms and soles

Diffuse hyperkeratosis, often unilateral, is seen and the plams appear floury. Histopathologically, the hyphae invade vertically and the inflammatory response is discrete.

(c) Tinea capitis—without perforating folliculitis

The spores may be within and/or outside the hair shaft (ectothrix or endothrix), large in *Trichophyton* species and small in *Microsporum* species. The inflammatory response is similar to that seen in dermatophyte infections of the skin.

(d) Onychomycosis

Fungal hyphae invade the nail bed which is hyperkeratotic and also the under surface of the nail plate, the hyphae may lie parallel to the nail plate or be randomly seen.

B. Perforating dermatophytoses

(a) Chronic perforating folliculitis

Fungal hyphae invade the hair sheath provoking a hyperkeratotic reaction resulting in marked perifolliculitis; the hair sheath disrupts and hyphae are discharged into the dermis, enhancing the inflammatory response. Giant cells engulf hyphae, but the infection is self limited. Clinically, nodular lesions are encountered.

(b) Kerion and Sycosis

This is an acute peri-folliculitis of the scalp. The fungi invade the hair shaft. Hyphae and arthrospores are numerous. After disruption of the hair, the horny debris falls into the dermal tissue where a limited foreign body reaction occurs.

(c) Favus

Common in Kashmir, it is clinically characterised by scutula, which is a mass of keratinised and parakeratotic cells, exudate and inflammatory cells intermingled with hyphae and spores. The masses are located in the infundibulum of the hair follicle.

C. Dermatophytes actively invading dermal tissues (Dermatophytic granulomas)

Dermatophytic granulomas occur in patients having immunological defects, asthenomycosis. They actively invade and proliferate in the dermal tissue.

(a) Dermatophytic granuloma following invasion of the hair follicle

Clinically, reddish violet, firm nodules may be present in immunodeficient patients. These nodules grow and ulcerate with crusting. Histopathologically, hyphae may be seen in the stratum corneum; more numerous in the hair sheath with disruption of hair sheaths. The granuloma extends and invades the subcutaneous tissue. It is polymorphous in nature with foci of necrosis.

(b) Majocchi's granuloma

This is clinically similar to the dermatophytic granuloma of the hair follicle. However, fragments of the hair infected by the dermatophytes are present along with numerous spores invading the hair shaft.

(c) Mycetoma

This dermatophytic granuloma shows grains—mycelial filaments surrounded by giant cells and histiocytes.

D. Generalised dermatophytoses

These are characterised by a marked defect of the host immune system. The entire organism is invaded by dermatophytes. Granulomatous lesions develop in the skin and deeper tissues leading to death.

This classification leads to some therapeutic conclusions. Dermatophytoses of group A can be treated topically except those of the palms, soles and nails. Groups B, C and D require systemic treatment with griseofulvin and/or ketoconazole.

3. Yeast-like fungi

Cryptococcosis : The causative organism *Cryptococcus neoformans* infects man and domestic and wild animals and has been isolated from the natural sources, pigeon excreta and air samples. Initial infection is pulmonary and cutaneous infection may be primary or disseminated in 10% of the cases. Littman and Walter[32] in a survey during 1952-53 reported 788 deaths. In India, lung, CNS, cardiac, kidney, bone and mediastinal involvement in post-mortem studies have been reported.[33-42] Muktabai et al[43] reported 3 cases with cutaneous involvement. The paucity of cutaneous lesions reported in India prompted us in 1980 to report a single case.[44] A male patient of Hodgkin's disease presented with cutaneous ulcers giving a mucilaginous discharge; smears with India ink showed the encapsulated yeast forms; culture showed the mucilaginous colonies. The yeast cells showed pinched budding and colonies showed ability to produce urease and specific nitrate sugar assimilation. Intracerebral injection in mouse further proved the pathogenicity. Skin biopsy showed masses of cryptococci with a sparse peripheral inflammatory response. The mucicarmine stain showed the brilliant red rose capsular material.

Candidiasis—refers to a primary or secondary infection of the skin and mucous membranes, and less commonly internal organs, caused by yeast-like fungi of the genus *Candida*, *C. albicans* being the principal species, *C. stellatoidea* and *C. tropicalis* being the next frequent pathogens, the other species being less frequently pathogenic.

Table IV shows the clinical profile of 500 cases of candidiasis; the main clinical entities being candidal intertrigo, vulvo-vaginitis, paronychia and thrush infections.[45-47].

Table IV. The clinical types of candidiasis observed in 500 cases.

	Clinical types	Number of cases	% age
1.	Intertrigo	128	25.6
2.	Vulvo-vaginitis	115	23.0
3.	Paronychia	102	20.4
4.	Thrush	61	12.2
5.	Erosio interdigitalis	27	5.4
6.	Peri-anal	18	3.6
7.	Balano-posthitis	10	2.0
8.	Generalised cutaneous candidiasis	8	1.6
9.	Perleche	3	0.6
10.	Miscellaneous	28	5.6
	Total	500	100.0

Table V shows the mycological profile of 500 cases of candidiasis. *C. albicans* was cultured in 63%, *C. tropicalis* in 11%, and *C. stellatoidea* and *C. krusei* in 5% each.[45-47]

Table V. The mycological species of candida isolated in 500 cases.

	Species	Number of cases	% age
1.	*C. albicans*	316	63.20
2.	*C. tropicalis*	58	11.60
3.	*C. stellatoidea*	26	5.20
4.	*C. krusei*	26	5.20
5.	*C. gullermondis*	10	2.00
6.	*C. parapsilosis*	6	1.20
7.	Others	58	11.60
	Total	500	100.00

Various environmental and host factors influence the pathogenicity of *C. albicans*. Heat, humidity, friction in intertriginous areas and chronic maceration predispose to infection. Besides, antibiotics, diabetes mellitus, corticosteroids, pregnancy and oral contraceptives are predisposing factors. Alteration in the host cellular and possibly effector immune mechanism mediates the predisposition. Humoral factors form a second line of defence; the alternative complement pathway products (C5a—a potent chemotactic agent) activated by the candidal cell wall products and iron-free transferrin exert an inhibitory influence on *C. albicans* possibly by removing the iron needed for growth. Cellular immunity and the capacity of PMN to phagocytose and kill the organisms are critical in handling the organism once penetration has been accomplished.

Chronic muco cutaneous candidiasis : It is characterised by candidal infection of the skin, nails, oral and genital mucosa which is persistent, usually from the first year of life. Chronic granulomatous lesions, hypertrophic mucosal lesions and hyperkeratotic cutaneous lesions may be seen. CMC is not a single disease entity but a final clinical presentation for a spectrum of immunodeficiencies ranging from life threatening to subtle deficiencies, usually of cellular immunity. Subgroups of CMC with various genetic patterns, immunodeficiency states or medical associations have been reported.

In candidal endocrinopathy syndrome, CMC may develop in children with hypoparathyroidism, hypoadrenalism, hypothyroidism and diabetes mellitus. In one subgroup, iron deficiency secondary to malabsorption of iron was noted. Correction of iron deficiency allowed improvement. Low dose amphotericin B (less than 15 mg/day for 3 weeks), or oral ketoconazole 200 mg daily controlled the infection. Besides, immune-enhancing agents like transfer factor, thymosin, cimetidine and levamisole have been advocated.

4. Subcutaneous mycosis

These fungal infections involve the skin and subcutaneous tissue, and rarely disseminate to internal organs. In this group are included sporotrichosis, chromomycosis and rhinosporidiosis.

Sporotrichosis : The causative organism is *Sporotrichum schenckii*. It has been reported from east and north east India and also from south India.[48-52] The infection is confined to the skin, subcutaneous tissue and lymphatics. Lesions which are granulomatous and suppurative, ulcerate and drain. The cutaneous lymphatic type is the commonest. Farmers, gardeners and timber workers are more prone to the infection. Culture shows creamy colonies which turn brown-black. Microscopically, the hyphae are thick and show two types of conidia—dark thick-walled conidia in sleeve-like arrangement, and hyaline conidia in bouquet arrangement.[53] The fungus being dimorphic, the yeast-like budding cells described as cigar shaped can be seen in the tissues. The histopathologic reaction is a combination of epithelioid cell granuloma with suppuration. The presence of asteroid body is compatible with the diagnosis of sporotrichosis. It is a central oval yeast cell, basophillic with a radiating eosinophillic structure (Splendore-Hoeppli phenomenon) composed of granular material deposited in an antigen-antibody reaction.

Chromomycosis : It has been widely reported from various parts of India.[54-65] Infection follows trauma to the leg. The lesions are verrucoid, plaque-like, ulcerated, crusted and pedunculated. Satellite lesions arise by autoinnoculation and lymphatic spread to the adjacent areas. The fungus culturally produces dark jet-like colonies with short aerial mycelia. Depending on their conidiophores the species are differentiated into three types, (1) *Phialophora* where the conidia are produced in flask-like phialides, (2) *Cladosporium* where the conidia occur in chains and the spores show

disjunctors on their surface, and (3) *Acrotheca* where the conidia from long irregular club shaped conidiophores. Histopathologically, the thick round chestnut brown fungus is diagnostic. The fungi are also described as cluster of pennies or peas in a pod within a giant cell.

Rhinosporidiosis : It is common in Tamil Nadu, Madhya Pradesh, Orissa and Kerala.[66-69] It is caused by *Rhinosporidium seeberi*. It is a chronic granulomatous disease characterised by polyps on the mucous membrane and skin. Lesions on the skin are papillomatous and become warty.[70] Histopathologically, H & E stain reveals globular cysts-sporangium in which the spores lie, the immature spores being at the periphery of the cyst. A foreign body giant cell reaction may develop around a sporangium.

Mycetoma : Carter in 1974 introduced the term mycetoma meaning a fungus tumour as he identified fungus elements in the grains of these lesions in the subcutaneous tissue. Clinically, the lesions occur on the foot, and less commonly on other body sites, extending deep into the subcutaneous tissue with suppuration and sinus formation; extruding granules which may be white, yellow, pink or black.

There are two types of mycetoma :

1. Actinomycotic mycetoma caused by the family of actinomycetaceae—*Actinomyces*, *Nocardia* and *Streptomyces*. These are commonly seen in south India; Nocardia species being more common in Maharashtra.[48] Their mycelia are extremely thin 1 nm or less in diameter and are closely related to bacteria; these tend to fragment into bacillary and coccoid forms. These are sensitive to antibiotics and techniques required to study them are generally bacteriological techniques.
2. Madduromycotic mycetoma or madduromycosis are caused by filamentous members of higher fungi (eumycetoma). Their mycelial filaments are 2-4 nm in diameter. These are commonly seen in northern India and Rajasthan.

Table VI shows the causative agents of mycetoma of 282 cases in India.[71-86] Of these, 167 were actinomycotic and 115 maduromycotic. In the actinomycotic group, 25 species were *Actinomycetes*, 43 *Nocardia asteroides* and 45 *Streptomyces madurae*. In the maduromycotic group *Madurella mycetomi* was the major species seen in 61 cases. Almost all species have been encountered in India.

Table VI. Causative species of mycetoma observed in 282 cases.

Actinomycotic—167	*Maduromycotic*—115
Actinomycetes—25	*M. mycetomi*—61
Nocardia asteroides—43	*M. grisea*—4
Nocardia brasiliensis—5	*P. romeroi*—2
Str. madurae—65	*A. boydii*—5
Str. pelletieri—14	*L. senegalensis*—9
Str. somaliensis—15	*C. infestans*—1
	C. madurae—1
	G. bemeni—7
	R. langeroni—1
	Unidentified—24

Histopathologic study of fungi in tissues : Lillie in 1947, called attention to the special value of the Bauer stain in studying the size, morphology and histochemical composition of fungi. Today, several excellent stains enable us to demonstrate and identify fungi accurately. Stains like the H & E, PAS, Gridley stain, Gomori methenamine silver stain (GMS), Mayers mucicarmine stain, Gram's stain and Ziehl Neelsen (modified) method have helped in identifying fungi.[53] In histopathologic material, the diagnosis of many mycoses can be made with confidence provided the organisms are typical and the technique adequate. However, histopathologic methods should never be used alone in cases where mycologic methods can be utilized.

Granules : Histopathologic examination of the granules may show certain diagnostic features helpful in identifying the fungus.[87]

The granules of *Actinomycetes* are oval or scalloped masses bordered by a radial corona of eosinophilic, club-like Splendore-Hoeppli material; the entire granule is basophilic in H & E. Neutrophils may be seen in intimate contact with the S H material. The delicate fungal filaments are Gram+ve, non-acid fast, beaded, project and interdigitate with the clubs of Splendore-Hoeppli material.

In *Nocardia* species the granules are not associated with Splendore-Hoeppli material on H & E stain. Gram's stain shows delicate branched filaments, beaded and partially acid fast.

The grains of *S. pelletieri* are distinctive; these appear circular, crescent moon in appearance and stain deep purple with a smooth periphery. The grains of *S. somaliensis* are round, pale pink and have a smooth periphery surrounded by a wall or membrane. The granule being hard, shows splitting due to cutting by the microtome. The granule of *M. grisea* on PAS staining appears deep brown or black and the hyphae are packed in the peripheral zone, the central area showing a clear space. The granules of *M. mycetomi* do not take the H & E stain but on PAS and GMS, the hyaline hyphae are not evident and the light brown cement predominates; fissure lines may be seen as the granules are hard. Granules of *A. boydii* are usually quite large, oval, rounded or lobulated; the centre stains pale lavender and the periphery deep purple.

Immunofluorescence diagnosis in mycology

The fluorescent antibody technique as a diagnostic and research tool in medical mycology is now firmly established. It is used for rapid detection and identification of fungi (viable or non-viable) in culture, clinical material and paraffin sections of formalin fixed tissues.[88]

Today, sensitive and specific reagents have been developed for detection and identification of fungi from clinical material. However, the non-availability of reagents and the need for trained personnel prevents its widespread application that it merits.[89]

Current therapies for mycotic diseases

Most antifungals were developed in the last 30 years. The first truly potent antimycotic nystatin and its related polyene amphotericin B were developed in the 1950's. In the late 50's griseofulvin the first oral antifungal was introduced. A decade later, the first broad spectrum antifungals, miconazole and clotrimazole heralded another therapeutic advance. More recently, econazole and isoconazole were marketed, while newer imidazoles like posconazole, tioconazole, sulconazole, butoconazole are under investigation.[90] Terconazole developed recently, shows promise as a hihgly fungicidal topical agent. Ketoconazole has been extensively studied. This oral drug represents a major advance in antifungal chemotherapy. It may well become the drug of choice in many mycotic diseases. Challenges have been met by ketoconazole, but challenges still remain; the future and the overall perspective is one of optimism.

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