The Dermatophytes

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INTRODUCTION

The dermatophytes are a group of closely related fungi that have the capacity to invade keratinized tissue (skin, hair, and nails) of humans and other animals to produce an infection, dermatophytosis, commonly referred to as ringworm. Infection is generally cutaneous and restricted to the nonliving cornified layers because of the inability of the fungi to penetrate the deeper tissues or organs of immunocompetent hosts (57, 140). Reactions to a dermatophyte infection may range from mild to severe as a consequence of the host's reactions to the metabolic products of the fungus, the virulence of the infecting strain or species, the anatomic location of the infection, and local environmental factors.

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HISTORICAL REVIEW

Historically, medical mycology, specifically relating to human disease, began with the discovery of the fungal etiology of favus and centered around three European physicians in the mid-19th century: Robert Remak, Johann L. Schönlein, and David Gruby. Details regarding their lives, specific achievements, and historical background may be found in several excellent reviews (4, 10, 141, 217, 283).

According to Seeliger (217), Remak in 1835 first observed peculiar microscopic structures appearing as rods and buds in crusts from favic lesions. He never published his observations, but he permitted those observations to be cited in a doctoral dissertation by Xavier Hube in 1837. Remak claimed that he did not recognize the structures as fungal (194) and credited this recognition to Schönlein, who described their mycotic nature in 1839 (214). However, Remak established that the etiologic agent of favus was infectious, cultured it on apple slices, and validly described it as *Achorion schoenleinii*, in honor of his mentor and his initial discovery (195).

The real founder of dermatomycology was David Gruby on the basis of his discoveries during 1841 to 1844, his communications to the French Academy of Science, and his publications during this period (86–89). Independently, and unaware of the work of Remak and Schönlein, he described the causative agent of favus, both clinically and in microscopic details of the crusts, and established the contagious nature of the disease (86, 87). He also described ectothrix invasion of the beard and scalp, naming the etiologic agent of the latter *Microsporum* (referring to the small spores around the hair shaft) *audouinii* (88), and described endothrix hair invasion by *Herpes* (*Trichophyton*) *tonsurans* (89). In addition to his observations on dermatophytes, he also described the clinical and microscopic appearance of thrush in children.

Raimond Sabouraud, one of the best known and most influential of the early medical mycologists, began his scientific studies of the dermatophytes around 1890, culminating in the publication of his classic volume, *Les Teignes*, in 1910 (210). Sabouraud's contributions included his studies on the taxonomy, morphology, and methods of culturing the dermatophytes and the therapy of the dermatophytoses. He classified the dermatophytes into four genera, *Achorion*, *Epidermophyton*, *Microsporum*, and *Trichophyton*, primarily on the basis of the clinical aspects of the disease, combined with cultural and microscopic observations. The medium that he developed is in use today for culturing fungi (although the ingredients are modified) and is named in his honor, Sabouraud glucose (dextrose) agar (177). Sabouraud's treatment of tinea capitis by a one-dose, single-point roentgenologic epilation achieved cures in 3 months as opposed to the then current therapy of manual epilation and topical application of medications (153).

In 1934, Chester Emmons (60) modernized the taxonomic scheme of Sabouraud and others and established the current classification of the dermatophytes on the bases of spore morphology and accessory organs. He eliminated the genus *Achorion* and recognized only the three genera *Microsporum*, *Trichophyton*, and *Epidermophyton* on the basis of mycological principles.

Nutritional and physiological studies of the dermatophytes pioneered at Columbia University by Rhoda Benham and Margarita Silva (25, 223) and at the Center for Disease Control, in Georgia, by Libero Ajello, Lucille K. Georg, and co-workers (8, 69, 74, 242) simplified the identification of dermatophytes and led to reduction of the number of species and varieties.

The discovery of the teleomorphs (perfect or sexual state) of

Trichophyton (*Keratinomyces*) *ajelloi* in 1959 by Dawson and Gentles (52), using the hair bait technique of Vanbreuseghem (255), led to the rapid discoveries of the teleomorphs of many dermatophytes and related keratinophilic fungi. Griffin in 1960 (84) and Stockdale in 1961 (231) and 1963 (232) independently obtained the teleomorphs of the *Microsporum gypseum* complex, thereby vindicating Nannizzi's original observation.

The discovery of sexual reproduction in the dermatophytes opened the door to classical genetic studies with these fungi, e.g., determining the cause of pleomorphism (269) and clarifying the taxonomy and understanding of the incompatibility systems operating in these fungi (268).

The successful oral therapy with griseofulvin of experimental dermatophytosis in guinea pigs reported by Gentles in 1958 (75) revolutionized the therapy of dermatophytosis and initiated the first major change in the therapy of tinea capitis since the work of Sabouraud.

ETIOLOGIC AGENTS

Anamorphs

The etiologic agents of the dermatophytoses are classified in three anamorphic (asexual or imperfect) genera, *Epidermophyton*, *Microsporum*, and *Trichophyton*, of anamorphic class Hyphomycetes of the Deuteromycota (Fungi Imperfecti). The descriptions of the genera essentially follow the classification scheme of Emmons (60) on the bases of conidial morphology and formation of conidia and are updated following the discovery of new species (2, 5, 165). The genera and their descriptions are as follows.

Epidermophyton **spp.** The type species is *Epidermophyton floccosum*. The macroconidia are broadly clavate with typically smooth, thin to moderately thick walls and one to nine septa, 20 to 60 by 4 to 13 μm in size. They are usually abundant and borne singly or in clusters. Microconidia are absent. This genus has only two known species to date, and only *E. floccosum* is pathogenic.

Microsporum **spp.** The type species is *Microsporum audouinii*. Macroconidia are characterized by the presence of rough walls which may be asperulate, echinulate, or verrucose. Originally, the macroconidia were described by Emmons as spindle shaped or fusiform, but the discovery of new species extended the range from obovate (egg shaped) as in *Microsporum nanum* (67) to cylindrofusiform as in *Microsporum vanbreuseghemii* (73). The macroconidia may have thin, moderately thick to thick walls and 1 to 15 septa and range in size from 6 to 160 by 6 to 25 μm. Microconidia are sessile or stalked and clavate and usually arranged singly along the hyphae or in racemes as in *Microsporum racemosum*, a rare pathogen (31).

Trichophyton **spp.** The type species is *Trichophyton tonsurans*. Macroconidia, when present, have smooth, usually thin walls and one to 12 septa, are borne singly or in clusters, and may be elongate and pencil shaped, clavate, fusiform, or cylindrical. They range in size from 8 to 86 by 4 to 14 μm. Microconidia, usually more abundant than macroconidia, may be globose, pyriform or clavate, or sessile or stalked, and are borne singly along the sides of the hyphae or in grape-like clusters.

The anamorphic species of the dermatophytes are listed in Table 1. Descriptions of the species and related keratinophilic fungi may be found in several publications (134, 153, 193, 200, 270, 274).

Since the classification of the dermatophytes by Emmons (60), as a result of the discovery of new species and variants, the rigid morphological distinction among the three genera has

TABLE 1. Anamorph genera and species of dermatophytes

Epidermophyton Sabouraud 1907
  E. floccosum (Harz) Langeron et Milochevitch 1930

Microsporum Gruby 1843
  M. audouinii Gruby 1843
  M. canis Bodin 1902
  M. equinum (Delacroix et Bodin) Gueguén 1904
  M. ferrugineum Ota 1921
  M. fulvum Uriburu 1909
  M. gallinae (Megnin) Grigorakis 1929
  M. gypseum (Bodin) Guiart et Grigorakis 1928
  M. nanum Fuentes 1956
  M. persicolor (Sabouraud) Guiart et Grigorakis 1928
  M. praecox Rivalier, ex Padhye, Ajello et McGinnis 1987
  M. racemosum Borelli 1965
  M. vanbreuseghemii Georg, Ajello, Friedman et Brinkman 1962

Trichophyton Malmsten 1845
  T. concentricum Blanchard 1895
  T. equinum (Matruchot et Dassonville) Gedoelst 1902
  T. gourvilii Catanei 1933
  T. kanei Summerbell 1989[a]
  T. megninii Blanchard 1896
  T. mentagrophytes (Robin) Blanchard 1896
  T. raubitschekii Kane, Salkin, Weitzman, Smitka 1981[a]
  T. rubrum (Castellani) Sabouraud 1911
  T. schoenleinii (Lebert) Langeron et Milochevitch 1930
  T. simii (Pinoy) Stockdale, Mackenzie et Austwick 1965
  T. soudanense Joyeux 1912
  T. tonsurans Malmsten 1845
  T. verrucosum Bodin 1902
  T. violaceum Bodin 1902
  T. yaoundei Cochet et Doby Dubois 1957 (not validly published)

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[a] Some mycologists consider *T. kanei* and *T. raubitschekii* to fall within the circumscription of *T. rubrum*.

become a morphological continuum based on overlapping characteristics; e.g., *Trichophyton kanei* (238), *Trichophyton longifusum* (65), and a variant of *T. tonsurans* (183) lack microconidia, and therefore are more suggestive of the genus *Epidermophyton*, whereas isolates of *Microsporum* spp. producing smooth-walled macronidia are more suggestive of *Trichophyton* spp. (258, 275).

Teleomorphs

Some dermatophytes, mostly the zoophilic and geophilic species of *Microsporum* and *Trichophyton*, are also capable of reproducing sexually and producing ascomata with asci and ascospores. These species are classified in the teleomorphic genus *Arthroderma* (271), family Arthrodermataceae of the Onygenales (45), phylum Ascomycota. Previously, the teleomorphs of the sexually reproducing *Microsporum* and *Trichophyton* species and related keratinophilic fungi had been classified in the genera *Nannizzia* and *Arthroderma*, respectively (5). However, on the basis of a careful evaluation of the morphological characteristics used to define these two genera, Weitzman et al. (271) concluded that the species making up these genera represented a continuum and that their minor differences did not merit maintaining them in two separate genera. *Nannizzia* and *Arthroderma* are considered to be congeneric, with *Arthroderma* having taxonomic priority.

The teleomorph-anamorph states of the dermatophytes and related species are listed in Table 2.

TABLE 2. Teleomorph-anamorph state of dermatophytes

Teleomorph (reference)	Anamorph
Arthroderma	*Microsporum, Trichophyton*
A. benhamiae (7)	*T. mentagrophytes*[a]
A. fulvum (232, 271)	*M. fulvum*[b]
A. grubyi (73, 271)	*M. vanbreuseghemii*
A. gypseum (231, 232, 271)	*M. gypseum*[b]
A. incurvatum (231, 232, 271)	*M. gypseum*[b]
A. obtusum (51, 271)	*M. nanum*
A. otae (94, 271)	*M. canis* var. *canis*, *M. canis* var. *distortum*
A. persicolor (233, 271)	*M. persicolor*
A. simii (236)	*T. simii*
A. racemosum (209, 271)	*M. racemosum*
A. vanbreuseghemii (245)	*T. mentagrophytes*[a]

[a,b] These anamorph species are considered complexes, each of which includes more than one teleomorph.

EPIDEMIOLOGY AND ECOLOGY

Dermatophytes are among the few fungi causing communicable disease, that is, diseases acquired from infected animals or birds or from the fomites they have engendered. All but one of the species known to cause disease primarily affect mammals. The exception, *Microsporum gallinae*, is primarily established in gallinaceous fowl. Apart from those species usually associated with disease, transitional species exist which appear to be primarily saprobic organisms occasionally or rarely causing infection. Finally, some *Trichophyton*, *Epidermophyton*, and *Microsporum* species closely related to the dermatophytes appear to be exclusively saprobic or nearly so. The members of these three genera have no collective designation. The term dermatophytes should be restricted to designate infectious organisms (3) and will be referred to below as dermatophytes and their congeners. Closely biologically related organisms not included in this group include *Chrysosporium* species with teleomorphs in the genus *Arthroderma*.

Dermatophytes and their congeners have long been divided into anthropophilic, zoophilic, and geophilic species on the basis of their primary habitat associations (1, 72). Anthropophilic dermatophytes are primarily associated with humans and rarely infect other animals (166). Zoophilic dermatophytes usually infect animals or are associated with animals but occasionally infect humans. Geophilic dermatophytes are primarily associated with keratinous materials such as hair, feathers, hooves, and horns after these materials have been dissociated from living animals and are in the process of decomposition. These species may cause human and animal infection. Geophilic species are thought to have been ancestral to the pathogenic dermatophytes, preadapted to cutaneous pathogenesis by their ability to decompose keratin and their consequent close association with animals living in hair and feather-lined nests in contact with soil (41).

The distinction between geophilic and zoophilic dermatophytes is based on detailed ecological analysis and may not be obvious in small-scale studies. Certain species known to be zoophilic may be isolated more often from soil and from fur of apparently healthy animals (62, 179) than from animals with frank disease. Many infections by zoophilic dermatophytes appear to be acquired indirectly from keratinous fomites, often deriving from apparently healthy animal carriers (59). Potentially infectious geophilic dermatophytes such as members of the *M. gypseum* complex, growing on similar keratinous debris, overlap in ecology with these zoophiles. They differ mainly by their greater persistence in soil and are found regularly in

TABLE 3. Current synopsis of dermatophyte species and congeners: ecological classification, host preference, and endemicity

Anthrophilic species (area of endemicity)	Zoophilic species (typical host)	Geophilic species
E. floccosum	*M. canis* (cat, dog)	*E. stockdaleae*
M. audouinii (Africa)	*M. equinum* (horse)	*M. amazonicum*
M. ferrugineum (East Asia, East Europe)	*M. gallinae* (fowl)	*Microsporum* anamorph of *A. cookiellum*
T. concentricum (Southeast Asia, Melanesia, Amazon area, Central America, Mexico)	*M. persicolor* (vole)	*M. boullardii*
T. gourvilii (Central Africa)	*T. equinum* (horse)	*M. cookei*
T. kanei	*T. mentagrophytes* (two sibling species and variants; rodents, rabbit, hedgehog)	*M. gypseum* (complex of three species)
T. megninii (Portugal, Sardinia)	*T. sarkisorii* (Bactrian camel)	*M. nanum*
T. mentagrophytes (complex of two species)	*T. simii* (monkey, fowl)	*M. praecox*
T. raubitschekii (Asia, Africa, Mediterranean)	*T. verrucosum* (cattle, sheep, dromedary)	*M. racemosum*
T. rubrum		*M. ripariae*
T. schoenleinii		*M. vanbreuseghemii*
T. soudanense (Subsaharan Africa)		*T. ajelloi*
T. tonsurans		*T. flavescens*
T. violaceum (North Africa, Middle East, Mediterranean)		*T. gloriae, T. longifusum*
T. yaoundei (Central Africa)		*T. phaseoliforme, T. terrestre* (complex of three species), *T. vanbreuseghemii*

habitats not strongly modified by the constant presence of animal associates. A synopsis of dermatophyte species and congeners, ecological and host preferences, and endemicity may be found in Table 3.

Rippon (200) has pointed out a correspondence between soil association and conidial production in dermatophytes: the less significant the growth on dissociated keratin in the ecology of a dermatophyte, the less likely is the dermatophyte to produce conidia abundantly. Soil association also tends to correlate with the ability to form heterothallic teleomorphs in nature (153), an ability not found in most anthropophilic dermatophytes and some zoophiles. Many anthropophilic and certain zoophilic species appear to consist predominantly or exclusively of isolates of a single mating type, as determined by the induction of infertile ascomata with *Arthroderma simii* mating type testers (234). Summerbell in reference 248 has pointed out that burrowing and denning animals tend to be associated with dermatophytes possessing a full roster of soil association characters, including conidial abundance and dimorphism, heterothallic mating, osmotolerance, and the possession of typical arthropod predation deterrent structures such as conidial ornamentation, helical setae (spirals), and the rigid peridial networks found in gymnothecia and pseudogymnothecia. To these soil association characters can be added vitamin and amino acid autotrophy, the elaboration of a urease enzyme, and the formation of perforating organs in dissociated hair. Dermatophytes primarily associated with humans or with nonburrowing, nondenning animals such as ungulates and equines tend to lack some or all of these characters. Several specialized anthropophilic species (e.g., *Trichophyton concentricum* and *Microsporum ferrugineum*) consist of highly morphologically simplified, asexual isolates with little or no ability to produce conidia.

The dermatophyte structure most commonly associated with contagion, especially in the poorly conidial anthropophilic dermatophytes, is the oblong to rounded, persistent "spore," "arthroconidium," or "chlamydospore" found within or attached to the exterior of infected hairs and within skin scales. These structures, particularly in certain species, may persist for years in the environment (200, 220) and are highly heat resistant (222), particularly when embedded in hair or skin scales (230). In some anthropophilic species studied in detail, arthroconidia

have a tendency to adhere in vitro to corneocytes derived from particular body sites (9, 284). It is possible that they may dissociate from skin cells in the environment and come in contact with new potential hosts as disseminated arthroconidia. Their persistence as an environmental source of contagion may lead to recurrent outbreaks of dermatophytosis in individuals and in institutions (128, 162). According to Rippon (200), the arthroconidia of *T. rubrum* do not survive as long as do those of other species, e.g., *E. floccosum*. The transition from potentially sexual to asexual life histories in the non-soil-associated dermatophytes appears to have led to adaptive radiation, at least in the anthropophilic dermatophytes (248). By most estimates, approximately two-thirds of the recognized dermatophyte species primarily associated with mammalian pathogenesis are anthropophiles (248). Within the anthropophiles, polymorphous morphological variation is common, and numerous atypical and variant types are recognized (133, 193, 279), probably indicating further genetic drift. Allopatric speciation appears to have been common in anthropophilic dermatophytes but rare in zoophiles, and several anthropophilic species have well-defined areas of endemicity (200) (Table 3) while others, such as *T. rubrum* and *T. tonsurans*, are now cosmopolitan but appear to have had a more restricted distribution in the past, having been transported widely as a result of human migration (the anthropophiles travel with their human hosts) (200). Also, spatial and ecological sympatric isolation appears to have been a predisposer to speciation in the anthropophiles: human-associated dermatophytes, unlike zoophiles, often have marked affinities for particular body sites. Most recognized asexual anthropophilic dermatophyte species are distinctive in morphology, physiology, and body site preference (127).

Recognition of dermatophyte taxa is clinically relevant. The need for species identification of dermatophytes in clinical settings is often related to epidemiological concerns. Especially relevant is the identification of dermatophytes that (i) may have animal carriers; (ii) are linked to recurrent institutional or family outbreaks, such as *T. tonsurans* and *Trichophyton violaceum* (17, 128, 146, 147, 162, 228); (iii) may cause rapidly progressing epidemics, such as *M. audouinii* and *T. tonsurans* (34); and (iv) are geographically endemic, reflecting exposure

during travel or residence in the area of endemicity or contact with a person with such a history (23, 261).

Epidemiology is important in infection control and public health issues related to the different types of dermatophytosis. In tinea capitis, the predominant agents in North America are *T. tonsurans* and *Microsporum canis*. The former is usually acquired from infected humans or their fomites and has caused a progressive, continent-wide epidemic now of some 40 years in duration (34, 70, 200). Urban areas and their communities of minorities have been particularly strongly affected (34). *M. canis* is usually acquired from infected cats or dogs, although limited human-to-human transfer leading to outbreaks can occur (219, 226). It is the predominant agent of tinea capitis in rural areas and in some parts of Europe, the eastern Mediterranean, and South America (12, 38, 221, 260).

Tinea capitis in general is a condition most commonly seen in children (200). In tinea capitis caused by *T. tonsurans*, however, a proportion of sufferers become long-term carriers of a subclinical scalp infection and may intermittently shed viable inoculum for decades (22, 102, 128, 190). When encountered in symptomatic adults, *T. tonsurans* is more frequently seen as an agent of tinea corporis (34), and other infections, such as tinea manuum and onychomycosis, occur uncommonly. Similar patterns of age and body site preferences are found in other more geographically concentrated agents of endothrix tinea capitis such as *T. violaceum* (216). Tinea corporis caused by *T. tonsurans* and other agents of endothrix tinea capitis may be more common in persons, particularly women, in close contact with children than among other adults. In institutional outbreaks, staff may transmit the fungus among immobile patients (128, 219). Contact sports may distribute the disease among adolescents and young adults (228). Among children, *T. tonsurans* is transmitted primarily by the sharing of combs, hats, bedding, and other materials contacting the scalp. Its environmental persistence on these fomites is noteworthy (128, 162).

Zoophilic and geophilic dermatophytes in general tend to form lesions that are more inflammatory than those formed by anthropophilic dermatophytes but are also more likely to resolve spontaneously (200). This pattern is seen in tinea capitis caused by *M. canis* (144, 145, 200). The closely related anthropophile *M. audouinii*, once common in North America but now mainly restricted to parts of Africa and Asia (200), appears particularly specialized as an agent of juvenile tinea capitis (200). Adult infections are rare, and spontaneous resolution usually occurs upon attainment of puberty (144).

Tinea other than tinea capitis, when caused by anthropophilic fungi, tends to be associated with adults and adolescents, although infection of children may occur. *Trichophyton rubrum*, *E. floccosum*, and the anthropophilic *Trichophyton mentagrophytes* (i.e., cottony and velvety forms [124, 133] known as *T. mentagrophytes* var. *interdigitale*) show a common pattern of association with tinea corporis, tinea cruris, and tinea pedis (61). In addition, *T. rubrum* and *T. mentagrophytes* are associated with tinea manuum and onychomycosis (221, 239). It is likely that exposure to these dermatophytes is a common occurrence. Although the ecological and host factors involved in developing symptomatic infection are poorly known, known risk factors include foot dampness and abrasion combined with likely exposure to high fungal inoculum in communal aquatic facilities, such as swimming pools and showers (21, 58). Exchange of clothing, towels, and linen, either directly or via substandard communal laundering, is another recognized risk (200) which may lead to outbreaks. Asymptomatic infection is common, especially in tinea pedis (21). Damp foot conditions may lead to aggravated symptoms due to mixed infection by dermatophytes and bacteria (21, 100).

Zoophilic dermatophytes, apart from causing tinea capitis, most commonly cause tinea corporis (including tinea faciei) in persons of any age group (221). Tinea of the extremities, tinea cruris, and onychomycosis caused by zoophiles are uncommon to rare (221).

CLINICAL MANIFESTATIONS

Traditionally, infections caused by dermatophytes (ringworm) have been named according to the anatomic locations involved by appending the Latin term designating the body site after the word tinea, e.g., tinea capitis for ringworm of the scalp. The clinical manifestations are as follows: (i) tinea barbae (ringworm of the beard and mustache); (ii) tinea capitis (scalp, eyebrows, and eyelashes); (iii) tinea corporis (glabrous skin); (iv) tinea cruris (groin); (v) tinea favosa (favus); (vi) tinea imbricata (ringworm caused by *T. concentricum*); (vii) tinea manuum (hand); (viii) tinea pedis (feet); and (ix) tinea unguium (nails). Several anatomic sites may be infected by a single dermatophyte species, and different species may produce clinically identical lesions. The major etiologic agents may be global, such as *T. rubrum*, while the distribution of others may vary geographically (Table 3).

The clinical conditions and their major etiologic agents are described briefly; more detailed information may be found in the texts by Rippon (200) and by Kwon-Chung and Bennett (153).

Tinea Barbae

Tinea barbae, an infection of the bearded area, may be mild and superficial or a severe inflammatory pustular folliculitis, the latter form more commonly caused by the zoophilic dermatophytes *Trichophyton verrucosum*, *T. mentagrophytes* var. *mentagrophytes*, and *T. mentagrophytes* var. *erinacei* (153).

Tinea Capitis

Tinea capitis, an infection commonly involving the scalp, is usually caused by members of the genera *Microsporum* and *Trichophyton*. The infection may range from mild, almost subclinical, with slight erythema and a few patchy areas of scaling with dull gray hair stumps to a highly inflammatory reaction with folliculitis, kerion formation, and extensive areas of scarring and alopecia, sometimes accompanied by fever, malaise, and regional lymphadenopathy. Both the skin surface and hairs are involved. Infection of the hair may be described as ectothrix (sheath of arthroconidia formed on the outside of the hair shaft) or endothrix (arthroconidia formed within the hair shaft). The current predominant cause of tinea capitis in most of North, Central, and South America is *T. tonsurans* (endothrix) replacing *M. audouinii* (ectothrix) (199).

Tinea Corporis

Ringworm of the body, usually involving the trunk, shoulders, or limbs, and occasionally the face (excluding the bearded area), may be caused by any dermatophyte. The infection may range from mild to severe, commonly appearing as annular, scaly patches with sharply marginated, raised erythematous vesicular borders.

Tinea Cruris ("Jock Itch")

Infection of the groin, perianal, and perineal areas, and occasionally the upper thighs, is usually seen in adult men. *T. rubrum* and *E. floccosum* are the most frequent etiologic

agents. Lesions are erythematous to tawny brown and covered with thin, dry scales. They are usually bilateral and often asymmetric, extending down the sides of the inner thigh and exhibiting a raised, sharply marginated border that is frequently studded with small vesicles.

Tinea Favosa

Tinea favosa, usually caused by *Trichophyton schoenleinii*, is severe and chronic, characterized by the presence on the scalp and glabrous skin of yellowish, cup-shaped crusts called scutula, which is composed of epithelial debris and dense masses of mycelium. The disease is most common in Eurasia and Africa.

Tinea Imbricata

Tinea imbricata, the chronic infection which is a specialized manifestation of tinea corporis, is characterized by concentric rings of overlapping scales scattered throughout the body. It is geographically restricted to certain of the Pacific islands of Oceana, Southeast Asia, Mexico, and Central and South America (200). *T. concentricum*, a strictly anthropophilic dermatophyte, is the only etiologic agent.

Tinea Manuum

The palmar and interdigital areas of the hand are usually involved in tinea manuum, most frequently presenting as unilateral diffuse hyperkeratosis with accentuation of the flexural creases. Most infections are caused by *T. rubrum.*

Tinea Pedis ("Athlete's Foot")

The feet, especially the soles and toe webs, are most frequently involved in tinea pedis. The most common clinical manifestation is the intertriginous form, which presents with maceration, peeling, and fissuring, mainly in the spaces between the fourth and fifth toes. Another common presentation is the chronic, squamous, hyperkeratotic type in which fine silvery scales cover pinkish skin of the soles, heels, and sides of the foot (moccasin foot). An acute inflammatory condition, characterized by the formation of vesicles, pustules, and sometimes bullae, is most frequently caused by *T. mentagrophytes*. The more chronic agents of tinea pedis are *T. rubrum*, *T. mentagrophytes* var. *interdigitale*, and *E. floccosum.*

Tinea Unguium

Invasion of the nail plate by a dermatophyte is referred to as tinea unguium; infection of the nail by nondermatophytic fungi is called onychomycosis. The latter word is often used as a general term for a nail infection. There are two main types of nail involvement: invasive subungual (distal and proximal) and superficial white mycotic infection (leukonychia trichophytica). *T. rubrum* and *T. mentagrophytes*, respectively, are the most common dermatophytes of this infection.

LABORATORY DIAGNOSIS

Collection and Transport of Specimens

Dermatophytes, as filamentous fungi, undergo radial growth. The centers of infected skin patches may consist of the older and poorly viable material, as may portions of older nail plate in onychomycosis. In tinea corporis, where the "rings" of ringworm are well defined, collection is best made by collecting epidermal scales from near the advancing edges of the rings. The lesion is lightly disinfected with alcohol in gauze and then scraped from center to edge, crossing the lesion margin, using a sterile scalpel blade or equivalent. If the lesions have vesicles or bullae, the tops of the vesicles or bullae should be clipped and included in the sample. Suppurating lesions may be sampled with a swab when it is impractical to obtain scrapings. Other skin dermatophytoses, such as tinea pedis and tinea manuum, are scraped in such a way that the whole infected area is represented, since an advancing margin is often not evident.

In tinea capitis and tinea barbae, the basal root portion of the hair is best for direct microscopy and culture. In prospective *Microsporum* infections, a Wood's light may be used to allow detection of the most heavily infected hairs. Hairs are best sampled by plucking so that the root is included. If this is not possible due to hair fragility, as in "black dot" tinea capitis, a scalpel may be used to scrape scales and excavate small portions of the hair root. Brushes with stiff bristles, run firmly across the lesion, have also been used successfully to sample tinea capitis (135, 147, 163). Similar techniques may be used to sample animal dermatophytoses (208).

The common distal-subungual type of tinea unguium is traditionally sampled, after light alcohol disinfection, by scraping the debris from beneath the distal end of the nail with a scalpel and collecting scrapings from near the nail bed, where viable inoculum is most likely to be encountered (270). Close clipping of the whole nail end is an alternative to this procedure, as is nail drilling. In difficult to sample, degraded nails, specialists may use a Skele curette, a surgical instrument with a small, spoon-like end with a sharpened edge. Superficial white onychomycosis is sampled by scraping material from the white spots on the surface of the nail. Discarding the uppermost layer of material is recommended in order to reduce the presence of contaminant inoculum.

Sample materials are best transported in dry, strong black paper folded in the manner of a herbarium packet. Bacteriological transport media should not be used as they may allow growth of contaminants and their viscosity may result in substantial loss of the available specimen. Moisture of any kind is to be avoided. Black paper allows easy visualization of small skin squames; it should be thin enough to fold tightly at the corners and not "leak" specimen.

Microscopic Examination and Culture

Direct microscopy, although false negative in 5 to 15% of cases in ordinary practice (200), is a highly efficient screening technique. Scrapings and hairs may be mounted for direct examination in 25% KOH or NaOH mixed with 5% glycerol, heated (e.g., for 1 h at 51 to 54°C) to emulsify lipids, and examined under ×400 magnification for fungal structures. Another formulation is 20% KOH–36% dimethyl sulfoxide (200), and two techniques for fluorescence microscopy, the calcofluor white technique (205) and the Congo red technique (224), may be used.

The classification of all structures seen in direct microscopy is beyond the scope of this article. The reader is referred to several excellent texts for descriptions and photographs (66, 134, 153, 200, 270, 274).

Culture is a valuable adjunct to direct microscopy and is essential at least in all nail infections and in any infection to be treated by systemic medication. In all cases, a medium selective against most nondermatophytic molds and bacteria is used as a primary isolation medium. Cycloheximide is incorporated into this medium as a semiselective agent to reduce the growth of

nondermatophytic fungi. Sabouraud peptone-glucose agar (Emmons' modification) amended with cycloheximide and chloramphenicol is commonly used (274). It is commercially available under various names such as Mycobiotic (Difco Laboratories, Detroit, Mich.) and Mycosel (BBL, Becton-Dickinson, Cockeysville, Md.) agars. Dermatophyte Test Medium (193) is an alternative; it normally shows alkalinity generated by dermatophyte growth as a color change to red in its constituent phenol red indicator. Some nonpathogenic fungi (e.g., *Trichophyton terrestre*), however, induce the red color change, while some *Microsporum* isolates (173) and bacterially contaminated isolates (134) may give a false-negative reaction. Therefore, this medium is good but is not an absolute indicator of the growth of a dermatophyte. It has the disadvantage of not allowing visualization of colony reverse pigmentation, a character often important in identification. Some laboratories use cycloheximide- and antibacterial agent-amended potato glucose or potato flake agar for primary isolation, a practice speeding the identification of *T. rubrum* by rapidly inducing red pigmentation in uncontaminated, typical isolates and typical isolates with relatively antibiotic-susceptible contaminants.

When nondermatophytic fungi or yeasts other than *Candida albicans* may be etiologic agents, it is critical to use a cycloheximide-free medium in addition to a selective dermatophyte medium incorporating this inhibitor. The use of a general medium is particularly important for culture of specimens from nail, sole, and palm lesions (172, 239) in which *Scytalidium* species and other nondermatophytes may be involved. Also, any skin lesion showing irregular or pigmented filaments should be cultured on cycloheximide-free medium. In nails, soles, and palms, direct specimen microscopy cannot be relied on to indicate the presence of a nondermatophyte, since some agents have nondescript, dermatophyte-like filaments in specimens from these sites (239). Cycloheximide-free Sabouraud glucose agar, i.e., Sabouraud glucose agar with gentamicin and chloramphenicol, may be used for isolation of nondermatophytes. Restrictive media such as Littman oxgall agar (Difco) (161, 239) are preferred by some, since such media reduce the colony diameters of fast-growing contaminants, thus allowing outgrowth of slower-growing etiologic agents.

When a nondermatophyte alone grows out from a specimen that is positive for fungal filaments by direct microscopy, the culture cannot be interpreted as diagnostic of a nondermatophyte infection. Tissue colonized by mature dermatophyte colonies may contain substantial areas of dead mycelium. A significant proportion of clinical specimens from patients with dermatophytoses (up to 20% in tinea unguium) contain only such dead dermatophyte material but may grow contaminant fungi from dormant propagules or surface colonization. It is for this reason that nondermatophytic fungi isolated from nails as either etiologic agents or contaminants, e.g., *Scopulariopsis*, *Aspergillus*, or *Fusarium* spp., must be confirmed by whether they are consistently isolated from successive specimens from the infected nails (229, 239). This practice, a case-by-case application of Koch's first postulate for establishing pathogenicity (constant association of the proposed etiologic agent with the disease) is currently widely misunderstood. An untreated dermatophytosis that showed dead mycelium on direct microscopy and grew a fortuitous mold will, on repeat sampling, almost invariably yield the etiologic dermatophyte, a second unrelated contaminant, or no fungal culture at all. The chance of it growing the same fortuitous contaminant a second time is small. Dermatophytoses recently treated with antifungal agents may repeatedly show uncultivable filaments and grow spurious molds, usually with revealing inconsistency from specimen to specimen.

Dermatophytes and other molds uncommonly occur together in mixed infections (178). Selective elimination of the dermatophyte by specific antifungal agents may result in consistent outgrowth of a drug-resistant mold from later specimens.

Some specialized isolation media are used in specific circumstances. Fischer and Kane (64) devised Casamino Acids-erythritol-albumin medium, a highly selective medium for isolating dermatophytes from lesions heavily contaminated by bacteria or by the cycloheximide-tolerant *C. albicans*. This medium contains cycloheximide, antibacterial agents, and suspended egg albumin. The albumin inhibits yeasts such as *C. albicans* which have an absolute requirement for exogenous biotin. This medium is most advantageous for showing the presence of etiologic dermatophytes in diabetics and other immunocompromised patients whose skin lesions may be profusely overgrown by *Candida* spp. (64). Another isolation medium is bromcresol purple (BCP)-casein-yeast extract agar (132), which grows all dermatophytes but is designed for the rapid recognition of microcolonies of *T. verrucosum*. This species elaborates a distinctive diffusing protease (90, 267) which produces a broad, distinct zone of clearing in the opaque casein solids surrounding the small colonies. This medium is used for specimens from rural areas.

Identification Characters and Diagnostic Media

This article makes no attempt to serve as a manual for identifying dermatophytes to species; rather, the reader is referred to appropriate identification references (134, 153, 193, 200, 270). General information about the mycological techniques most commonly employed in dermatophyte identification is outlined in Table 4.

Many typical isolates of common dermatophytes can be identified directly from primary isolation media, particularly, Sabouraud glucose agar and potato glucose or potato flake agar. Identification characters include colony pigmentation, texture, and growth rate and distinctive morphological structures, such as microconidia, macroconidia, spirals, pectinate branches, pedicels, and nodular organs. Details of these characters may be found in various sources (134, 193, 270). It is helpful if the worker is familiar with the less common species easily confused with common dermatophytes, particularly, *Microsporum persicolor*, *Trichophyton equinum*, *T. violaceum*, *Trichophyton soudanense*, *Trichophyton megninii*, and *Microsporum praecox*, so that primary isolates compatible with these species are recognized as unusual and studied under more exacting identification procedures. These species, although uncommon, are found with some regularity in North America and European clinical laboratories.

The development of microscopic structures may be enhanced by use of sporulation media such as lactrimel (122), pablum cereal (134), or oatmeal agars (276). Conditions for inducing macroconidial formation vary from species to species: e.g., for *M. canis*, somewhat depauperate media such as rice grains (193); for *T. mentagrophytes* and *M. persicolor*, Sabouraud agar with 3 to 5% added sodium chloride (124); and for *M. equinum*, niger seed medium 8 (110).

A series of vitamin and amino acid test agars (74, 200) is available as the *Trichophyton* agars (Difco) and is used to confirm the identity of several species with distinctive responses to growth substance (134, 193, 200, 270, 274). An unknown but characteristic nutrient requirement of *M. audouinii* is elucidated on autoclaved polished rice grains. The organism grows poorly on the grains and secretes a brownish pigment; *M. canis*, the main dermatophyte of differential

TABLE 4. Sequence of procedures for the identification of dermatophytes in pure culture[a]

Procedure
1. Examine the colony for color of the surface and reverse, topography, texture, and rate of growth. Proceed to step 2.
2. Prepare teased mounts and search for identifying microscopic morphology, especially presence, appearance, and arrangement of macroconidia and microconidia. If results are inconclusive, proceed to step 3.
3. Prepare and examine slide culture for characteristic morphology as indicated above if teased mounts do not provide sufficient information. Consider special medium if sporulation is absent (potato glucose agar, Sabouraud glucose agar plus 3 to 5% NaCl, or lactrimel). If results are inconclusive, proceed to step 4.
4. Perform as many of the physiological tests listed below as necessary for identification
a. Urease
b. Nutritional requirement if a *Trichophyton* sp. is suspected
c. Growth on rice grains if a *Microsporum* sp. is suspected
d. In vitro hair perforation
e. Temperature tolerance and/or optimum temperature of growth
f. Special media to differentiate *T. mentagrophytes* from *M. persicolor* (131), *T. rubrum* from *T. mentagrophytes* (240), and *T. soudanense* from *M. ferrugineum* (193, 273)
g. Mating studies to be performed in reference laboratories

[a] It may be necessary to incubate culture on brain heart infusion agar or similar medium to determine absence of bacterial contamination before proceeding to step 4. Procedures are adapted from Weitzman and Kane (270).

diagnosis, grows well and usually secretes a yellow pigment (193).

Urea agar or broth is used to facilitate recognition of the small number of urease-negative species, particularly, *T. rubrum* but also most isolates of *T. soudanense* (123, 188, 207, 273). This test must be used with caution given the prevalence of poorly visible, antibiotic-resistant bacteria in *T. rubrum* colonies which may cause false-positive reactions. Urease-positive isolates, formerly considered granular and African types of *T. rubrum* (61), are now placed in the segregate species *Trichophyton raubitschekii* by many mycologists (130). Persons not making this distinction should anticipate some urease-positive isolates of *T. rubrum*. The urease test is not normally used for slow-growing, glabrous species such as *T. verrucosum*, *T. violaceum*, and *T. schoenleinii*, as results may be variable or slow to develop.

BCP-milk solids-glucose agar may be used to differentiate a number of dermatophytes, particularly, *T. rubrum*, *T. mentagrophytes* (63, 240), *M. persicolor* (131), *M. equinum* (129), *T. soudanense* (134), and *T. megninii* (126), on the basis of their differences in the release of ammonium ion from casein and the catabolite repression of this process by glucose. The most common use of this medium is to differentiate the constitutively ammonifying *T. mentagrophytes* from *T. rubrum*, in which ammonification is suppressed and radial growth is restricted by glucose for approximately the first 10 days at growth at 25°C. With the former fungus, the BCP indicator in the medium turns from its original sky blue color to violet within 4 to 7 days, indicating a pH change to alkaline, whereas with the latter fungus, the sky blue color indicating neutral pH is maintained until after 10 to 14 days.

A confirmatory test for atypical isolates is the in vitro hair perforation test of Ajello and Georg (8). This test relies on the development by certain dermatophytes of specialized perforating organs invading detached hairs and engendering conspicuous conical pits at right angles to the long axis of the hair. The most common use of this test is to differentiate atypical isolates of *T. mentagrophytes* (perforation positive) from atypical *T. rubrum* (negative), but it is also useful for many other determinations, including differentiation of atypical *M. canis* (positive) from *M. audouinii* and *M. equinum* (negative) (184).

IMMUNOLOGY

Dermatophyte colonization is characteristically limited to the dead keratinized tissue of the stratum corneum and results in either a mild or intense inflammatory reaction. Although the cornified layers of the skin lack a specific immune system to recognize this infection and rid itself of it, nevertheless, both humoral and cell-mediated reactions and specific and nonspecific host defense mechanisms respond and eventually eliminate the fungus, preventing invasion into the deeper viable tissue. This array of defense mechanisms thought to be active against dermatophytes consists of α2-macroglobulin keratinase inhibitor (281), unsaturated transferrin (140), epidermal desquamation (27), and lymphocytes, macrophages, neutrophils, and mast cells (36).

There are two major classes of dermatophyte antigens: glycopeptides and keratinases. The protein portion of the glycopeptides preferentially stimulates cell-mediated immunity (CMI), whereas the polysaccharide portion preferentially stimulates humoral immunity (47). Keratinases, produced by the dermatophytes to enable skin invasion, elicit delayed-type hypersensitivity (DTH) responses when injected intradermally into the skin of animals (81).

Although the host develops a variety of antibodies to dermatophyte infection, i.e., immunoglobulin M (IgM), IgG, IgA, and IgE, they apparently do not help eliminate the infection since the highest level of antibodies is found in those patients with chronic infection (46). IgE, which mediates immediate hypersensitivity, appears to play no role in the defense process (47, 117). Rather, the development of CMI which is correlated with DTH is usually associated with clinical cure and ridding the stratum corneum of the offending dermatophyte (47, 117). In contrast, the lack of CMI or defective CMI prevents an effective response and predisposes the host to chronic or recurrent dermatophyte infections (116, 117, 119).

Several in vitro systems have been studied to assess CMI in dermatophyte-infected hosts, e.g., lymphocyte transformation (108, 241), leukocyte migration inhibition (98, 101), and leukocyte adherence inhibition (98, 101, 265, 266). Lymphocyte transformation is a widely used in vitro assay of cellular immune function (36).

Experimental animal models have been used to study the role of CMI during dermatophytosis, and the results are summarized by Calderon (36). Clearance of infection was found to

correlate with DTH to dermatophyte antigens on skin testing. Green et al. (82) showed that athymic (nude) rats that lack T-cell-mediated immunity could not clear *T. mentagrophytes* infections compared with genetically matched euthymic control rats. Calderon (36) demonstrated in experiments with mice that the T-helper lymphocytes bearing the phenotype Thy-1$^+$ Ly2 mediate immunity to dermatophytosis. Immunity to dermatophyte infection in experimentally infected mice could be achieved by adoptive transfer of lymphoid cells but not serum from infected donors (36, 37).

The classical studies of Jones and coworkers (116–119) in human volunteers suggested that CMI is the major immunologic defense in clearing dermatophyte infections. Experimentally infected volunteers deliberately infected with *T. mentagrophytes* who developed CMI associated with intense inflammation accompanied by T-cell-mediated DTH to the trichophytin skin test (glycoprotein skin test antigen) achieved a mycologic cure. A protective immunologic memory was indicated by the rapid inflammatory response and elimination of the fungus on reinoculation and a continued positive trichophytin test. A single volunteer, who was atopic, characterized another group of individuals having a second type of reaction: i.e., development of a chronic or recurrent infection, high immediate-type (anti-*Trichophyton* IgE mediated) hypersensitivity, and low or waning DTH to trichophytin (117). These individuals, however, had a normal response to other skin test antigens, indicating a selective or induced immune deficit that was found in 10 to 20% of the population in temperate climates (118). An association between chronic dermatophytosis and atopy (asthma or allergic rhinitis) is well recognized (93, 97–99, 118, 142, 227), and several mechanisms explaining this association have been suggested by Jones (117).

Approximately 80 to 93% of chronic or recurrent dermatophyte infections are estimated to be caused by *T. rubrum*; these patients often fail to express a DTH reaction to trichophytin when injected intradermally (30, 97).

Infections by anthropophilic fungi, like *T. rubrum*, often elicit less of an inflammatory response and are less likely to elicit an intense DTH response than infections caused by geophilic or zoophilic dermatophytes which characteristically evoke an intense inflammatory reaction. Much of this inflammation is produced by activated lymphocytes and macrophages which are involved in the DTH reaction to the trichophytin glycopeptides. Enhanced proliferation of the skin in response to the inflammation may be the final mechanism that removes the fungus from the skin by epidermal desquamation (47). Berk et al. (27) had earlier reported that dermatophytes can be removed from the skin by accelerated epidermal turnover.

There is some evidence that certain dermatophytes, like *T. rubrum*, produce substances that diminish the immune response. Mannan, a glycoprotein component of the fungal cell wall, may suppress the inflammatory response especially in atopic or other persons susceptible to the mannan-induced suppression of CMI (47). Blake et al. (30) demonstrated that incubation of purified *T. rubrum* mannan (TRM) with peripheral blood mononuclear cells suppressed lymphoblast formation and inhibited the lymphocyte proliferation response to mitogens and a variety of antigenic stimuli. Also, Cabrera et al. (35) showed that TRM inhibits keratinocyte proliferation, thus slowing epidermal turnover and allowing for a more persistent chronic infection.

Grando et al. (79) identified the monocyte as the likely target cell for the immunosuppressive influence of TRM on the basis of observations made by using a fluorescein conjugate of TRM (fluorescein isothiocyanate-TRM) in conjunction with fluorescence microscopy and flow cytometry. They found that monocytes, not lymphocytes, bound fluorescein isothiocyanate-TRM and that the surface-bound ligand appeared to be internalized and digested over time. They suggested that this binding, which appeared to be receptor cell mediated, interferes with accessory cell functions of the monocyte in CMI (79).

Blake et al. (29) compared the abilities of the cell wall mannan glycoproteins from two dermatophyte species to inhibit CMI in vitro. He used a zoophilic dermatophyte (*M. canis*), which causes an intense inflammatory reaction, and *T. rubrum*, which is associated with a chronic, noninflammatory reaction. Although mannan from both species significantly inhibited OKT3 antibody-stimulated lymphoproliferation, which was dose dependent, TRM was isolated in a greater amount than was *M. canis* mannan and was more inhibitory. The investigators speculated that the increased amount and potency of TRM compared with that of *M. canis* may explain why *T. rubrum* elicits less inflammation and causes a more chronic infection than *M. canis*.

Chronic dermatophytosis may also be caused by the anthropophilic form of *T. mentagrophytes*, *T. mentagrophytes* var. *interdigitale* (*T. interdigitale*) (83). Gregurek-Novak et al. (83) studied primary chronic trichophytosis in Croatia and found it to be mostly caused by this fungus. They found that this clinical entity was associated with defective phagocytosis by peripheral blood leukocytes, i.e., impaired random mobility, and ingestion and digestion of foreign material. The patients were not abnormal in their skin test reactions with *Mycobacterium tuberculosis* purified protein derivative, the numbers of T and B lymphocytes in their peripheral blood, or their concentrations of immunoglobulins in serum. They concluded that primary chronic trichophytosis appears to be associated with defective phagocytosis of peripheral blood leukocytes and that this defect is probably caused by the fungus itself.

Although there are no serological kits commercially available to specifically detect and identify antibodies to dermatophytes, studies of dermatophyte antigens by monoclonal antibodies indicate a potential use of such reagents in the immunoidentification of dermatophytes (56, 191). Polonelli and Morace (191) suggested that the effectiveness of monoclonal antibodies may be enhanced by using the Western blotting (immunoblotting) technique and that difficulties in finding specific monoclonal antibodies devoid of cross-reacting antibodies may be overcome by newer methods such as affinity chromatography. A compilation of serological procedures to detect dermatophytic antigens may be found in the review by Polonelli and Morace (191).

The early literature on the immunology and immunochemistry of dermatophytosis is reviewed by Grappel et al. (80); a more recent characterization of dermatophyte antigens is presented by De Haan et al. (56).

Descriptions of the immunoregulation and immunology of dermatophytosis may be found in review articles by Dahl (47), Calderon (36), and Jones (117). An update on the suppression of immunity by dermatophytes is given by Dahl (47).

PREVENTION AND CONTROL

Prevention and control of dermatophyte infections must take into consideration the area invaded, the etiologic agent, and the source of infection.

In tinea capitis caused by *M. canis* or *M. audouinii*, for example, all potentially infected contacts can be screened for infected fluorescent hairs with the Wood's light. In the more common nonfluorescent tinea capitis such as that caused by *T. tonsurans*, detection is more difficult, especially in minimal

infections. In this situation, scalps should be checked carefully for spotty alopecia and lesions, and suspicious areas should be cultured. The hairbrush technique (163) may be helpful in detecting and culturing subclinical infections. Routine inspection of scalps of young children should be performed at the beginning of the school term. All outbreaks in schools or institutions should be reported to the proper authorities. Good hygiene should be impressed upon those infected, and they must be instructed not to share headgear, combs, and brushes. Barbershop instruments (combs, brushes, and scissors) must be disinfected after use. All those infected must be treated promptly to prevent further spread of the infection.

Although nosocomial spread of dermatophytosis is rare, a few outbreaks have been reported (17, 128, 174, 219, 226). In one of these outbreaks, nosocomial tinea corporis caused by *T. tonsurans* was transmitted to hospital personnel as the result of direct contact with an infected child (17). Two other outbreaks resulted from transmission of *M. canis* to neonates by nursing personnel (174, 226). Such outbreaks must be investigated promptly to avoid further spread. When an outbreak occurs, personnel handling infants must be screened for areas of fluorescence by the Wood's light and for obvious skin or scalp lesions. If these are negative, infection control measures must be implemented to detect the source, such as a review of staffing patterns, a questionnaire to determine "high-risk" personnel, culturing of equipment in the nursery, and repeated cultures of hands and scalp of the involved health care workers. The last measure resulted in identifying the common source, a nurse, whose culture grew *M. canis* despite a lack of any obvious skin or scalp lesions (174). Until the source of infection in a nursery is identified and treated, protective clothing (gloves, gowns, and head covering) should be worn by health care workers handling infants. Routine wearing of long sleeves by health care workers handling infants stopped one outbreak of *M. canis* (174).

Since tinea corporis and tinea cruris caused by anthropophilic fungi can be transmitted by infected clothing, towels, and bedding, these items should be disinfected after use and infected individuals should not permit others to share them. Individuals with tinea corporis should not engage in contact sports such as wrestling (228).

It is important to locate the animal reservoir in infections caused by the zoophilic dermatophytes such as *M. canis*, *T. mentagrophytes* var. *mentagrophytes*, and *T. verrucosum*. *M. canis* infections of a cat or dog can usually be detected by a Wood's light examination. It is more difficult to detect and eliminate cattle ringworm caused by *T. verrucosum* because infected hairs do not fluoresce, and infected hair and scales have been shown to survive for years on fomites such as wooden fences (199). Good hygiene and sanitation and fungicidal sprays and washes have been effective in controlling these infections (197). When economically feasible, systemic griseofulvin could be used to treat infected cattle.

Human infections with *T. mentagrophytes* var. *mentagrophytes* and *M. canis* are common in personnel handling animals (dogs, cats, and rodents) infected with a dermatophyte. Many of these infections are subclinical; therefore, routine wearing of protective clothing, especially gloves, is recommended.

Prevention of tinea pedis may be enhanced by using good foot hygiene (includes regular washing of the feet, thorough drying, and application of foot powder); avoiding excessive moisture and occlusion by wearing sandals or other well-ventilated shoes; avoiding trauma to the feet, especially blistering by ill-fitting footgear; and not sharing towels, socks, or shoes. Since tinea pedis is considered contagious, i.e., transferred by infected shed skin scales, control may be accomplished by

educating infected individuals not to expose others by walking barefoot near swimming pools, locker rooms, and public showers and by not sharing footgear. Frequent hosing of floors of public baths, swimming pools, etc., and discouraging antifungal foot dips (which may harbor dermatophytes) near swimming pools may be helpful as preventive measures. However, some dermatologists, citing experience, observation, and experimentation, have concluded that exogenous measures to avoid contact with pathogenic fungi or to disinfect the environment are useless (24, 237). According to these investigators, individuals carry pathogenic fungi in quiescent foci on their nails, feet, and groin and the infection exacerbates when trigger factors lower resistance. Measures for prevention should be based on maintenance of local resistance to infection by individual care and hygiene of the feet and groin.

PHYSIOLOGY

Few groups of fungi are specialized protein degraders. The order Onygenales, however, contains certain families, including the Arthrodermataceae (45), which are highly specialized in the degradation of refractory proteins, particularly keratin. *Arthroderma* species, including those with dermatophyte anamorphs in addition to their asexual congeners, produce a variety of enzymes for the degradation of keratin and other proteins. Keratinases are produced by all dermatophytes studied (200). *T. rubrum* has recently been extensively studied by Apodaca and collaborators (14, 15) and shown to produce two strongly keratinolytic proteinases with molecular weights of 93,000 and 71,000 (as detected under nonreducing conditions in dimerized form), as well as a poorly keratinolytic, trypsin- or chymotrypsin-like general proteinase with a molecular weight of 27,000. These proteinases all have a pH optimum of approximately 8. In another study with *T. rubrum*, a chymotrypsin-like acidic proteinase with a pH optimum of 4.5 was detected (248). Activity of the enzyme increased during the first 2 weeks of growth but then dropped and was superseded by the activity of neutral proteinases (248). Human skin has a weakly acidic pH, and it is noteworthy that proteinases with an optimal activity under acidic conditions are reported to be important virulence factors in *T. mentagrophytes* (252, 253). The production of elastase has been associated with inflammatory dermatophytosis (196, 202, 204). The velvety form of *T. mentagrophytes*, var. *interdigitale*, associated with a low degree of extracellular elastin-degrading activity, provokes much less inflammation in the guinea pig than does the highly elastolytic, granular form (71). The varieties of *T. mentagrophytes* produce small amounts of protease activity in skin from hosts to which they are well adapted but produce large amounts on material from an unfamiliar potential host species (198). Decreased production of potentially reactive secretions and constituents on contact with normal hosts is a universal feature in highly specialized symbiotic (including parasitic) fungi.

Dermatophyte proteolysis results in the liberation of excess ammonium ion, raising the pH of the growth medium (186). This reaction, an attribute relatively uncommon in fungi isolated clinically, has been used as the basis of screening media such as Dermatophyte Test Medium (193). The medium detects most dermatophytes, although a small proportion of *Microsporum* isolates are not detected (173).

Production of any dermatophyte proteases is repressed by small molecules such as carbohydrates and amino acids (33, 167). Apodaca and McKerrow (15, 16) have recently shown that during log-phase growth most of the proteolytic enzymes of *T. rubrum* are repressible in vitro by small molecules and are likely repressed during early growth in vivo. The entire com-

plement of proteinases in *T. rubrum* tends to be produced constitutively during the stationary phase of growth in vitro (15, 16).

The particularly strong repression by glucose of the ammonifying lysis of casein during log-phase growth in *T. rubrum* has been exploited in a determinative medium, BCP-milk solids-glucose agar (63, 240). *T. mentagrophytes* begins detectable ammonification rapidly on this medium, while detectable activity in *T. rubrum* is repressed by glucose for over 10 days. The majority of *Microsporum* species do not cause any ammonification detectable by the BCP indicator. Another diagnostically important ammonification is that produced by the catalysis of urea, a capacity for which is found in all dermatophytes except a few anthropophiles (193).

Arthroconidia from infected material are stimulated to germinate by components of the urea cycle (169, 203) and by certain amino acids. L-Leucine, for example, stimulates the germination of *T. mentagrophytes* arthroconidia (96). Carbohydrates do not stimulate germination of conidia of this species (95, 96), an effect that may be important for prolonging dormancy in fomites. Carotenoid pigments are formed in substrate arthroconidia of *T. mentagrophytes* but are not formed in hyphae or microconidia (95). These likely have a protective function in dormant propagules.

Soil-associated geophilic and zoophilic dermatophytes and congeners tend to produce all vitamins and amino acids constitutively, while numerous anthropophiles and dermatophytes specific to grazing animals show the usual tendency of parasites to have lost some of these abilities. Heterotrophy for thiamine is particularly common and is found both in some anthropophiles, e.g., *T. tonsurans*, and in some zoophiles, e.g., *T. verrucosum* var. *verrucosum* (74).

Dermatophytes and congeners, like most filamentous fungi of ascomycetous affinity, have a secondary metabolism characterized by the production of substantial quantities of distinctive metabolites. Three classes of such metabolites have received attention: (i) antibiotic substances related to penicillin, which are lactam derivatives of fungal-type lysine synthesis (91, 264, 280); (ii) antibiotic fusidanes (91), which are terpenoid compounds related to sterols; and (iii) pigments derived from polyketide biosynthesis. The pigments are mostly heptaketide naphthoquinones (254). Each dermatophyte species studied produced a mixture of pigments, with the proportion of each compound in the mixture dependent on the medium and growth conditions (277). Antibiotic substances are produced by fungi in vivo and may result in the selection of a population of resistant bacteria in lesions (280). Inhibition of such bacterial isolates in vitro may be difficult. On the basis of observations made in vitro, *T. rubrum* appears particularly likely to be associated with such antibiotic-resistant bacteria (63). These bacteria tend to prevent pigment formation in vitro (63, 133), perhaps by competing for carbohydrates that may be required for the production of pigments (230). Misidentification in the clinical laboratory is a possible consequence when laboratories depend on colony pigmentation as a determinative character (63).

Apart from antibiotics, complex interactive substances formed by dermatophytes include a steroid-binding macromolecule, which is likely a protein (43), that slows fungal growth in the presence of the progesterone and certain analogs and hydroxamate siderophores capable of increasing the bioavailability of iron (26). Dermatophytes are moderately thermotolerant: most grow well at 37°C in vitro. An exception is *M. persicolor*, a zoophile mainly associated with voles; this species grows poorly or not at all at 37°C (131). Growth optima for most dermatophytes are 25 to 35°C, probably reflecting an

external habitat with a temperature slightly below body temperature (230). Growth at temperatures over 40°C is uncommon. Nonpathogenic congeners often do not grow at 37°C: for example, members of the *T. terrestre* complex, ubiquitous on soil keratin, are unable to do so.

Geophilic dermatophytes and congeners are moderately salt tolerant (125) and therefore are likely moderately osmotolerant in general, as would be expected of organisms growing on easily desiccated keratin fragments. Anthropophilic dermatophytes in general have lower salt tolerance than do zoophilic and geophilic species, perhaps reflecting a lack of adaptation for growth on desiccated substrates (125).

HISTOPATHOLOGY

Dermatophytosis tends to be restricted to the horny epidermal layers of the skin and to the nails and hair. In tinea capitis, infection begins with hyphal penetration of the stratum corneum of the scalp. Several weeks later, the fungus colonizes the base of hairs within the hair follicles and penetrates the medulla of the hair shaft (143, 148). The newly keratinized material of the growing hair, extending through the aperture of the follicle, carries either within it (endothrix) or on and just beneath its cuticular surface (ectothrix) hyphae that round up and become converted into arthroconidia. In tinea favosa of the scalp, filaments, often empty or vacuolated, are seen within infected hairs, while the scalp bears conspicuous cup-shaped areas of densely interwoven mycelium, scales, and debris referred to as scutula. Inflammation with round-cell infiltrate is seen in the adjacent dermis (200). Affected hair follicles tend to atrophy. In affected skin, peripherally raised and centrally depressed areas of scutula also tend to form.

Development of a hypersensitive, kerion reaction on the scalp or similar tinea profunda lesions elsewhere is accompanied by extensive infiltration of lymphocytes, plasma cells, neutrophils, and eosinophils into the dermis (153). Other features may include penetration of hyphae into the dermis and perivascular and perifollicular inflammation.

In tinea corporis, cylindrical fungal filaments are seen in affected areas, and rounded arthroconidia may develop. Affected skin may develop vesicles and papules accompanied by dermal infiltrates in infections caused by the zoophilic dermatophytes, while dry, scaly lesions marked by hyperkeratosis are characteristic of chronic infections caused by the anthropophilic dermatophytes. In an acute form, tinea pedis may reveal intercellular edema and leukocytic infiltrate in the epidermis, or in a chronic state, it may show hyperkeratosis and acanthosis. Folliculitis caused by *T. rubrum* is characterized by the presence of fungal elements in follicles and signs of a foreign-body reaction, with foreign-body giant cells in dermal infiltrates. Granuloma formation may occur. Majocchi's granuloma, with small granulomata in hair follicles, typically occurs after minor trauma due to shaving of the legs (200). In patients in whom immune deficiency (e.g., Cushing's syndrome) removes the usual barriers to dermal penetration by dermatophytes, extensive granulomatous lesions may develop. A mycetoma-like presentation with well-defined fungal grains enveloped in an eosinophilic matrix is well known (153). Systemic invasion of immunodeficient fetuses and neonates may occur (200).

The common distal subungual type of tinea unguium is characterized by the presence of cylindrical fungal filaments and rounded arthroconidia penetrating between the lamellae of the lower nail plate. Proximal white subungual onychomycosis occurs almost exclusively in immunodeficient patients (206). The white patches initially limited to the lunula may eventually

involve the entire nail. The etiologic agents are *T. rubrum*, *T. megninii*, *T. schoenleinii*, and *E. floccosum*. Superficial white onychomycosis, by contrast, is restricted to the surface of the nail and is characterized by the presence of irregular hyphae, often with flattened, spreading, frondose branching (282). The etiologic agent in these cases is usually *T. mentagrophytes*, but it may be a nondermatophyte such as *Fusarium oxysporum* (282).

THERAPY

This section contains a survey of established and recent trends in the therapy of the dermatophytoses and is not intended to be prescriptive of therapy in individual cases. The most noteworthy recent trend in dermatophytosis therapy is the proliferation of new drugs and even new classes of drugs, such as the allylamines (28), the orally active triazoles (256), and hydroxypyridones (249). The new agents are rendering some previously difficult to treat conditions susceptible to rapid resolution. The strong biological variability of the dermatophytoses, however, has so far prevented the emergence of a single agent or regimen effective against all manifestations of these diseases. The relative cost of different therapies has also been an important factor in bringing about therapeutic diversity; this topic, however, will not be dealt with here.

The major types of dermatophytoses are dealt with separately below. Note that tinea faciei and tinea manuum tend to be treated similarly to tinea corporis (134) and that there is considerable overlap between treatment strategies for tinea corporis, tinea cruris, and tinea pedis. Similarly, tinea barbae overlaps strongly with tinea capitis.

Tinea Capitis

To date, no effective topical remedy against tinea capitis has been discovered. Therapy is systemic, although topical agents such as miconazole, clotrimazole, Whitfield's ointment, and selenium sulfide (11) may be used as adjuncts to eliminate the shedding of viable inoculum from infected lesions. Griseofulvin is the long-standing drug of choice and has a success rate of over 90% (158). It is often given as a dosage of 500 mg/day in adults or 250 mg/day in children, administered as a four-part divided dose (200). Chronic infections may require 2 or more months of treatment. Porphyria is a counterindication.

Azoles may also be effective. Ketoconazole, however, in at least some studies has achieved remission in only approximately 60% of patients (44, 103). The allylamine agent terbinafine has proven highly effective (263), as has the triazole itraconazole (159). In addition to drug treatment, general sanitation measures are usually employed to prevent recurrence and spread. Infected headgear is often boiled; infected hair is clipped to reduce the chance of contagion, and the lesions are scrubbed daily, ideally with an antifungal agent such as selenium sulfide (11). Kerion lesions may require debridement or other local care, and the use of antibacterial agents may be indicated to treat secondary infections. Steroids such as prednisone may cause a significant decrease in inflammation (158).

Tinea Barbae

Systemic therapy with griseofulvin, terbinafine, or itraconazole is usually indicated, as for tinea capitis.

Tinea Corporis

In many patients, tinea corporis resolves spontaneously within a few months, particularly when the lesions are caused by zoophilic or geophilic dermatophytes. Recurrence may follow upon reexposure to the source of infection, e.g., animal fomites. In *T. rubrum* infection in some patients, the organism may persist within villous hair shafts and follicles (200), leading to chronic recurrences of the infection.

Topical agents are frequently applied to speed the resolution of uncomplicated lesions. A variety of drugs are effective, including tolnaftate, haloprogin, and amorolfine (176); azoles such as miconazole, clotrimazole, econazole, ketoconazole, oxiconazole, tioconazole, isoconazole, sulconazole, bifonazole (109, 155, 259), fenticonazole (20), and sertaconazole (187); allylamines such as terbinafine and naftifine (48, 168, 171); and hydroxypyridones such as ciclopirox olamine (192). The combination of clotrimazole and beta-methasone dipropionate is useful for early relief of inflammatory reactions as well as clinical cure of the dermatophytoses (136).

In cases of widespread tinea corporis or where granulomatous lesions or tinea profunda occur, systemic therapy may be indicated. Griseofulvin has long been used for this purpose, although cure rates of ca. 60% only have been noted (19). Griseofulvin-resistant isolates have been obtained from clinical sources and from laboratory mutagenesis experiments (18, 19, 150, 160); however, some cases of apparent resistance may be due to host factors (215). Ketoconazole has been used and has a lower relapse rate (99, 115) but a greater chance of inducing side effects, such as hepatotoxicity and depressed adrenal activity (200). In recent times, itraconazole and terbinafine have become widely available for this purpose. Itraconazole given as a single dose of 100 mg before breakfast has been shown to eliminate *T. rubrum* and *T. mentagrophytes* in cases of tinea corporis as well as tinea cruris, tinea pedis, and tinea manuum (278). It is of greater efficacy than griseofulvin in most applications in tinea corporis, tinea cruris, tinea manuum, and tinea pedis (154). Mycological cure rates of tinea corporis and tinea cruris 1 month after 15 days of therapy with itraconazole at 100 mg/day were approximately 80% (55). Rates of success for terbinafine have been 75 to 90% in tinea corporis and chronic tinea pedis (262).

Tinea Cruris

Tolnaftate is frequently used in uncomplicated cases of tinea cruris with excellent results. Also used topically are thiabendazole 10% cream, haloprogin, ciclopirox olamine, naftifine, and various azoles (134). Clotrimazole is used in combination with beta-methasone for inflamed lesions. Bifonazole cream may be used with the advantage that application once every other day is as effective as daily application, minimizing problems due to poor compliance (109). In more severe cases, systemic griseofulvin gives rapid relief and a high rate of cure after 4 to 6 weeks (85, 200). Itraconazole also gives excellent results (185, 211), as does terbinafine (262).

Tinea Pedis

Uncomplicated tinea pedis can often be treated successfully with topical medications; however, chronic lesions caused by *T. rubrum* may be very resistant to treatment (200). Tolnaftate is very widely used and highly effective in most cases, as is haloprogin (134). Many topical azoles have been used effectively (134). Tioconazole has been found somewhat more effective than the widely used miconazole cream, itself an efficaceous agent (42, 68). Sulconazole nitrate 1% cream has been shown to be effective against the fungi in uncomplicated lesions and also to effect a significant decrease in erythema and scaling during the course of healing (157). In a study of naftifine compared with clotrimazole–beta-methasone, the former

agent was found to have a higher cure rate (225). Ciclopirox olamine was approximately as effective as bifonazole in a small trial, with both drugs effecting mycological cure and remission of symptoms rapidly in over 90% of patients (92). In cases complicated with bacterial infection, as often seen in workers such as miners at high risk for foot infections, topical antifungal agents such as clotrimazole and ketoconazole may be effective but, if used alone, may exacerbate bacterial infection (100). Antibacterial agents may need to be used in concert with antifungal agents in these cases. In most cases of resistant and chronic tinea pedis, systemic griseofulvin has been used with success (18, 19, 200). Symptomatic improvement may require 2 to 6 weeks, and clinical cure of resistant cases may require 6 or more months of therapy. A recent study comparing terbinafine, 125 mg twice daily, and griseofulvin, 250 mg twice daily, for chronic moccasin-type tinea pedis showed an 88% cure rate in the terbinafine group and only a 45% cure rate in the griseofulvin group, with some relapse occurring in the latter group but not in the former (212).

Tinea Unguium

For tinea unguium, the most resistant of dermatophytoses, topical therapy is seldom efficaceous and spontaneous resolution is rare. One long-standing strategy is avulsion or chemical ablation of the nail, followed by treatment of the nail bed with fungistatic agents (137, 149). Chemical ablation is often accomplished with urea paste under occlusion. Tinea unguium resistant to other forms of therapy has been found susceptible to 2% tolnaftate used in combination with an occlusive, 20% urea dressing (111). An alternative strategy is systemic therapy. Long-term griseofulvin therapy, e.g., 1 g/day for 3 to 15 months, has effected clinical cure in a large percentage of patients with fingernail infections but only in 12 to 16% of patients with toenail infections (19, 114). Poor penetration is the most likely reason for this unresponsiveness, not the development of resistance in the fungus involved. Ketoconazole, once used as an alternative, is now seldom used because of rare instances of hepatotoxicity (137, 149, 156, 189). Recently, the much greater success rates of terbinafine and itraconazole in toenail infection have made a strong impact (13, 78, 189, 257). Short-duration therapy with terbinafine was studied in 85 patients and was completely curative in 82% of toenail onychomycoses and in 71% of a small sample of fingernail onychomycoses (77).

GENETICS

Heterothallism

Heterothallism was first demonstrated by Stockdale (231) in *Arthroderma incurvatum* (*Nannizzia incurvata*), one of the teleomorphs of the *M. gypseum* complex, and has since been reported in other dermatophytes. Weitzman (268) defined the mating type system in *A. incurvatum* and in *Arthroderma gypseum* (*Gymnoascus gypseus*) as a one-locus, two-allele incompatibility system. The same system was also demonstrated in *Arthroderma simii* (151, 236) and *Arthroderma benhamiae* (7). Maniotis and Chu-Cheung (164) reported that the incompatibility locus in *A. benhamiae* is either nonlinked or distal to the colonial morphology locus, e.g., regulating the downy and granular phenotypes.

Not all A or a (+ or −) crosses within the same teleomorphic species are compatible since genetic factors blocking compatibility occur (182, 268). Although this compatibility system typically yields the two mating types of the ascospore progeny

in a 1:1 ratio, significant deviation from the ratio has been observed in other dermatophyte progeny, e.g., *A. simii* (151) and *A. benhamiae* (181), and in isolates of zoophilic dermatophytes isolated from human and animal lesions (272). For example, almost all isolates of *Arthroderma otae* (*M. canis*) were the (−) mating type (272), and the zoophilic isolates of *Arthroderma vanbreuseghemii* (*T. mentagrophytes* var. *granulosum-asteroides* strains) and *A. benhamiae* (*T. mentagrophytes* var. *erinacei*) were the (+) mating type (180). The predominance or almost exclusive existence of one mating type has also been demonstrated in anthropophilic anamorphs on the basis of the ability of *A. simii* (*T. simii*) to stimulate interspecific sexual reactions (234, 235, 245). For example, pairing of certain anthrophophilic anamorphs with *A. simii* (+) and (−) tester strains revealed that *T. rubrum* exists exclusively as the (−) mating type and *M. audouinii* and *T. mentagrophytes* var. *interdigitale* exist as the (+) mating type (234, 235).

Pleomorphism

Understanding the cause of pleomorphism in the dermatophytes was made possible by the discovery of sexual reproduction and the application of classical genetic analysis of the progeny of sexual crosses. Pleomorphism in the dermatophytes is the spontaneous appearance of white fluffy tufts of aerial mycelium on the surface of colonies which results in the loss of characteristic pigmentation and conidiation. Weitzman (269) analyzed the ascospore progeny of crosses between spontaneous pleomorphic mutants and wild types of both *A. incurvatum* and *A. gypseum* and found that this phenomenon resulted from single chromosomal gene mutations in mutants showing diminished conidiation and double nonallelic gene mutations in those totally aconidial mutants capable of reproducing sexually. Weitzman and Silva (275) extended their genetic studies of both UV and spontaneous mutants of *A. incurvatum* to construct a genetic map of linkage group I.

Virulence

Rippon (196) demonstrated close linkage between the gene for elastase activity (a suggested virulence factor) and the gene for mating type in *A. fulvum* (*N. fulva*). Furthermore, Rippon and Garber (202) suggested an association of dermatophyte pathogenicity as a function of mating type and associated enzymes in *A. benhamiae*. However, Cheung and Maniotis (40) demonstrated in *A. benhamiae* that elastolytic activity segregated independently of mating type but was closely linked to the locus governing colonial morphology. Hejtmánek and Lenhart (105) studied the genetic basis for virulence in *A. incurvatum* (*N. incurvata*) and demonstrated that multiple chromosomal genes were involved. The locus for virulence was independent of colonial morphology but was related to growth rate. All cultures with a normal growth rate were virulent, whereas those with a lower growth rate were avirulent. In a later study they obtained genetic complementation of virulence in avirulent mutants by heterokaryon formation in a nutrient agar medium (106) and on soil (107). They did not address mating type or enzymes in their studies.

Griseofulvin Resistance

Lenhart (160) investigated griseofulvin resistance in spontaneous and UV-induced mutants in *A. incurvatum* (*N. incurvata*) by analyzing ascospore progeny of sexual crosses. He found two different unlinked gene loci, *grf-1* and *grf-2*, resulting in the same level of resistance to griseofulvin. However, most

of the other griseofulvin-resistant mutants did not cross with the wild type, preventing further genetic studies.

Pigmentation in *A. benhamiae*

Ghani et al. (76) studied the genetics of pigmentation (yellow-brown) in *A. benhamiae*. On the basis of the segregation patterns obtained in their F1 progeny, they concluded that the alleles for pigmentation and mating compatibility are linked on the same chromosome, 20 map units apart.

More detailed information on the genetics of dermatophytes may be found in a review by Kwon-Chung (152) and more recently in one by Hejtmánek et al. (104). The latter also includes studies on heterokaryosis and the parasexual cycle.

MOLECULAR BIOLOGY

The traditional taxonomy of the dermatophytes is based essentially on gross and microscopic morphology, with minor emphasis on physiology and nutrition. However, identification of isolates has been complicated by their overlapping characteristics, variability, and pleomorphism. Mating as a means of identification is not always practical because of the need to keep a library of opposite mating types for each species; also, many of the anamorphic species lack a teleomorph.

A variety of chemotaxonomic methods have been developed to bypass the traditional methods of identification and to determine relationships between the various species. These include disc electrophoresis of culture filtrate proteins (213), pyrolysis–gas-liquid chromatography to study fatty acids (39, 120, 218, 243), polyacrylamide gradient gel electrophoresis of total cell protein extracts for zymogram patterns (121), and isoelectric focusing of somatic extracts in thin-layer polyacrylamide gels (113, 244).

More recent studies have attempted to determine if differences or similarities between dermatophyte genera and species established by traditional criteria were reflected in the molecular composition of their genetic material. Davidson et al. (50) studied the base composition of chromosomal DNA of 55 dermatophyte isolates, representing 34 species, by CsCl density gradient centrifugation. They found the G+C content of all *Microsporum*, *Trichophyton*, and *Epidermophyton* species studied to be in the narrow range of 48.7 to 50.0 mol%. On this basis, they suggested that the distinctions made on existing morphological characteristics may not be fully justified in view of the high overall phenetic and genomic similarity.

Davidson and Mackenzie (49) proceeded to study the taxonomy of the three dermatophyte genera through determination of DNA homology. DNA from 10 isolates (seven species) was extracted and reannealed by hydroxyapatite chromatography. DNA homology levels of 65 to 80% corresponded to species within a genus. Their results showed a general agreement with the established classification scheme, particularly in assigning species to separate genera, with the exception of *T. terrestre*, which revealed a low homology with *A. benhamiae* (*T. mentagrophytes*) and *T. rubrum* (25 and 24%, respectively), and *A.* (*N.*) *incurvatum* (*M. gypseum*), which showed a low homology with *M. canis* (28%). A fairly close relationship was suggested by DNA hybridization levels obtained for *A. benhamiae* and two strains of *T. rubrum* (73 and 76%).

Investigations in the late 1980s and early 1990s employed mitochondrial DNA (mtDNA) as a genetic marker to elucidate the taxonomy and phylogeny of the dermatophytes (53, 112, 138, 139, 170, 175). mtDNA was isolated, purified, and digested by restriction endonucleases, electrophoresed on an 0.8% agarose gel, stained with ethidium bromide, and observed under UV light to compare characteristic fragment patterns.

In this manner, de Bièvre et al. (53) studied mtDNA from six isolates of *T. rubrum* (morphological variants with different geographic distributions), using four restriction endonucleases (*Hin*dIII, *Hae*III, *Alu*I, and *Eco*RI). They concluded that *T. rubrum* could be classified into two groups (I and II) on the basis of fragmentation patterns. However, these groups did not correspond to either morphologic variation or geographic distribution.

Similarly, Mochizuki et al. (170) investigated the relationship between 22 isolates of *T. interdigitale* (*T. mentagrophytes* var. *interdigitale*) from Japan and other members of the *T. mentagrophytes* complex by restriction enzyme analysis (*Hae*III, *Msp*I, and *Hin*dIII) of mtDNA. They compared the restriction profiles of their *T. mentagrophytes* var. *interdigitale* isolates with those of *A. simii*, *A. benhamiae*, and *A. vanbreuseghemii*; they found that all of the restriction profiles of *T. mentagrophytes* var. *interdigitale* were identical to those of *A. vanbreuseghemii* only and concluded that these two species are closely related. The restriction profiles of *A. vanbreuseghemii* digested by *Msp*I and *Hin*dIII were different from those of *A. simii*; those of *A. benhamiae* differed greatly from those of the other species.

Nishio et al. (175) extended the study of mtDNA analysis with five endonucleases (*Hae*III, *Msp*I, *Hin*dIII, *Xba*I, and *Bgl*II) to define the taxonomic relationships of the species within the genus *Trichophyton* and to construct a phylogenetic tree based on sequence divergence. The *Trichophyton* species were divided into seven groups. (i) *T. rubrum* was divided into two groups, I and II (identical to those of de Bièvre et al. [53]), and was suggested to be a complex; also, *T. rubrum* type I was genetically more closely related to *A. benhamiae* than was type II (Davidson and Mackenzie [49] had reported a 76% DNA homology of *A. benhamiae* with *T. rubrum*). (ii) *A. benhamiae* was closely related to *T. mentagrophytes* var. *erinacei* (successful mating was reported by Takashio [246, 247]). (iii) *T. rubrum* type II, *T. tonsurans*, and *A. vanbreuseghemii* showed identical restriction profiles and were suggested to be closely related or identical. (iv) *Trichophyton quinckeanum* (*T. mentagrophytes* var. *quinckeanum* according to Ajello et al. [6]) and *T. schoenleinii* showed identical restriction profiles which differed slightly from those of *A. vanbreuseghemii*. Last, (v) mtDNA analysis was useful in identifying pleomorphic strains. The authors concluded that conventional taxonomy based on morphology does not necessarily correlate with data obtained from mtDNA restriction profile analysis.

Kawasaki et al. (139) studied the digestion profiles of *A.* (*N.*) *incurvatum*, *A. gypseum*, *A. fulvum*, and *A. otae*, using endonucleases *Hae*III, *Hha*I, *Hin*dIII, and *Xba*I. They found *A. fulvum* to be divided into two types on the basis of restriction profiles. A phylogenetic tree constructed from sequence divergence revealed that (i) *A. gypseum* was more closely related to *A. fulvum* than to *A. incurvata*; (ii) the phylogenetic difference between *A. otae* and the three species is larger than the distance between the three species; and (iii) the phenotypic classification of *A. gypseum*, *A. incurvatum*, and *A. fulvum* is not completely consistent with the genotypic classification.

In a later paper, Kawasaki et al. (138) extended their phylogenetic relationship studies of *Arthroderma* species (including former *Nannizzia* species) by restriction fragment length polymorphisms of mtDNA. Phylogenetic trees constructed from studies of 10 species showed no definite distinctions between the genus *Arthroderma* and the former genus *Nannizzia*, supporting the conclusion by Weitzman et al. (271) that the two are congeneric.

Ishizaki (112) analyzed mtDNA patterns of a variety of

fungi, including *Trichophyton* species. On the basis of his investigations with restriction endonucleases *Hae*III, *Msp*I, *Bgl*II, and *Hin*dIII, he concluded that some species of dermatophytes revealed identical restriction patterns, suggesting overclassification of the *Trichophyton* species. For example, the restriction patterns from three strains of *Trichophyton raubitschekii* were the same as those of *T. rubrum* type I, suggesting that *T. raubitschekii* is a variant of *T. rubrum.*

Other recent molecular investigations of dermatophytes include the following: that of Bowman and Taylor (32) regarding the evolutionary origins of pathogenic fungi based on 18S ribosomal DNA sequences; de Bièvre and Dujon's (54) mtDNA sequence analysis of a 5,248-bp-long region of *T. rubrum*; and the Tortajada et al. report (250) on molecular cloning of *T. mentagrophytes* DNA sequences with promoter activity in *Escherichia coli* and their studies (251) on the sequencing of a 0.85-kb *Hin*dIII mtDNA fragment of *T. mentagrophytes* which corresponds to a tRNA gene cluster.

FUTURE PROSPECTS

Dermatophyes have been among humanity's most constant parasitic associates and have survived several generations of therapeutic regimens, ranging from Sabouraud one-dose, single-point, X-ray epilation to griseofulvin, tolnaftate, and the early imidazoles. At the same time, however, certain individual dermatophyte species have declined drastically in the face of the drug therapies of the last three decades. *T. schoenleinii* has now been expunged in all but a few pockets worldwide and clearly should be placed on the list of human disease agents that are candidates for complete eradication. The once abundant *M. audouinii* is also now rare and geographically restricted, with its primary African geographic distribution probably mediated more by economic than by ecological factors. Finally, *M. ferrugineum* appears to be increasingly rare and highly vulnerable to conventional therapies. The radical decline in abundance of these species implies that other anthropophilic dermatophytes, as well as the zoophilic parasites restricted to domesticated species, may also suffer decline if suitable advances in therapy or vaccination occur. The strong success of terbinafine and itraconazole recently reported in tinea unguium trials raises the possibility that, if the traditionally difficult to cure nail infections have been an epidemiologically important inoculum reservoir for certain dermatophytes such as *T. rubrum*, these dermatophytes may suffer significant population decline in upcoming decades. Even if they do not decline, their persistence may depend more on the sort of socioeconomic epidemicity now seen in communities of minorities with *T. tonsurans* than on rapid genetic modification. In this age of multidrug-resistant tuberculosis, it may seem naive to speculate that any microbial disease could decline permanently as a result of antibiotic therapies. Nonetheless, anthropophilic dermatophytes are arguably now at a vulnerable point in their evolutionary history.

Within the next few years, it is likely that the prior evolution of dermatophytes will be inferred through molecular cladistic comparison. Relationships between species will be clarified and some species may be reduced to synonomy. Since anthropophilic dermatophytes appear to be the products of one or more recent adaptive radiations, the genetic distinctions within some lineages may be subtle, and potentially insensitive techniques such as mtDNA restriction typing should not be taken as sole arbiters of species status. The molecular taxonomic analysis of dermatophyte relationships will require a consilience of induction among characters obtained by a vari-

ety of methods, as is axiomatically recommended for all well-constituted taxonomic work.

The immunology of the dermatophytoses is a continuously developing field with clear relevance to the new immunological perspectives derived from the human immunodeficiency virus pandemic. The immunobiology of the skin is a subject rich with possibilities for advancing our understanding of disease processes, and the dermatophytes provide a signal case of well-adapted, yet normally well-controlled, cutaneous pathogens. The severe dermatophytoses often seen in persons with AIDS attest to the importance of cellular immunity in the control of the dermatophytoses and indicate that much may be learned about cutaneous cellular immunity by studying these infections. Dermatophyte infections, while not usually life threatening, offer an interesting approach to a variety of fundamental problems in human, animal, and fungal biology.

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