PRESENTED AT THE SYMPOSIUM, "CUTANEOUS DERMATOPHYTE INFECTIONS: PATHOGENESIS AND TREATMENT," SUPPORTED BY AN EDUCATIONAL GRANT FROM SANDOZ PHARMACEUTICALS CORPORATION

Pathophysiology of dermatophyte infections

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Dermatophyte infections are among the most common infections encountered in medicine. Often considered trivial, these infections are in fact frequently refractory and recurrent. This article presents an overview of the causes, symptoms, differential diagnosis, and clinical course of the most prevalent dermatophyte infections: tinea pedis, tinea cruris, tinea capitis, tinea corporis, and onychomycosis. Complicated situations such as follicular involvement, dermatophytoses in patients who are immunocompromised, and the exaggerated response to zoologically acquired fungal infections are also discussed. (J AM ACAD DERMATOL 1993;28:S2-S7.)

Approximately 50,000 species compose the kingdom Fungi, but only 300 of these have been shown to be pathogenic. In fact, approximately 90% of all fungal disease is caused by less than a dozen of these fungal species.[1] Dermatophytoses are by far the most prevalent of the three major classes of superficial fungal infections; the others are superficial mycoses and candidiases.[2] Dermatophytes invade, infect, and persist in the stratum corneum and rarely penetrate below the surface of the epidermis and its appendages. At a minimum, the skin responds to the irritation of superficial infection by increased proliferation in the basal cell layer, which causes scaling and epidermal thickening.[3]

The fungal pathogens responsible for the dermatophytoses are *Trichophyton, Microsporum*, and *Epidermophyton* species (Table I).[4] The clinical manifestation of the infection does not serve to identify the causative organism. In the United States the most common pathogenic dermatophyte organism is *Trichophyton rubrum*; this can cause tinea corporis, tinea pedis, tinea manuum, and onychomycosis.[6] The organism that is the second most commonly isolated from lesions in humans is *T. tonsurans*, followed by *T. mentagrophytes*.[6] These two organisms also cause an assortment of other skin diseases. The source of the fungal reservoir is clinically significant: fungi that are indigenous to soil (geophilic fungi) or animals (zoophilic fungi) tend to produce more marked skin reactions than those acquired from humans (anthropophilic fungi).[7]

The currently available systemic antifungal therapies and their indications are listed in Table II. Dr. Smith addresses the topical antifungal drugs and their indications elsewhere in this supplement.

COMMON DERMATOPHYTE INFECTIONS

Tinea pedis

Tinea pedis, or "athlete's foot," is the most common symptomatic form of dermatophytosis and is most often caused by infection with *T. rubrum*, *T. mentagrophytes*, or *E. floccosum*.[2] An estimated 30% to 70% of adults carry these pathogens, but this exposure does not result in tinea pedis in most carriers.[8] The incidence of symptomatic disease increases with age; young children are infrequently affected.[8]

The general term "tinea pedis" includes three grossly definable diseases. The most common is the scaly, hyperkeratotic moccasin-type disease. It is usually caused by *T. rubrum* and affects mainly the plantar surfaces (Fig. 1). Symptoms and signs are limited to mild itching and fine silvery white flakes on slightly erythematous skin. The scaly areas may be patchy or may cover the entire sole. Although symptoms are mild, the condition is extremely persistent.[8]

The second category is interdigital infection characterized by exfoliation and sometimes maceration

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Table I. Commonly isolated dermatophytes and their primary manifestations

Organism	Origin	Primary manifestations	Prevalence (approximate % of all cases of dermatophytosis)
T. rubrum	Tinea corporis, tinea pedis, tinea cruris, tinea manuum, onychomycosis	Anthropophilic	54.8
T. tonsurans	Tinea capitis, tinea corporis, tinea pedis, tinea manuum, onychomycosis	Anthropophilic	31.3
T. mentagrophytes	Tinea pedis, tinea corporis, tinea capitis, tinea barbae, tinea cruris, tinea unguium	Zoophilic, anthropophilic	6.0
T. verrucosum	Tinea corporis, tinea capitis, tinea barbae	Zoophilic	0.2
M. canis	Tinea capitis, tinea corporis	Zoophilic	4.0
M. gypseum	Tinea capitis, tinea corporis, tinea barbae	Geophilic	0.6
E. floccosum	Tinea cruris, tinea pedis, onychomycosis, tinea corporis	Anthropophilic	2.0

Data from references 5, 6, and 8.

of the skin, especially between the third and fourth or fourth and fifth toes; a foul odor frequently accompanies the lesions.[2] The epidermis under the desquamating debris is erythematous and weeping. Flare-ups often are associated with hot, humid weather, excessive sweating, and occlusive footwear.[8] In its uncomplicated form, intertriginous tinea pedis has been termed *dermatophytosis simplex*.[9]

The last type of tinea pedis, which can be severe enough to disable the patient, is the vesicular, often appearing as an acute eruption of highly inflamed vesicles; bullae and fissures may also appear. Patchy areas of involvement can include the web spaces, dorsum of the foot, instep, and even the heel and anterior area.[8] The disease is accompanied by thickening of the soles, secondary bacterial infection, pruritus, and maceration. Patients with this severe form may be subject to frequent recurrences. Occasionally in tinea pedis one or both hands also become involved, with one-hand two-foot or two-hand one-foot presentations characteristic.[2] To complicate the clinical situation further, a primary fungal infection can lead to secondary bacterial involvement. When secondary bacterial infection is involved, the condition may be referred to as *dermatophytosis complex*.[9] *T. mentagrophytes*, a fungus of animal origin, can be responsible for an especially fulminating form of the disease, including ulceration of the epidermis, purulent vesicle fluid, and rapid spread.[8]

Table II. Systemic antifungal medications*

Drug	Indicated for
Amphotericin B	Cryptococcosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, mucormycosis, sporotrichosis, aspergillosis
Fluconazole	Candidiasis, cryptococcal meningitis
Flucytosine	Candidiasis, cryptococcosis
Clotrimazole	Candidiasis
Ketoconazole	Candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, paracoccidioidomycosis
Miconazole	Coccidioidomycosis, cryptococcosis, candidiasis, pseudoallescheriosis, paracoccidioidomycosis
Griseofulvin	Tinea pedis, tinea cruris, tinea corporis, tinea barbae, tinea capitis, tinea unguium
Nystatin	Candidiasis
Itraconazole	Histoplasmosis, blastomycosis

*Manufacturer's prescribing information.

Tinea cruris

Tinea cruris (or "jock itch"), an extremely pruritic infection of the groin and surrounding areas, is the second most common dermatophytosis. Heat,

Fig. 1. Tinea pedis of the hyperkeratotic moccasin type. This condition is persistent.

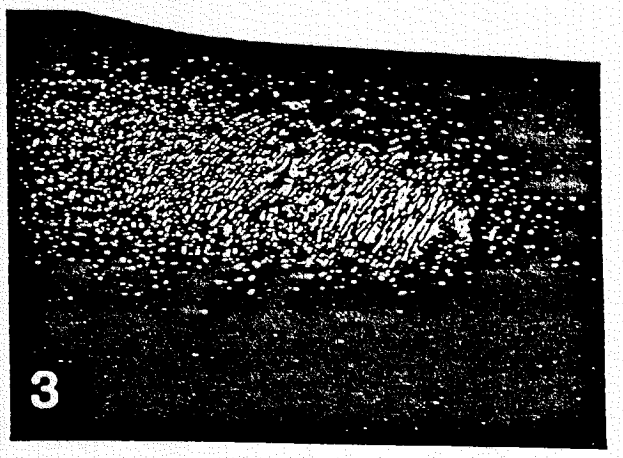

Fig. 3. Infected arm of mother of two children with tinea capitis caused by *T. tonsurans*. The infection on her arm was also caused by *T. tonsurans*, which suggests that she may have served as a carrier.

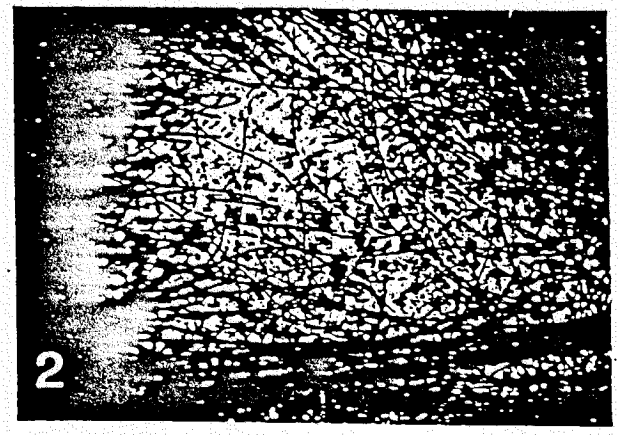

Fig. 2. Tinea capitis caused by *T. tonsurans* in patient with acquired immunodeficiency syndrome. Tinea capitis is mostly seen in children, but the patient who is immunocompromised is also susceptible.

Fig. 4. Onychomycosis in a patient with HIV disease. The white nail is characteristic. The small papule on the thumb represents disseminated cryptococcosis.

humidity, excessive sweating, and occlusive undergarments can predispose to this condition that occurs most commonly in men. Tinea cruris is generally easy to diagnose because of its characteristic, sharply defined peripheral scale; areas of skin from the inguinal folds and perineum to the inner thighs and even the buttocks may appear reddened and inflamed.[2] Older lesions can have a leathery appearance. The most common causative organisms are *T. rubrum* and *E. floccosum; T. rubrum* tinea cruris tends to spread further, even to the waist.[8] In contrast to candidal infection, signs of tinea cruris are seldom apparent on the scrotum or penis. Weeping, scattered lesions may be indicative of candidiasis.[5]

It is important to recognize the frequently associated follicular involvement, because this can be pustular and misdiagnosed as folliculitis or furuncles and treated with antibiotics unnecessarily. Generally speaking, tinea cruris responds well to treatment with an antifungal solution or cream. The area should be kept dry and free from occlusion.

Tinea capitis

Tinea capitis, ringworm of the scalp, is most commonly caused by *T. tonsurans*, although *Microsporum audouinii* and *M. canis* are other possible pathogens.[2] It is most common in school-aged children and takes a variety of clinical forms,

including seborrheic dermatitis–like, impetigo-like lesions, black-dot ringworm (with hair breakage at the ostium causing the "black-dot" appearance), and kerion formation, in which an inflammatory mass is frequently associated with lymphadenopathy and an eczematous reaction (Fig. 2).[2] Because mixed presentations are also possible, a potassium hydroxide (KOH) preparation is important in making the diagnosis, and culture is necessary to identify the specific organism involved. *T. tonsurans* (the cause of black-dot ringworm) causes an endothrix type of infection, whereas *Microsporum* species cause an ectothrix type.

One major problem in controlling tinea capitis is that many children or adult family members without symptoms serve as carriers of *T. tonsurans*, either on the scalp or on other parts of the body (Fig. 3). A second problem is that viable *T. tonsurans* can persist for a long period during treatment. Often, even after a month of systemic griseofulvin therapy—considered to be the best treatment for tinea capitis—colony-forming spores still can be recovered from the scalp.[2,8] Therefore a second culture should be performed with a sample from these patients after 6 to 8 weeks, with use of a toothbrush or similar implement to collect the sample.

Also helpful in the treatment of tinea capitis is the use of shampoos that contain ketoconazole or selenium sulfide. However, griseofulvin is the only systemic therapy currently approved for the treatment of tinea capitis.[2]

Tinea corporis

Tinea corporis, ringworm of the body, includes any dermatophyte infection that does not involve the scalp, beard, face, hands, groin, feet, or nails.[2] It usually appears as one or more dry, scaly patches. Patients who are overweight or under stress appear to be more susceptible, and children are also frequently infected.[4] Although the causative pathogens vary widely, *T. rubrum, T. mentagrophytes*, and *M. canis* are frequent. A KOH and a fungal culture should be performed because several other skin diseases have a similar appearance. As with other fungal infections, recurrence may develop and severe infections are often difficult to treat.

Onychomycosis

Onychomycosis, fungal infection of the nail, is referred to as tinea unguium when caused by a dermatophytic pathogen.[2] The characteristic yellow-white thickening of the nail is caused by a proliferative response of the stratum corneum under the nail plate.[4] Like tinea pedis, tinea unguium is most often caused by *T. rubrum, T. mentagrophytes*, or *E. floccosum*.[2] Both toenails and fingernails can become infected, and a patient may have both infected and uninfected nails (Fig. 4). If steps are not taken to resolve the infection, painful secondary bacterial infection may occur. Swollen, painful paronychial tissues also can reflect a candidal cause.[4]

Treatment of onychomycosis of the fingernails is more successful than treatment of toenails, for which long-term systemic therapy is necessary; such therapy is effective in only 30% of cases. Frequently, more dramatic steps are required to achieve a cure of dermatophyte toenail infections, including even nail removal plus a combination of topical therapy and 1 to 2 years of systemic therapy.[2] Griseofulvin and ketoconazole are the standard systemic treatments; however, early reports suggest that the triazoles (fluconazole and itraconazole) for short periods (3 months) are effective.

Follicular involvement

When the hair follicles become involved in a dermatophyte infection, the presentation can be atypical. Lesions may mimic acne, rosacea, bacterial folliculitis, pyoderma, or herpes; thus KOH, culture, and biopsy may be necessary to make a definitive diagnosis. Shaving may facilitate spread of the infection, creating follicular involvement on the face or legs. Once the follicles are involved, 2 to 3 months of systemic treatment may be required to clear the infection.

DIAGNOSTIC TECHNIQUES

Interdigital infections can be difficult to diagnose and treat because candidiasis, psoriasis, erythrasma, gram-negative toe web infection, or intertrigo can also occur in this site. The differential diagnosis also includes contact dermatitis, idiopathic hyperkeratosis, dyshidrosis, acrodermatitis perstans, dermatitis repens, erysipelas, secondary syphilis, pyoderma, arsenical keratosis, and fixed drug eruptions.[8] Mycologic assessment of patients with mild signs of athlete's foot (peeling, erythema, maceration, or slight fissures) yields fungal isolates less than 25% of the time. As signs become more severe (dermatitis or vesicles), the rate of fungal isolation rises to 75% or higher.[10] In most but not all cases, a KOH preparation that is viewed with dark-field illumination or

stained with gentian violet (Swartz-Lampkin stain) or periodic acid–Schiff will establish the diagnosis of fungal origin. Detectible fungal forms appear to be more abundant in samples taken from the undersurface of the tops of small vesicles or bullae (in the vesicular form of tinea pedis)[8] or from the active borders of advancing lesions.[4]

Recalcitrant and recurrent infections

Refractory dermatophyte infections may occur even in patients who are seemingly immunologically intact. Recalcitrant dermatophyte infections often are caused by *T. rubrum*. *T. rubrum* may invade beyond the stratum corneum to involve the follicles, progressing to form chronic inflammatory lesions. Once this organism becomes established, it tends to spread and become chronic. Although a response may be obtained with topical or systemic therapy, there is recurrence in 60% to 70% of patients. Frequently these infections require prolonged therapy with systemic and topical agents for 2 to 3 months or longer, often with high doses (as many as 2 gm per day) of griseofulvin.

Even after such infections appear to be cleared, it may be difficult to prevent recurrences. Recurrence may sometimes be caused by failure to eradicate the original infection rather than by reinfection.

Part of the recurrence problem may stem from undertreatment. Patients frequently stop applying topical therapy when their symptoms improve. Unfortunately, most topical antifungals are fungistatic rather than fungicidal, and short courses of therapy may not eliminate the pathogen. For that reason, when a patient has a recurrence of tinea pedis or tinea cruris within a year of being cleared, culture frequently reveals the same organism that was found in the initial infection. Recalcitrant infections are best treated with ketoconazole or the newer triazoles.

Infections in patients who are immunocompromised

An active immune system is critical to achieve a mycologic cure; in patients with an immune deficiency, especially those infected with human immunodeficiency virus (HIV), fungal infections can be severe, aggressive, and persistent. Frequently, these infections are caused by *T. rubrum*.[11] Childhood types of infections, such as tinea capitis, can occur in an adult with HIV disease. Likewise, "white nails" caused by a dermatophyte are characteristic of patients with HIV disease. Many other types of immunodeficient patients are at increased risk for opportunistic fungal infections, including those with an organ transplant, those who take immunosuppressant or myelotoxic drugs, and patients with lymphoma, leukemia, diabetes, a primary immunodeficiency, or an autoimmune disorder.

Patients with locally compromised immunity resulting from the use of topical steroids are also at risk for infection. Fungal lesions that are mistaken for eczema or dry skin and treated with topical steroids tend to become more severe. One of my patients originally had received a diagnosis of psoriasis of the buttocks and was treated with a potent topical steroid, which resulted in expanding rings of dermatophyte infection. In another patient, treatment with topical steroids for what was believed to be lupus erythematosus resulted in extensive dermatophyte spread. The initial clinical response of such patients can be misleading, because the infection at first appears to subside as a result of the steroid's antiinflammatory activity. The initial response may be followed by an extensive, progressive infection. The adverse effects of treating dermatophyte infections with topical steroids call into question the use of combination products that contain antifungal and steroid drugs. A patient's use of over-the-counter treatments can also result in a misleading clinical appearance; these agents may reduce signs and symptoms but can fail to produce a mycologic cure.

Zoologically acquired infections

The diagnosis and treatment of zoologically acquired infections are potential problems because some may be highly inflammatory and unusual in appearance. Infections transferred from household pets such as dogs and cats are not uncommon and are usually easily diagnosed. Occupational exposures are more unusual and are therefore more easily misdiagnosed. For these reasons it is worthwhile to inquire about a patient's occupation and whether it involves exposure to animals, especially when a lesion is morphologically atypical or fails to respond to treatment.

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PRESENTED AT THE SYMPOSIUM, "CUTANEOUS DERMATOPHYTE INFECTIONS: PATHOGENESIS AND TREATMENT," SUPPORTED BY AN EDUCATIONAL GRANT FROM SANDOZ PHARMACEUTICALS CORPORATION

Progression of interdigital infections from simplex to complex

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The dynamics of symptomatic toe web infections often involve an ecologic interplay in which an initial dermatophyte infection provides a hospitable niche for subsequent colonization by bacteria. Several studies suggest that exacerbation of a mild dermatophyte infection (dermatophytosis simplex) can arise in the occlusive environment of the toe web space. Fungal infection induces damage to the stratum corneum, which allows overgrowth of resident bacteria and maceration, itching, and often malodor at the site (dermatophytosis complex). Because fungi frequently elaborate antibacterial substances, the superinfecting bacteria generally are resistant to penicillin and other antibiotics. A flourishing bacterial superinfection may mask the underlying fungal cause, making it difficult to obtain a positive fungal culture. (J AM ACAD DERMATOL 1993;28:S7-S11.)

Historically, interdigital toe infections have been categorized as fungal diseases. Dermatology texts commonly designate these conditions as tinea pedis or foot ringworm and assign them to a chapter on dermatophyte infections.[1] Although this classification is convenient, it does not tell the whole story.

Reported rates of viable dermatophyte recovery from macerated interspaces are generally only in the 30% range. Furthermore, in patients from whom fungus is recovered, concentrations of the organisms tend to be low.[2] A survey of the literature indicates the difficulty in recovering fungi from interdigital lesions (Table I).[2]

Furthermore, another well-reported discrepancy that requires an explanation is that some persons appear to be carriers of dermatophytes but show no clinical signs of infection of toe webs: dermatophyte fungi can be cultured from 9% to 21% of clinically normal interspaces.[1-3, 9]

RELATIONSHIP BETWEEN FUNGI, BACTERIA, AND ENVIRONMENT

The paradoxical phenomenon described above has become more understandable through studies that have evaluated the histologic location of the fungus, secondary invasion by bacteria, and environmental conditions. The recovery of dermatophytes from clinically normal interspaces might be possible because the stratum corneum in the inter-

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PRESENTED AT THE SYMPOSIUM "ONYCHOMYCOSIS: ISSUES AND OBSERVATIONS," SUPPORTED BY AN UNRESTRICTED EDUCATIONAL GRANT FROM JANSSEN PHARMACEUTICA

Chronic dermatophytosis caused by *Trichophyton rubrum*

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We believe that patients are genetically predisposed to *Trichophyton rubrum* infections in a dominant autosomal pattern and that persons with distal subungual onychomycosis caused by *T. rubrum* invariably have preexisting *T. rubrum* tinea pedis of the soles. This relationship has many potentially important clinical implications with respect to diagnosis, treatment, and the prevention of reinfection. (J Am Acad Dermatol 1996;35:S17-S20.)

In 1972, Zaias[1] proposed four clinical types of fungal nail disease, each of which has its own host-parasite relationship. The most common is distal subungual onychomycosis, which is usually caused by invasion of the distal portion of the nail bed by *Trichophyton rubrum*, and less commonly by *Epidermophyton floccosum* or *Scytalidium* species. The other primary types of fungal nail infections are proximal subungual onychomycosis (also usually caused by *T. rubrum*), white superficial onychomycosis (caused by *T. mentagrophytes*), and onychomycosis caused by *Candida albicans*.

However, as the preceding nomenclature has illustrated, the term, "onychomycosis," is too general to be used for diagnostic and treatment purposes. For accuracy, fungal nail infections should always be differentiated according to both their site(s) of involvement and the causative pathogen(s).

This paper discusses a possible genetic link in distal subungual onychomycosis, with particular emphasis on the host-parasite relationship of *T. rubrum* infections.

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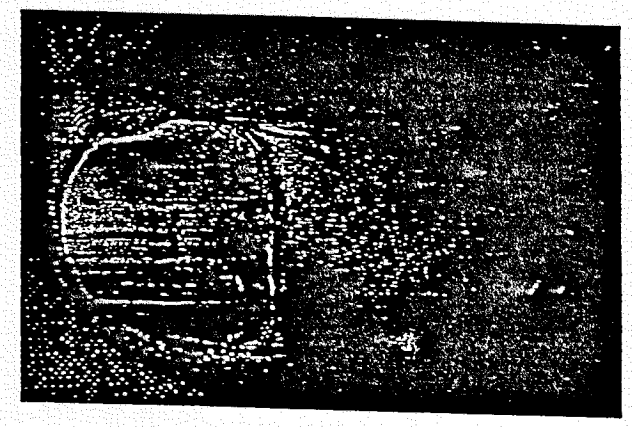

Fig. 1. Distal subungual onychomycosis. *T. rubrum*, early invasion of nail bed—nail plate not involved.

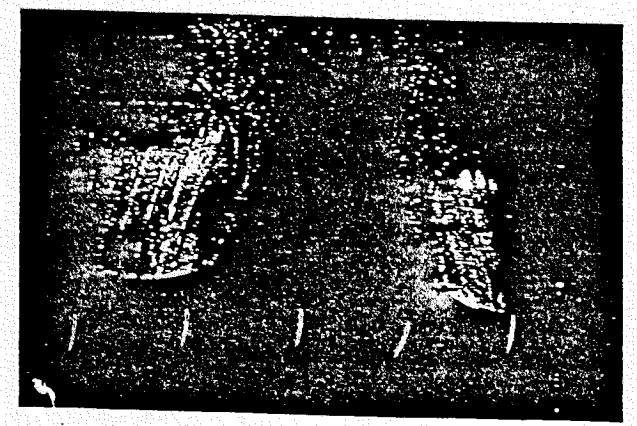

Fig. 2. Distal subungual onychomycosis. *T. rubrum*. Total involvement of nail beds with intact nail plates.

Fig. 3. Distal subungual onychomycosis by *T. rubrum*. End view of toe to show thick nail bed hyperkeratosis. This increase of stratum corneum is seen in a minority of patients.

Fig. 6. Distal subungual onychomycosis by *T. rubrum*. Note damaged nail plate produced by patient's attempt to clean accumulated debris under nail.

Fig. 4. Longitudinal section of toe with distal subungual onychomycosis by *T. rubrum* demonstrating normal nail plate and fungus in nail bed. Severe nail bed hyperkeratosis uplifting nail plate (Hematoxylin-eosin stain; original magnification ×4).

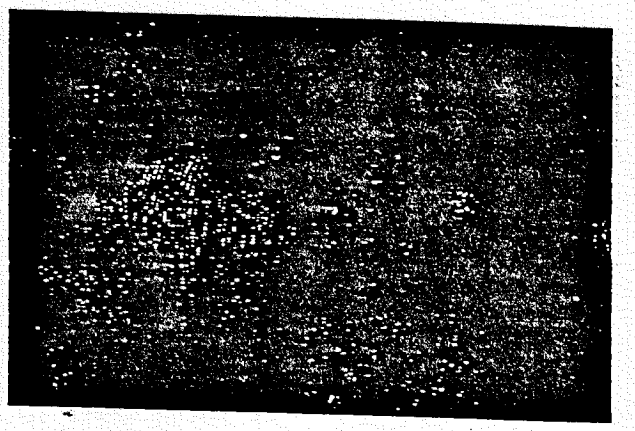

Fig. 7. *T. rubrum* chronic dermatophyte syndrome showing often missed corneal collarette remnant of a minute vesicle, asymptomatic but KOH positive. This minimal sign is more common than the more inflammatory moccasin-type tinea pedis.

Fig. 5. Cross section of toe in Fig. 4 (Hematoxylin-eosin stain; original magnification ×4).

DISTAL SUBUNGUAL ONYCHOMYCOSIS

Distal subungual onychomycosis is exclusively a nail bed disease, as shown in Figs. 1-3. Histologic studies by Zaias[2] have shown that the nail bed remains intact, even when there is massive nail plate hyperkeratosis leading to actual uplifting of the nail plate (Figs. 4 and 5). Nail plate changes are almost invariably traumatic or otherwise inflicted by the patient (Fig. 6). In some cases, a patient may present with a normal nail plate, but have a nail bed that is almost completely disrupted (Figs. 2 and 3). The degree of subungual debris varies markedly from one person to another, possibly because of differences in

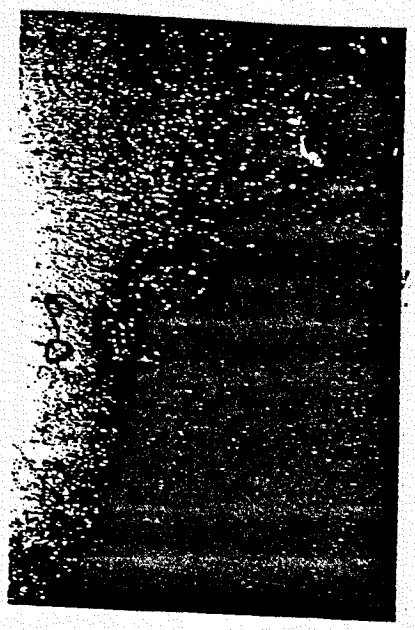

Fig. 8. Tinea cruris by *T. rubrum*. This patient must have tinea pedis as shown in Figs. 10 and 11.

Fig. 9. Tinea pedis interdigitalis by *T. rubrum*. An opportunistic episodic phenomenon in chronic dermatophyte syndrome by *T. rubrum* and *T. mentagrophytes*.

Fig. 10. Plantar thick stratum corneum collarettes and scales by *T. rubrum*, usually on weight-bearing plantar surfaces.

Fig. 11. Mild case of moccasin-type tinea pedis by *T. rubrum*.

cellular immunity reactions to the antigens released by the fungus.

CHRONIC *T. RUBRUM* DISEASE[3]

The question of whether distal subungual onychomycosis might be associated with other infections caused by *T. rubrum* at other sites led Zaias[3] to examine the soles of more than 2000 patients with distal subungual onychomycosis during a 20-year period. This investigation revealed that although only about 1% to 2% of patients had typical moccasin-type tinea pedis caused by *T. rubrum*, most had nonsymptomatic. *T. rubrum*-related tinea pedis that consisted of asymptomatic microvesicles with little or no erythema on the soles.[4]

A study performed by the authors and colleagues in Argentina and France confirmed that patients with *T. rubrum*-related distal subungual onychomycosis almost invariably had disease on the soles, and that these conditions are inherited.[4] Namely, at least one parent had a similar infection confirmed by clinical examination, KOH, or culture. If the patient had children, there was a high likelihood that they, too, had the same infection. This raised the question of why some persons are more susceptible to this infection than others. For example, in a family of five children, tinea pedis may develop only in three.

Based on these data, it was concluded that certain persons may inherit a susceptibility to *T. rubrum* infection in a dominant autosomal pattern. The clini-

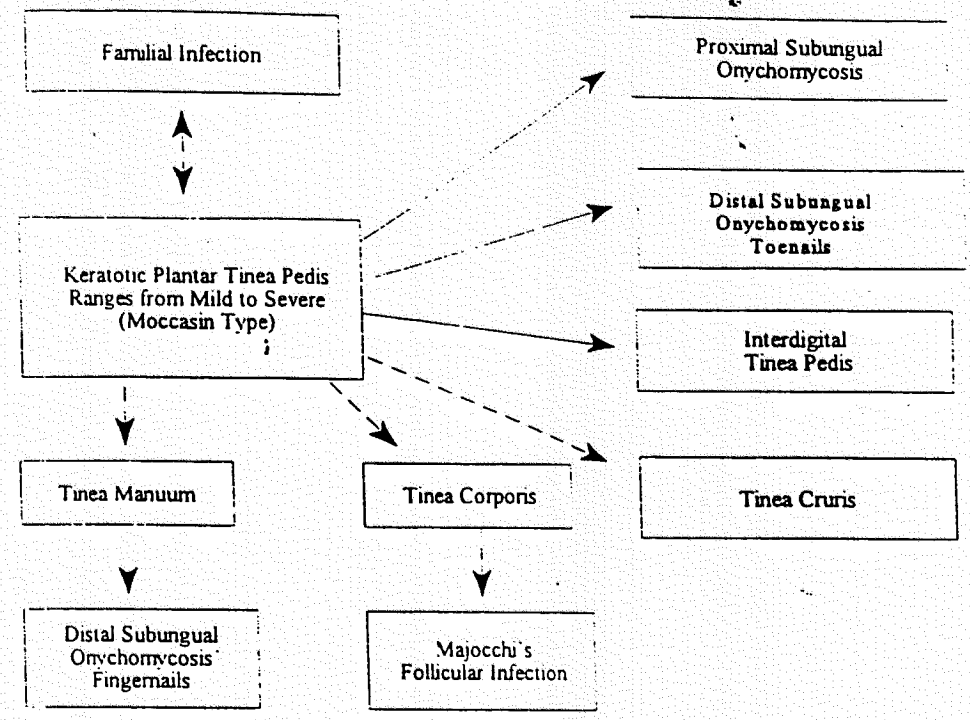

Fig. 12. Clinical signs of chronic dermatomycosis syndrome by *Trichophyton rubrum*.

cal signs of chronic dermatophytosis associated with this disease are shown in Fig. 12. As children, patients with this disease harbor this pathogen on the soles (Fig. 7), but it is not until a later time that the infection spreads to their toenails (Figs. 1 through 3 and 6). It may also spread episodically to the groin (Fig. 8), toe interspaces (Fig. 9), the palms and fingernail beds, other sites on the skin, and even to hair follicles.

The host's own biochemical or immune response to the pathogen determines the clinical appearance of the lesions. Hence, the wide variability in the clinical presentation of tinea pedis, which may range from a few, almost invisible vesicle remnants on the feet (Figs. 7 and 10) to the more readily recognized but less prevalent inflammatory moccasin-type disorder (Fig. 11).

Unless some method is employed for preventing reinfection of the soles with *T. rubrum*, distal subungual onychomycosis will inevitably recur, because transmission is from the sole to the nails rather than vice versa.

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