FITZPATRICK'S

DERMATOLOGY IN GENERAL MEDICINE

SIXTH EDITION

Note: Dr. Stephen Katz's work as editor and author was performed outside the scope of his employment as a U.S. government employee. This work represents his personal and professional views and not necessarily those of the U.S. government.

FITZPATRICK'S DERMATOLOGY IN GENERAL MEDICINE
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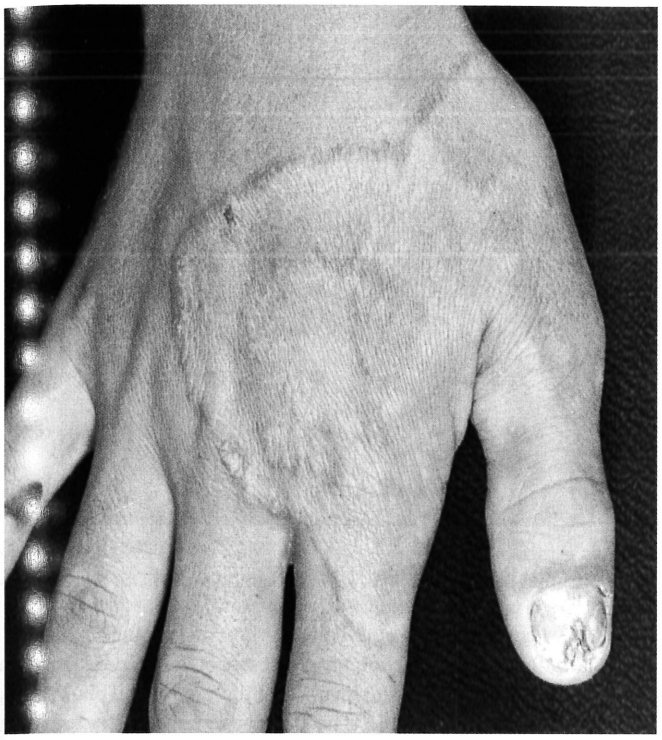
FIGURE 205-18



Tinea manus. Polycyclic pattern of an eruption composed of scaling vesicles with involvement of the thumb nail; the nail exhibits destruction of the nail plate.

include psoriasis, soft corns, bacterial coinfection, candidiasis, and erythrasma. The likelihood of candidal and bacterial infection increases with the severity of maceration, denudation, and pruritus.[51] Unlike tinea pedis, erythrasma fluoresces coral red under a Wood lamp. The hyperkeratotic type must be differentiated from psoriasis, hereditary or acquired keratodermas of the palms and soles, dyshydrosis, pityriasis rubra pilaris, and Reiter's syndrome. Contact dermatitis may also be considered, although it more commonly affects the dorsal foot than tinea pedis. Children are more likely to have peridigital dermatitis or atopic dermatitis. Vesiculobullous or vesiculopustular presentations may be confused with pustular psoriasis, palmoplantar pustulosis, and bacterial pyodermas.

PREVENTION AND TREATMENT Minimizing chronic moisture is important in preventing tinea pedis. This may be achieved through talcum powder, absorbent socks, nonocclusive shoes, and, occasionally, 20 to 25% aluminum chloride hexahydrate powder. Antifungal powders such as undecylenic acid and tolnaftate are also beneficial.[38] Mild interdigital tinea pedis without bacterial involvement can be treated topically with an allylamine, azole, ciclopirox, tolnaftate, or undecenoic acid.[52] Topical terbinafine for 1 week is 66 percent effective,[53] while the other topicals generally require 4 to 6 weeks of application.

The newer oral antifungals have replaced griseofulvin as the treatments of choice for severe or refractory tinea pedis. The dosing schedule of terbinafine is 250 mg daily for 2 weeks. Effective regimens of itraconazole for adults are 200 mg twice daily for 1 week, 200 mg daily for 3 weeks, or 100 mg daily for 4 weeks,[44] while children should receive 5 mg/kg per day for 2 weeks.[45] Fluconazole 150 mg weekly for 3 to 4 weeks or 50 mg daily for 30 days is also effective.[44] Associated onychomycosis is common; if present, treatment of the onychomycosis is necessary to prevent recurrence of tinea pedis.

Maceration, denudation, pruritus, and malodor obligate a search for bacterial coinfection by Gram stain and culture. Antibiotics should be started once bacterial infection is documented and chosen based on sensitivity studies. Adjunctive topical therapy such as 0.25% acetic acid for *Pseudomonas* and colorless Castellani's paint are also helpful.

Finally, because vesiculobullous tinea pedis is the result of a T cell–mediated immune reaction, symptomatic relief with topical or systemic corticosteroids may be warranted during the beginning of antifungal treatment.[54]

ONYCHOMYCOSIS

Onychomycosis denotes any infection of the nail caused by dermatophyte fungi, nondermatophyte fungi, or yeasts. Tinea unguium, however, refers strictly to dermatophyte infection of the nail plate. The four clinical types of onychomycosis are: (1) distal subungual onychomycosis (DSO), (2) proximal subungual onychomycosis (PSO), (3) white superficial onychomycosis (WSO), and (4) candidal onychomycosis.

Epidemiology

Onychomycosis is a common infection, with a prevalence estimated at 2 to 18 percent worldwide and up to 48 percent incidence by age 70.[55] Higher rates of onychomycosis are associated with male gender, age, smoking, and peripheral arterial disease.[56] Finally, 30 percent of patients with dermatophytoses elsewhere also have tinea unguium. The dermatophytosis commonly begins as tinea pedis before extending to the nail bed, where eradication is more difficult. This site then serves as a reservoir for recurrent distal infections, particularly in the setting of a hot and humid environment created by occlusion or tropical climates.[1]

Etiology and Pathogenesis

The dermatophytes, especially *T. rubrum, T. mentagrophytes* var. *interdigitale, T. tonsurans,* and *E. floccosum,* cause the great majority of onychomycosis. Table 205-5 categorizes the most likely causative dermatophytes according to patterns of concurrent infection in other areas.[57]

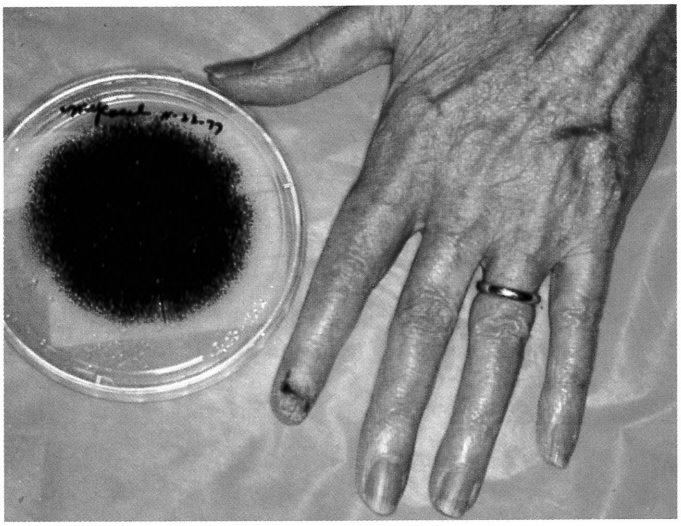
Yeasts are the source of approximately 5 percent of onychomycosis, the majority of which is caused by *Candida albicans* and occurs in conjunction with chronic mucocutaneous candidiasis. The nondermatophyte molds *Acremonium, Aspergillus, Fusarium, Onychocola canadensis, Scopulariopsis brevicaulis,* and *Scytalidium dimidiatum* account for approximately 4 percent of onychomycosis.[55] The nondermatophyte molds appear to have a predilection for antecedently diseased or aged nails (Fig. 205-19).[38]

TABLE 205-5

Causative Organisms According to Anatomic Patterns of Infection

Tinea unguium + tinea pedis and/or tinea corporis
T. rubrum
T. mentagrophytes var. interdigitale
E. floccosum
Tinea unguium + tinea capitis or favus
T. tonsurans
T. violaceum
T. megninii
T. schoenleinii
Tinea unguium + tinea imbricata
T. concentricum

FIGURE 205-19



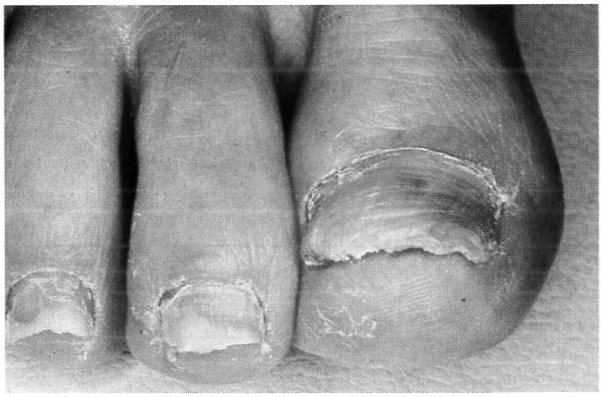
Onychomycosis can be caused by nondermatophyte fungi such as *Aspergillus niger.*

DSO may be caused by any of the organisms listed above, beginning with invasion of the stratum corneum of the hyponychium and distal nail bed. The infection then spreads proximally up the nail bed to the ventral nail plate. Hyperproliferation of the nail bed in response to the infection creates subungual hyperkeratosis, and progressive invasion of the nail plate results in an increasingly dystrophic nail. PSO results primarily from *T. rubrum* and *T. megninii* infection of the proximal nail fold, which then spreads to the proximal ventral nail plate.[58] *T. rubrum* causes PSO almost exclusively in those infected with HIV.[6] WSO is a direct invasion of the dorsal nail plate. Seen only on toenails, it is usually caused by *T. mentagrophytes,* although nondermatophyte molds such as *Aspergillus, Scopulariopsis,* and *Fusarium* are also known etiologies. *Candida* species invade via the hyponychial epithelium to affect the entire thickness of the nail plate.[58]

Clinical Manifestations

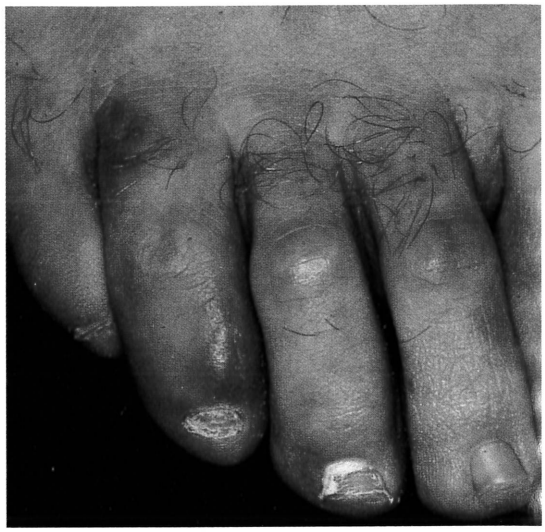
DSO (Fig. 205-20), the most common form, begins as a whitish to brownish-yellow opacification at the distal edge of the nail or near the

FIGURE 205-20



Distal subungual onychomycosis.

FIGURE 205-21



Proximal subungual onychomycosis in a patient with AIDS; Kaposi's sarcoma is also seen on the fourth toe.

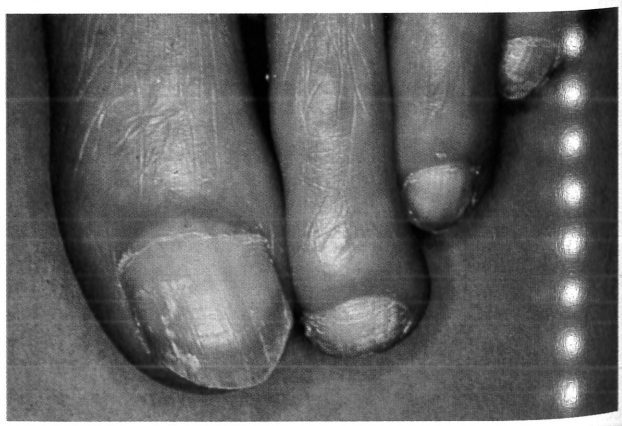
lateral nail fold. As the infection progresses, subungual hyperkeratosis leads to onycholysis. Increasing invasion of the ventral nail plate makes it thick, discolored, and friable. The subungual debris also provides a site for secondary infection by bacteria, other molds, and yeasts.

Early PSO (Fig. 205-21) is evident as a white to beige opacity on the proximal nail plate that may gradually enlarge to affect the entire nail. WSO (Fig. 205-22) is recognized as white to dull yellow sharply bordered patches anywhere on the surface of the toenail. The affected areas are rough and friable, and may coalesce with time. Candidal onychomycosis is rare, affecting either the fingernails or toenails of those with chronic mucocutaneous candidiasis. These lesions resemble DSO as the nail may be thickened, rough, and opaque or darkened. Nailbed thickening also occurs and may be severe enough to create "pseudoclubbing."[58] In contrast to DSO, a paronychial inflammatory response is often present, and subungual debris does not accumulate.[32]

Laboratory Findings

Because onychomycosis is responsible for only 50 percent of dystrophic nails, laboratory diagnostic confirmation is often helpful prior to treatment with an oral antifungal. KOH examination, nail biopsy, and fungal

FIGURE 205-22



White superficial onychomycosis.

culture on SDA (with and without antimicrobials) are most useful. However, microscopy is often negative even when there is a high clinical suspicion of onychomycosis, and nails with positive microscopy often yield negative cultures. As most false-negatives are caused by sampling error, the simplest measures to maximize yield are to maximize sample size and perform repeat collections.[59]

Finally, because of the difficulty in discerning pathogens from contaminants, the following guidelines should be followed: (1) if a dermatophyte is isolated on culture, it is a pathogen; (2) if a nondermatophyte mold or yeast is cultured, it is considered significant only if hyphae, spores, or yeast cells are seen on microscopic examination; and (3) confirmation of an infection by a nondermatophyte requires repeated isolation, classically defined as at least 5 of 20 inocula without concurrent isolation of a dermatophyte.[60]

Pathology

Hyphae are seen lying between the nail laminae parallel to the surface, with a predilection for the ventral nail and nail bed stratum corneum.[61] The epidermis may show spongiosis and focal parakeratosis and there is a minimal dermal inflammatory response. In WSO, the organisms are present superficially on the dorsal nail and display unique "perforating organs" and "eroding fronds." Candidal onychomycosis displays invasion of pseudohyphae throughout the entire nail plate, adjacent cuticle, granular layer and stratum spinosum of the nail bed, and the hyponychial stratum corneum.[58]

Differential Diagnosis

A variety of disorders may cause nail changes similar to onychomycosis, including hand eczema, pachyonychia congenita, Darier's disease, Reiter's syndrome, lichen planus, exfoliative dermatitis, and Norwegian scabies. Neither the pitting produced by psoriasis nor the typically transverse ridges seen in the dystrophic nails of hand eczema are seen with fungal nail infections. Otherwise, most of the above disorders are differentiated by related skin findings and history. WSO must be distinguished from the acquired and congenital leukonychias. All leukonychia of the fingernails not WSO.

Treatment

The only effective topical agent for tinea unguium is ciclopirox (8% lacquer) applied daily for 48 weeks. When used for mild to moderate disease, it is 34 percent effective in achieving mycologic cure alone and 7 percent effective in achieving mycologic cure and clear nails.[62] Despite its poorer efficacy when compared to the newer oral antifungals, topical ciclopirox is more cost effective because of its relatively low cost.[63]

Oral antifungals may be used for refractory, severe, or nondermatophytic onychomycosis, or when a shorter treatment regimen is desired. Selecting an antifungal should be based primarily on the causative organism, potential adverse effects, and drug interactions. As potent inhibitors of cytochrome P450 3A4, the azole antifungals are contraindicated with drugs such as astemizole, terfenadine, lovastatin, simvastatin, triazolam, and midazolam. Baseline and interval testing of liver enzymes is prudent for each agent discussed below.

Terbinafine is fungicidal against dermatophytes, *Aspergillus,* and *Scopulariopsis,* but demonstrates variable activity against *Candida* species. A course of 250 mg daily for 6 weeks is effective for most fingernail infections, while a 12-week course is required for toenail infections. Most adverse effects are gastrointestinal, and cytochrome P450 interactions are insignificant.

Itraconazole is fungistatic against dermatophytes, nondermatophyte molds, and yeasts. Safe and effective schedules include pulse dosing at 400 mg daily for 1 week per month or a continuous dose of 200 mg daily, both of which require 2 months of treatment for fingernails and 3 months for toenails.[55] Children may receive 5 mg/kg daily.[45] Elevated liver enzymes occur in 0.3 to 5 percent of patients, returning to normal within 12 weeks of discontinuation.

Fluconazole is fungistatic against dermatophytes, some nondermatophyte molds, and *Candida*. The usual dosage is 150 to 300 mg once per week for 3 to 12 months, although 450 mg weekly may be used in refractory onychomycosis. Adverse effects include gastrointestinal disturbance and elevated liver enzymes.[55]

Griseofulvin is no longer considered standard treatment for onychomycosis because of its adverse effects, drug interactions, prolonged treatment course, and low cure rates. Final options for refractory cases include surgical avulsion or chemical removal of the nail with 40% urea compounds in combination with topical or oral antifungals.[64]

TINEA NIGRA

Tinea nigra is a rare infection, usually of the palmar stratum corneum, caused by the nondermatophyte *Phaeoannellomyces werneckii* (formerly called *Exophiala werneckii*).

Epidemiology

Tinea nigra usually occurs in tropical or subtropical areas, including Central and South America, Africa, and Asia. Of the approximately 150 cases reported in North America since 1950, the majority were associated with tropical travel.[65] However, endemic foci exist in the coastal southeastern United States. Person-to-person transmission is rare.[66]

Etiology

Nearly always caused by *Phaeoannellomyces werneckii,* other dematiaceous fungi may produce the disease. *Stenella araguata,* for example, has been isolated from clinical tinea nigra. Such dematiaceous fungi are commonly found in soil, sewage, and decaying vegetation,[66] although *P. werneckii* was also recently isolated from the surfaces of rocks in the Mediterranean and Northern Europe.[67]

Clinical Manifestations

Tinea nigra presents as an asymptomatic, mottled brown to greenish-black macule with minimal to no scale (Fig. 205-23). The macule is often darkest at the advancing border. Although usually seen on the palm or ventral surface of the fingers, plantar involvement is possible.

Laboratory Findings

KOH examination of scrapings from the lesion reveals brown to olive-colored hyphae and oval to spindle-shaped yeast cells occurring singly or in pairs with a central transverse septum. Cultures may be performed on SDA with cycloheximide and chloramphenicol. Growth is initially yeastlike and brown to shiny black, appearing as the typical two-celled yeast forms under microscopic examination. With time, mycelial growth predominates as aerial hyphae create a fuzzy grayish-black colony. Deeply pigmented, thick, septate hyphae 7 to 10 μm in diameter are seen microscopically.

Pathology

Skin biopsy shows brown, branching hyphae in the upper stratum corneum on hematoxylin and eosin stain. Hyperkeratosis is present without dermal inflammation.

of topical terbinafine with clotrimazole in the treatment of tinea pedis, a significantly higher cure rate and lower relapse rate for terbinafine was reported.[16,17] In summary, topical allylamines, especially terbinafine, are marginally superior to topical imidazoles in cure rates and probably require shorter duration of therapy. Terbinafine is now available over the counter.

Butenafine, the newest topical antifungal agent, is the only member of the benzylamine class of antifungals. It is structurally similar to the allylamines, and like the allylamines, it works by inhibiting squalene epoxidase. Like the allylamines it is both fungistatic and fungicidal. The minimal fungicidal concentrations for butenafine are 4 to 130 times lower than for naftifine, tolnaftate, clotrimazole, and bifonazole.[18] Like the allylamines, this drug also demonstrates anti-inflammatory effects as measured by reduced cutaneous erythema in response to UVB irradiation.[19] Results in clinical trials suggest that it is very similar to the allylamines in terms of clinical responses.

Tinea unguium is the third major category of superficial dermatophytoses. Although pharmacokinetic studies demonstrate that imidazoles and allylamines are capable of penetrating the nail plate in concentrations sufficient to exceed the MICs of most dermatophytes,[20] they typically fail to produce clinical cures. A prescription product composed of triacetin, sodium propionate, benzalkonium chloride, cetylpyridium chloride, and chloroxylenol has been marketed in a tincture base (Fungoid) for the treatment of onychomycosis. An uncontrolled study has reported a 100 percent cure rate after 12 months of treatment; however, treatment also included monthly nail débridement and there was only a 2-month follow-up. Because of its excellent penetration of the nail plate, ciclopirox nail lacquer 8% solution was developed and introduced for the topical treatment of onychomycosis. The most commonly used treatment regimen is to apply the lacquer to the affected nail once per day for 48 weeks. The reported mycologic cure rates have ranged from 29 to 85.7 percent with the meta-analytic average cure rate being 53 percent. The reported relapse rate is 21 percent.[21] Ciclopirox nail lacquer has an advantage over systemic antifungal agents in that it does not require physician monitoring, laboratory testing is not required, and it has a reduced cost per mycologic cure.[21]

CANDIDIASIS (CANDIDOSIS)

Candida albicans is the primary pathogen in most cases of superficial candidiasis, although other species, such as *C. parapsilosis* and *C. guilliermondii,* may also produce infection (see Chap. 206). *Candida* species are commensal organisms that usually require a change in the host milieu, usually alterations in nutrition (e.g., diabetes mellitus), microbial flora (e.g., antibiotic therapy), or host immune defenses (e.g., neutropenia) to produce infections. This is an important consideration in assessing the efficacy of topical therapies, since the recurrence rate is very high if the underlying disease is not corrected.

Before the advent of the imidazoles, the polyenes were the mainstay of topical candidial therapy. There are more than 80 polyene antibiotics, but only nystatin and amphotericin B have been used as topical agents. Polyene antimycotics are primarily fungistatic at low concentrations and fungicidal at high concentrations. They act by binding irreversibly with ergosterol in the cell membrane, which leads to altered cellular permeability and leakage of cell contents. Nystatin is available in powder, suspension, lozenges, and as creams for topical therapy. The suspension and lozenge formulations are used for oral candidiasis, and the powder and creams are used for cutaneous infections. Older studies comparing topical nystatin with imidazoles suggested that the two were comparable in efficacy, but more recent studies suggest that imidazole drugs are more effective than nystatin in vaginal candidiasis.[22] This may be related to the increased nystatin resistance which is now observed in up to 20 percent of isolates. Nystatin resistance may be encountered in wild strains (primary resistance) but may also be induced during therapy (secondary resistance). Nystatin and amphotericin, while effective against candidial infections, are not effective against dermatophytes.

Topical imidazoles are the mainstay of topical therapy for candidiasis. Imidazoles are available as lotions, creams, and troches (clotrimazole). Clotrimazole troches are used for the management of oral candidiasis, and imidazole lotions and creams are used for superficial cutaneous candidiasis. The susceptibility of different strains of *C. albicans* to imidazoles is highly variable (MIC of 0.5 to 100 μg/mL). The implication of this difference in susceptibility to imidazoles has not been studied to determine if it is clinically significant in terms of response rates. All of the topical imidazoles are clinically and mycologically effective in treating superficial candidal infections and can be used interchangeably. As discussed in the management of dermatophyte infections, there is evidence to suggest that clotrimazole and miconazole are potentially irritating and may not be the preferred imidazoles in sensitive flexural areas infected with *Candida.*

Ciclopirox olamine, like the imidazoles, is a broad-spectrum antimycotic drug that is effective against *Candida* species. Ciclopirox olamine is indicated for the management of cutaneous candidial infections but it does not come in formulations for oral use. Head-to-head studies comparing this drug to the topical imidazoles have not been done, but ciclopirox olamine appears to be equivalent to the topical imidazoles in terms of clinical efficacy.

Topical allylamines (naftifine, terbinafine) demonstrate moderate activity against yeast, including *Candida* species. In vitro studies demonstrate that *Candida* species are more sensitive to the imidazole class of drugs than the allylamines.[8] Despite the higher measured in vitro MICs for yeasts, clinical studies have demonstrated that most cases of cutaneous candidiasis can be successfully treated with topical allylamines; they compare with topical imidazoles in terms of mycologic cure. Despite the therapeutic efficacy of the allylamines, they should not be considered as a primary topical therapy for candidiasis because they are expensive, have not received approval for this indication, and demonstrate less-favorable MICs.

PITYROSPORUM (*MALASSEZIA*) INFECTIONS

Pityrosporum orbiculare is a lipophilic yeast that produces superficial fungal infections in the form of tinea (pityriasis) versicolor and, less commonly, as a folliculitis (see Chap. 206). Because these two forms of infection respond to the same topical therapies, they are discussed together. Because this yeast is a normal component of the skin flora, its total eradication is usually not possible by using topical therapies. The ubiquitous nature of the organism also accounts for the high recurrence rate following treatment. For this reason, it is difficult to compare different studies since the follow-up periods are usually of different lengths. Patients with extensive involvement are usually best treated with oral antimycotics, whereas patients with limited involvement may be treated with either systemic or topical antimycotics. A number of less-conventional agents that are not regarded as antimycotics have been reported in the literature, including salicylic acid, propylene glycol, and zinc pyrithione. These are not discussed because they do not appear to offer significant advantages over specific antimycotic agents.

Selenium sulfide (2.5%) lotion has been shown in uncontrolled and controlled studies to be useful in the management of both tinea versicolor and *Pityrosporum* folliculitis. A variety of different methods and durations of applications have been utilized but one of the most

CHAPTER 261

Nellie Konnikov
Helen Raynham

Oral Antifungal Agents

Oral antifungal agents are now widely and frequently used for the treatment of superficial fungal infections.[1] The first and the only synthetic agent was griseofulvin. Subsequently, other drugs, including amphotericin B and ketoconazole, were introduced. As a result of recent advances in antifungal chemotherapy, new drugs with a broad spectrum of activity, high efficacy, tolerability, and rare, mild side effects are now available. The three newer, released oral antifungal agents are the first oral allylamine, terbinafine, and the triazoles fluconazole and itraconazole.

ALLYLAMINES

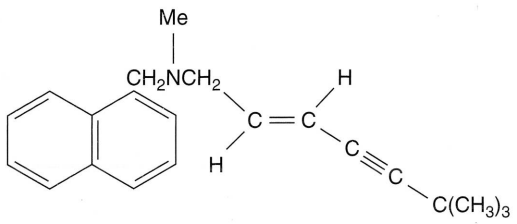
Terbinafine

Terbinafine hydrochloride is a synthetic antimycotic agent that belongs to a new family of compounds known as the allylamines. All allylamine derivatives possess a tertiary allylamine, a structural component crucial for antifungal activity (Fig. 261-1).[2] In vitro the drug is primarily a fungicidal agent and highly active against dermatophytes, but less active against molds, dimorphic fungi, and various yeasts.

PHARMACOLOGY Terbinafine is well absorbed from the gastrointestinal tract, mostly in chylomicrons. The distribution half-life is 1.5 h, and the elimination half-life is approximately 22 h.[3] Terbinafine is highly lipophilic and keratophilic in nature and, therefore, is widely distributed upon absorption throughout skin and adipose tissue. Terbinafine is extensively biotransformed by the liver, mostly through oxidation by a very small fraction of P450 isoenzymes. More than 80 percent of the drug is excreted in urine; the rest is eliminated with feces.[4]

MECHANISM OF ACTION Terbinafine inhibits the enzyme squalene epoxidase in the fungal membrane, thereby blocking the biosynthesis of ergosterol.[5] Squalene epoxidase, a complex, microsomal, noncytochrome P450 enzyme, catalyzes the first enzymatic step of ergosterol synthesis—the conversion of squalene into squalene epoxide. Consequently, terbinafine causes an abnormal intracellular accumulation of squalene and deficiency in ergosterol.[6] Accumulation of squalene accounts for the drug's fungicidal activity, whereas in vitro deficiency of ergosterol is associated with the drug's fungistatic activity.[6]

FIGURE 261-1



Terbinafine.

CLINICAL USES

Pediatric For the treatment of tinea capitis in children, the dosage guidelines are 3 to 6 mg/kg per day.[7] Children weighing 10 to 20 kg can be given 62.5 mg/day; children weighing 20 to 40 kg can be given 125 mg/day; and those children weighing more than 40 kg can be given 250 mg/day.[8] The treatment course for *Trichophyton* infections is 4 weeks. In a study of tinea capitis in children, comparing a 4-week course of terbinafine with an 8-week course of griseofulvin (10 mg/kg day), oral terbinafine was shown to have efficacy similar to griseofulvin.[9] Other studies suggest that for treatment of *M. canis* with terbinafine, 6 or more weeks may be needed.[8,10]

Adult Terbinafine is indicated for the treatment of onychomycosis of the toenails and fingernails caused by dermatophytes.[11] In a study comparing continuous terbinafine with intermittent itraconazole in the treatment of toenail onychomycosis, terbinafine was significantly more effective than itraconazole in the treatment of toenail dermatophyte onychomycosis.[12] At week 72, the mycologic cure in those patients treated with a 3-month course of terbinafine was 75.5 percent, compared with a mycologic cure rate of 38.3 percent in those patients treated with a 3-month course of intermittent pulse therapy with itraconazole. Terbinafine is superior to itraconazole in maintaining mycologic and clinical cure for at least 2 years after completion of therapy.[13] In a study of 22 patients with tinea corporis and tinea cruris who used terbinafine 250 mg daily for 1 week, 100 percent clinical and mycologic clearing was observed at 6 weeks.[14] In a study of moccasin tinea pedis and tinea manuum, after a 2-week course of terbinafine 250 mg daily, there was an 86 percent mycologic cure rate at 8 weeks.[15] A placebo-controlled trial demonstrated that a 4-week course of terbinafine 250 mg daily was effective in the treatment of seborrheic dermatitis.[16] Terbinafine is not effective orally for the treatment of tinea versicolor.[14]

Geriatric Terbinafine is well tolerated by the elderly.[17]

Pregnancy considerations Terbinafine is a pregnancy category B drug and should not be taken by nursing mothers.[11]

DOSAGE SCHEDULES AND FORMULATIONS Terbinafine is supplied as a 250 mg tablet and should be taken once daily for 6 weeks for fingernail onychomycosis and once daily for 12 weeks for toenail onychomycosis. Pretreatment serum transaminase tests are advised for all patients before taking terbinafine, and the drug is not recommended for patients with liver disease.[18] Because of transient lymphopenia observed in patients on terbinafine, complete blood counts should be

infection,[61] and at 5 mg/kg per day for 30 days.[44] When *M. canis* is present, a longer treatment course is recommended.[45]

Adult For the treatment of tinea pedis, weekly doses of fluconazole 150 mg were given for a period of 3 to 4 weeks,[62] with a 75 percent mycologic cure rate at 4 weeks. Fluconazole at a dose of 150 mg weekly for 24 weeks is significantly inferior to terbinafine 250 mg daily for 12 weeks in the treatment of onychomycosis.[63] Tinea versicolor can be treated with a single 400 mg dose of fluconazole.[64]

Geriatric Fluconazole is well tolerated in the elderly;[65] however, dose modification is required in elderly patients with renal impairment.[58]

Pregnancy considerations Fluconazole is a pregnancy category C drug and is not recommended in nursing mothers.[66]

DOSAGE SCHEDULES AND FORMULATIONS Fluconazole is available in 50 mg, 100 mg, 150 mg, and 200 mg tablets, and in a liquid form at concentrations of 10 mg/mL and 40 mg/mL. Because it is cleared primarily by renal excretion, dosage should be adjusted in patients with impaired renal function. Fluconazole is indicated for the treatment of vaginal, oropharyngeal, and esophageal candidiasis, cryptococcal meningitis, and for prevention of candidiasis in bone marrow transplant patients.[66] It is approved for use in children age 6 months and older, but not specifically for tinea capitis.

ADVERSE EFFECTS The most common recognized side effects of fluconazole therapy are gastrointestinal.[67] Adverse reactions such as fixed drug eruptions, thrombocytopenia, transient amenorrhea, elevated liver function tests, mild increase in levels of serum creatine phosphokinase, dizziness, anorexia, and alopecia have been observed, and most resolve with continuing fluconazole therapy.[66,68]

DRUG INTERACTIONS In humans, fluconazole inhibits both CYP3A4 and CYP2C9 in a dose-dependent manner,[5] and consequently may increase plasma concentrations of drugs metabolized by these pathways. Therefore, a number of drugs that are metabolized by CYP3A4 or CYP2C9 are contraindicated or require close monitoring (Tables 261-1 and 261-2). Coadministration of terfenadine or cisapride with fluconazole is contraindicated.[66]

TABLE 261-2

Examples of CYP2C9 Subfamily Substrates, Inducers, and Inhibitors*

CYP2C9 SUBSTRATES	CYP2C9 INDUCERS	CYP2C9 INHIBITORS
Amitriptyline	Carbamazepine	Amiodarone
Diazepam	Dexamethasone	Disulfiram
Diclofenac	Phenobarbital	Fluconazole
Glipizide	Rifampin	Fluvastatin
Glyburide		Miconazole
Ibuprofen		Omeprazole
Losartan		Ritonavir
Mefenamic acid		Troglitazone
Naproxen		Zafirlukast
Phenytoin		
Piroxicam		
Propranolol		
Terbinafine		
Tolbutamide		
Torsemide		
Zafirlukast		

*This is not a complete list, and readers should refer to the manufacturer's individual package insert for current information

IMIDAZOLES

Ketoconazole

Ketoconazole was introduced in the 1970s as the first effective oral azole antifungal. However, because of the drug's many adverse reactions, it is not used as a first-line agent for the treatment of dermatophyte infections or candida.

Griseofulvin

Griseofulvin has been used since 1958 for the treatment of dermatophyte infections.[45]

PHARMACOLOGY The absorption of griseofulvin is enhanced by several factors, including concurrent intake of a fatty meal and a smaller particle size formulation. Griseofulvin is mainly metabolized by the liver before excretion.[69]

MECHANISM OF ACTION Griseofulvin is fungistatic in vitro,[45] and has a narrow spectrum of antimycotic activity. It disrupts microtubule mitotic spindle formation, thereby causing mitotic arrest at the metaphase stage.[70]

CLINICAL USES

Pediatric Griseofulvin is the drug of choice for the treatment of tinea capitis, but this may alter with new studies emerging about shorter effective courses with the newer antifungal agents.[37] Griseofulvin is recommended at a dosage higher than that suggested by the manufacturers at 20 to 25 mg/kg per day (microsize), or 15 to 20 mg/kg per day (ultramicrosize) to complete a minimum course of 6 to 8 weeks for *T. tonsurans*.[44] However, longer treatment with griseofulvin is recommended for *M. canis* infections.[44]

Adult Although griseofulvin is indicated for the treatment of fingernail and toenail onychomycosis, therapy is prolonged with low cure and high relapse rates, requiring approximately 6 months for the treatment of fingernails and 12 months for toenails.[70]

Geriatric The safety of griseofulvin therapy in the elderly has not been formally evaluated in trials.

Pregnancy considerations Griseofulvin is a pregnancy category C drug. Because griseofulvin interferes with chromosomal distribution during cell division, males should wait at least 6 months after completing griseofulvin therapy before fathering a child.[71]

DOSAGE SCHEDULES AND FORMULATIONS Griseofulvin is indicated for the treatment of dermatophytosis, onychomycosis, and tinea capitis.[71] Griseofulvin is formulated as ultramicrosize tablets in 125 mg, 165 mg, 250 mg, and 330 mg doses.[72] It is also formulated as griseofulvin microsize and is available as 250 mg and 500 mg tablets and in a 125 mg/5 mL suspension.[71] To maximize absorption it should be taken with fatty foods. The manufacturers' recommended dosing is 5 to 10 mg/kg per day (ultramicrosize) or 10 to 20 mg/kg per day (microsize).

ADVERSE EFFECTS The most common side effects are related to the gastrointestinal tract and the central nervous system.[70] The drug is reported to precipitate lupus erythematosus and severe skin reactions. As a result of impaired porphyrin metabolism, griseofulvin therapy is

Nail growth rate varies among different individuals and among the different digits of the same individual. It depends on the turnover rate of the nail matrix cells and is influenced by several physiologic and pathologic conditions. Nail growth rate is slow at birth, slightly increases during childhood, usually reaches its maximum between the second and the third decades of life, and then sharply decreases after the age of 50 years.[26] Conditions that are associated with a slow growth rate include systemic illness, malnutrition, peripheral vascular or neurologic diseases, and treatment with antimitotic drugs. Nails affected by onychomycosis frequently exhibit a slow growth rate. An arrest of nail growth is a typical feature of the yellow-nail syndrome (see Chap. 72). A reduction in the longitudinal nail growth is usually associated with nail thickening. Accelerate nail growth may cause nail thinning and/or longitudinal ridging of the nail plate (nail beading).

Due to their slow growth rate, the nails may provide information on pathologic conditions that have occurred up to several months before the time of observation. Because drugs and toxic substances are stored within the nail, nail clippings can be used to detect previous exposure to drugs or chemicals. The nail of the big toe is the best site for investigation because of its size and slow growth rate.

In some metabolic diseases, nail plate analysis can be used for diagnostic and therapeutic purposes. Nail clippings may also be used for genetic analysis and determination of blood groups. DNA can, in fact, be extracted easily from fingernail clippings and used for enzymatic amplification and genotypic or individual identification.

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TABLE 72-2

Differential Diagnosis of Nail Psoriasis

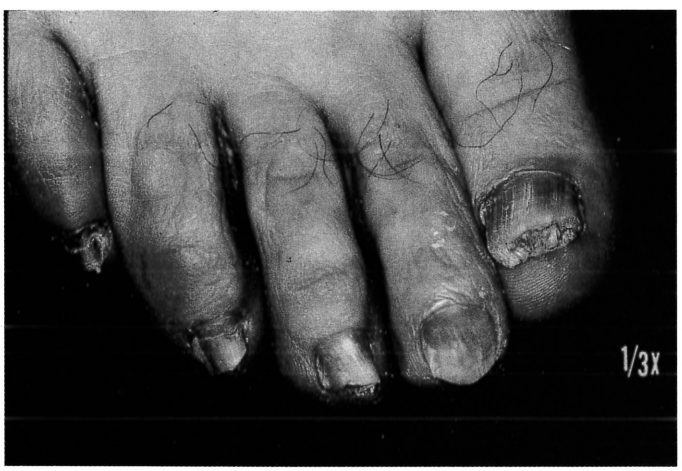
Contact dermatitis
Inflammatory linear verrucous epidermal nevus
Keratoderma
Keratoderma blennorrhagica
Keratotic scabies
Lichen planus
Onychomycosis
Parakeratosis pustulosa
Pityriasis rubra pilaris
Reiter's disease

(Fig. 72-21). Psoriasis and onychomycosis actually are also frequently associated because psoriatic nails are more susceptible to fungal invasion than healthy nails.

Nail psoriasis is difficult to treat.[3] Patients must be instructed to avoid traumas that may trigger or worsen their condition (Koebner's phenomenon). When onycholysis is present, the detached nail plate should be removed. Systemic administration of methotrexate or cyclosporin A may improve the nail changes, but these drugs are not recommended in the absence of extensive skin psoriasis. Intralesional steroid injections (10 mg/mL) are effective but very painful. Retinoids and PUVA are scarcely effective and may even worsen the nail changes. Topical application of creams containing steroids and salicylic acid, and/or topical application of calcipotriol ointment may be useful. Because nail psoriasis is frequently associated with psoriatic arthropathy (Fig. 72-22), a rheumatological evaluation is advisable.

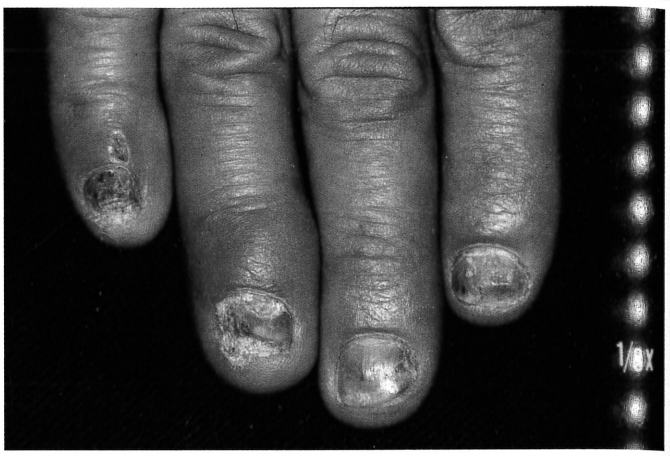
PUSTULAR PSORIASIS/HALLOPEAU'S ACRODERMATITIS CONTINUA This condition frequently involves the nails and the periungual tissues. The disease, which is most frequently localized to one digit (usually a finger), typically shows a chronic course with periodic episodes of painful acute inflammation. In the acute phase, the affected digit shows severe inflammatory changes with pustular lesions of the nail bed and periungual skin (Fig. 72-23). In the chronic phase, the nail bed and the periungual tissues show erythema and scaling. The nail plate is onycholytic or absent. The condition often

FIGURE 72-21



Toenail psoriasis showing massive nail bed hyperkeratosis.

FIGURE 72-22



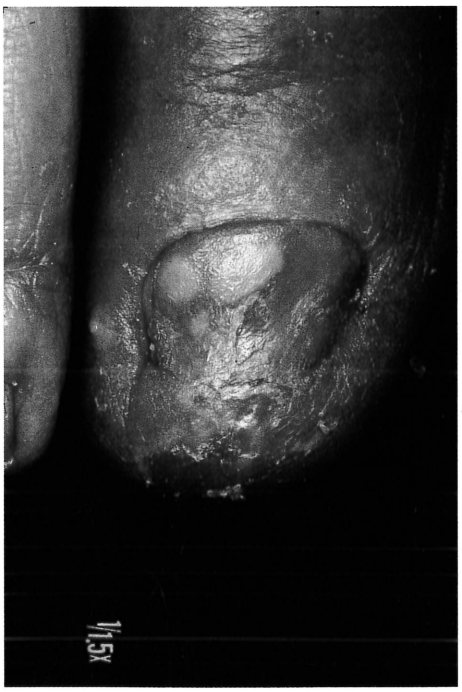
Nail psoriasis associated with psoriatic arthropathy.

improves with topical calcipotriol. Systemic retinoids may be useful in severe cases.[4]

PARAKERATOSIS PUSTULOSA This condition, which is exclusively seen in children, usually involves one finger, most commonly the thumb or the index finger. The affected nail shows subungual hyperkeratosis and onycholysis, which are usually more marked on one side of the nail (Fig. 72-24). Erythema and scaling of the fingertip is typical, but not always present. Parakeratosis pustulosa is possibly a variety of psoriasis and some children develop typical nail psoriasis later in life. The disease usually regresses spontaneously at puberty.

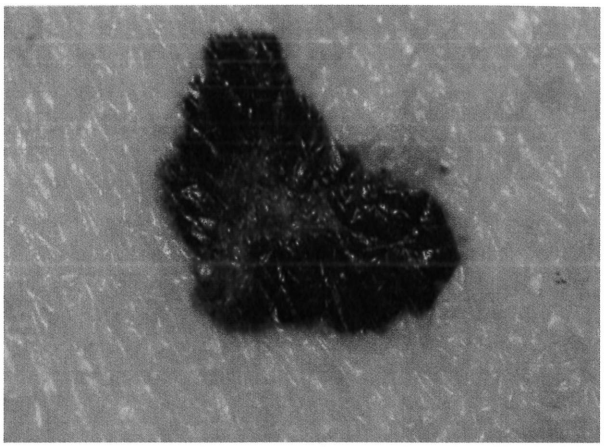
LICHEN PLANUS Nail involvement occurs in about 10 percent of patients with lichen planus. Lichen planus limited to the nails is uncommon but not exceptional. It may be observed in children.[5]

FIGURE 72-23

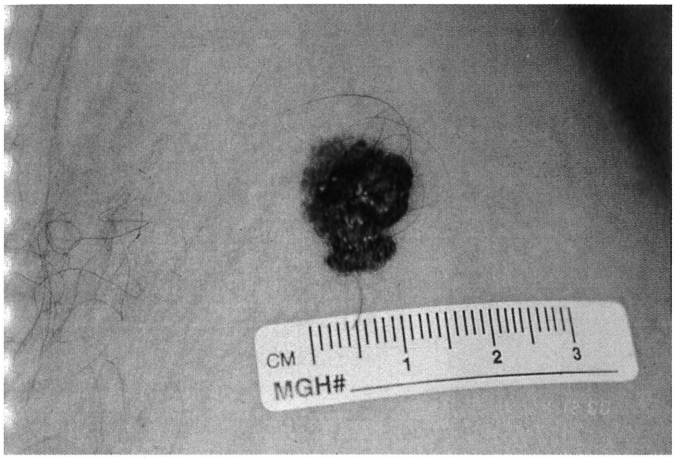


Hallopeau's acrodermatitis. Pustular lesions of the nail bed.

FIGURE 93-8



A.



B.

"ABCD's" of melanoma. The two lesions (*A* and *B*) shown here are SSMs: *A, asymmetry:* the melanoma is not symmetrical. Also note the irregular border. *B, border:* note the highly irregular, uneven, and notched border. *C,* color: the color is variegated with different shades of brown, black, tan. *D, diameter:* the diameter is usually >6 mm in melanomas. This does not mean that a melanoma cannot be smaller but, except for atypical (dysplastic) nevi, acquired nevi are usually not >5 mm in diameter.

brown to black discoloration in the nail bed, usually at a proximal location. Hutchinson's sign is the finding of pigmentation of the posterior nail fold and has been considered an ominous finding associated with advanced subungual melanoma (Fig. 93-16*A*). Benign lesions that can mimic subungual melanoma include longitudinal melanonychia, subungual hematoma, onychomycosis, paronychia, ingrown toenail, nevus, or pyogenic granuloma. Subungual hematomas may appear as sharply localized, black, maroon, or multicolored lesions, often within the nail bed or matrix. These lesions are often acutely painful, and a history of trauma at the site can usually be obtained. If the diagnosis is uncertain and the lesion is of recent onset, a diagnostic and therapeutic procedure involves piercing the nail with a large-bore needle to release the blood.

HISTOPATHOLOGY The macular areas exhibit basilar proliferation of large melanocytes with large nuclei showing atypical chromatin patterns. The cytoplasm is filled with melanin granules, and there are elongated dendrites that may extend to the granular cell layer (Fig. 93-17). In the papular or nodular areas, malignant melanocytes are frequently spindle-shaped and extend into the dermis. As discussed below, desmoplastic–neurotropic patterns of the invasive component are frequently associated with ALM.

Other Melanoma Variants

MELANOMA OF THE MUCOSA Melanoma infrequently can arise from mucosal surfaces. The most common sites are the mucosal surfaces of the head and neck (typically involving the nasal and oral cavity) and vulva or anorectal mucosa. Patients may present with bleeding at these sites or with a mass lesion but most often with a deeply pigmented, irregular mucosa. Melanoma of the mucosa may occur with or without a radial growth phase. The intraepithelial growth phases of malignant melanomas of the vulva and of the conjunctiva can be divided into three subtypes: a pagetoid pattern, which shows the typical characteristics of SSM of the skin; a lentiginous pattern, which shares some features with LM and ALM; and a mixed pattern, in which a profusion of nests of malignant, often ovoid, cells is admixed with a lentiginous proliferation.

LM of the eyelid can involve the conjunctiva and is similar to lentiginous melanocytic hyperplasia of the conjunctiva, without LM, occurring on the palpebral or cutaneous surface. The two lesions, therefore, cannot be distinguished histologically.

DESMOPLASTIC–NEUROTROPIC MELANOMA Desmoplastic melanoma is a rare subtype of melanoma that is locally aggressive with high rates of local recurrence. Desmoplastic melanoma most commonly develops in sun-exposed skin of the head and neck region of elderly individuals, usually in the sixth or seventh decade. Desmoplastic melanomas are variants of invasive melanoma that may arise in association with LM, ALM, and mucosal lentiginous melanoma, as well as de novo. Thus, on clinical examination, one may observe a pigmented macule with or without a nodular component, or a flesh-colored nodule without any surrounding pigmentation. Typically, the latter lesions have a firm, sclerotic or indurated quality.

Histologically, desmoplastic melanoma appears as a nodule of fibrous tissue containing hyperchromatic cells that either are scattered singly, lie in fascicles, or aggregate in nests. Variable degrees of mucin deposition may also be present. Interspersed throughout a dense collagenous tissue are fascicles of hyperchromatic melanoma cells, most often spindle-shaped. Many resemble irregularly shaped fibroblasts. Macrophages filled with melanin may be scattered throughout the dense collagenous tissue.

In general, desmoplastic melanomas have a propensity to infiltrate the perineurium and endoneurium of the cutaneous nerves. The large nerves may have thickened perineurium populated by hyperchromatic cells. Endoneurial involvement usually consists of hypercellularity, with an increase in the size and pleomorphism of the cells. The term *neurotropic melanoma* applies to a subset of desmoplastic melanomas in which the constituent cells, in addition to showing prominent infiltration of nerves, form patterns that resemble nerves or neuroidal structures.[36] The result is a florid proliferation of cells, often with wavy configurations, running parallel to one another, associated with a fibrous response.

The differential diagnosis includes morpheaform (desmoplastic) basal cell carcinoma, desmoplastic nevus, sclerosing variants of blue nevus, scar, fibrous histiocytoma, fibromatosis, atypical fibroxanthoma, malignant fibrous histiocytoma, neurothekeoma, and malignant peripheral nerve sheath tumors (see Chaps. 102 and 107). Helpful features in recognizing desmoplastic malignant melanoma are the usual clinical setting: sun-exposed skin of the head and neck of an elderly individual, an intraepidermal lentiginous melanocytic proliferation, and the presence of cytologic atypia of dermal spindle cells with mitoses. Immunohistochemistry (see below) is usually quite helpful as the tumors

from skin infection is not common.[8] Several cutaneous signs (arterial emboli, conjunctival hemorrhages, splinter hemorrhages, Janeway lesions, Osler nodes) may be present.

FUNGAL INFECTION

Even in the absence of HIV infection, the incidence of dermatophytosis, including onychomycosis, tinea pedis, tinea cruris, and tinea corporis, is higher among intravenous drug addicts.[38] Injections of brown heroin have caused disseminated candidiasis due to yeast overgrowth in the lemon juice used to dissolve the heroin. The initial symptoms are high fever, rigors, headaches, myalgia, and occasionally jaundice, but at this stage, blood and urine cultures rarely grow organisms. After approximately 7 days, 88 percent of the patients develop pustular folliculitis and painful nodules on the scalp and other hairy areas. The folliculitis is often misdiagnosed as bacterial, but potassium hydroxide examination and biopsy demonstrates the presence of yeasts. Other complications include ocular disease (uveitis, endophthalmitis), monarthritis, osteochondritis, and pleuritis.[39] Unlike HIV infection, intravenous drug use is a predisposing factor to zygomycosis. The charcteristic cutaneous lesion is a cellulitic plaque or abscess that becomes necrotic.

DRUG-INDUCED REACTIONS

As expected, hypersensitivity reactions to drugs, especially exanthematous eruptions, urticaria, fixed drug reactions, leukocytoclastic vasculitis, erythema multiforme, and toxic epidermal necrolysis, occur more frequently in users of illicit drugs than in the general population. Dermatographism was found in 26 percent of patients comatose from heroin overdose.[40] Pigmented patches on the skin and mucous membranes may be extensive in addicts with fixed drug eruptions.

Narcotic abuse is a common cause of falsely reactive nontreponemal tests for syphilis (VDRL, RPR). In these cases, treponemal tests (MHATP, FTA-ABS) will be nonreactive. However, in addicts who have had syphilis, not only will both tests be positive but the titers of the treponemal test also may not decrease after treatment.

ASSOCIATED NONINFECTIOUS SKIN DISEASES

Seborrheic dermatitis may be more frequent in chronic cocaine users. Eczemas, especially contact dermatitis, have been reported to occur more frequently. Drug abuse may indirectly cause skin lesions through congenital malformations in the offspring, domestic violence, or systemic disease. Pseudoacanthosis nigricans has been observed in heroin addicts.

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encapsulated yeasts can be identified readily in tissue biopsies, as well as in purulent material obtained from skin lesions. They stain red with periodic acid–Schiff and mucicarmine stains and black with methenamine silver stain. *Cryptococcus* also can be isolated in culture from cutaneous tissue. The treatment of choice for cryptococcosis is intravenous amphotericin B with or without flucytosine. Fluconazole is used as alternative primary treatment. However, fluconazole is the treatment of choice for prophylaxis in individuals at high risk for primary or recurrent infection.

HISTOPLASMOSIS (See Chap. 207) *Histoplasma capsulatum* is a dimorphic fungus that is found commonly in soil in central and eastern regions of the United States. Endemic foci also exist in South America, Africa, and Asia. As with cryptococcosis, inhalation of airborne spores causes primary pulmonary infection that usually leads to self-limited disease in otherwise healthy individuals. However, disseminated disease may occur, particularly in individuals with deficiencies in cell-mediated immunity.[18] In addition to pneumonia, immunosuppressed hosts may present with fever, renal failure, central nervous system involvement, hepatosplenomegaly, lymphadenopathy, and myelosuppression.

With disseminated infection, skin lesions occur in 5 to 25 percent of patients and may be an initial sign of disease.[10] Mucocutaneous lesions commonly manifest as painful nodules or plaques that progress to ulcers with indurated borders. However, numerous other morphologies have been described, including molluscum-like papules, acneiform papules and pustules, and cellulitis. In addition, as with cryptococcosis, the head and neck region is involved most commonly. In fact, the oropharynx is the most common site for lesions of mucocutaneous histoplasmosis. Because the organism grows very slowly in culture, histoplasmosis is best diagnosed by direct examination of tissue. Numerous small, oval, yeastlike fungi can be seen within the cytoplasm of dermal macrophages. The treatment of choice for disseminated histoplasmosis in an immunosuppressed host is intravenous amphotericin B. For patients who are not acutely ill, oral itraconazole may be used; itraconazole is also recommended for immunosuppressed patients to prevent recurrent disease.

COCCIDIOIDOMYCOSIS (See Chap. 207) *Coccidioides immitis,* the causative agent of coccidioidomycosis, is endemic to soil in the southwestern United States, and primary pulmonary infection is acquired through inhalation of spores.[19] Although progressive primary infection may occur in immunosuppressed patients, reactivation of prior, clinically inapparent infection appears to be more common. The risks of dissemination and fatal infection are greater among pregnant women, non-Caucasians, and immunosuppressed patients with defects in cell-mediated immunity, e.g., transplant patients receiving cyclosporine. Thus disseminated coccidioidomycosis can occur in any immunocompromised patient who lives or has lived previously in an endemic area.

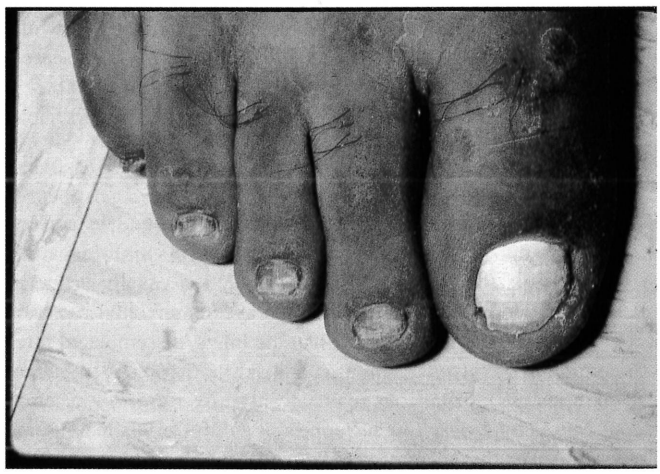
Immunosuppressed patients with disseminated disease may present with fever, pneumonia, bone involvement, and meningitis. Mortality is high. Cutaneous lesions are common and appear as reddish brown papules and nodules, pustules, abscesses, or ulcers. Lesions occur most commonly on the face. Definitive diagnosis of coccidioidomycosis is made by demonstrating characteristic endosporulating spherules in smears or biopsy specimens or by culture of infected tissue. For disseminated infections in immunosuppressed hosts, treatments include intravenous amphotericin B and oral fluconazole.

BLASTOMYCOSIS (See Chap. 207) *Blastomyces dermatiditis* is endemic to the soil of the Ohio and Mississippi river valleys. Infection is acquired through inhalation of spores. Immunosuppressed patients are prone to disseminated disease involving the lungs, bone, genital tract, and skin.[18] The most common lesion appears as a verrucous or crusted plaque with serpiginous borders located on the head, neck, or distal extremities. Subcutaneous nodules and ulcers are also not uncommon. Diagnosis is made on demonstration of broad-based, budding, thick-walled yeasts in pus or skin scrapings from the edges of lesions or by tissue culture. In life-threatening disseminated infection, intravenous amphotericin B is the treatment of choice; however, less severe disease is treated with oral itraconazole.

DERMATOPHYTOSIS (See Chap. 205) Dermatophytes commonly infect normal hosts and typically cause superficial scaly annular plaques and onychomycosis. However, immunosuppressed patients may have widespread, aggressive infection that can be resistant to topical and systemic therapy.[10] The morphology of individual lesions in immunosuppressed patients is usually similar to lesions seen in normal individuals. However, both white superficial onychomycosis and proximal subungual onychomycosis are types of fungal nail infections that are uncommon in immunocompetent hosts. In the former, the surfaces of affected nails have a white chalky appearance (Fig. 119-5), and hyphae are observed readily in superficial nail plate scrapings. These conditions should prompt a search for underlying immune deficiency.

OTHER FUNGAL INFECTIONS *Penicillium marneffei* is a dimorphic fungus that has emerged as an opportunistic pathogen in immunosuppressed patients (most but not all AIDS patients) who live in or who have traveled to Southeast Asia.[20] Initial infection is acquired through inhalation or ingestion of spores. Patients with disseminated disease develop fever, weight loss, anemia, pneumonia, hepatosplenomegaly, lymphadenopathy, and molluscum-like papules on the head and upper body (70–80 percent of patients). The mold *Scedosporium prolificans* can cause asymptomatic colonization, localized infection related to trauma or surgery, and disseminated infection.[21] The latter is particularly common in patients with neutropenia secondary to hematologic malignancies. *Alternaria* is a common saprophytic fungus that can cause opportunistic infection in the setting of hypercorticism (e.g., glucocorticoid treatment, Cushing's disease) and skin fragility.[22] *Paecilomyces lilacinus,* a fairly new opportunistic fungal pathogen, has been reported to contaminate topical preparations and cause deep-seated cutaneous nodules in immunosuppressed patients.[23] A number of dematiaceous fungi cause primary cutaneous phaeohyphomycosis. Immunosuppressed patients are particularly susceptible to infection and

FIGURE 119-5



White superficial onychomycosis in a renal transplant patient receiving cyclosporine.

Also, the elderly frequently take medications that aggravate psoriasis, such as β-blockers, nonsteroidal anti-inflammatory drugs, and ACE inhibitors. Among the other triggering factors, urinary incontinence or the use of hearing aids, corsets, or braces may lead to koebnerization. Perhaps because of altered proliferative homeostasis, psoriasis in the elderly is often exquisitely sensitive to antiproliferative drugs such as methotrexate. Minute doses may lead to resolution of plaques, and conversely, standard doses may cause extensive erosions.

Xerosis/asteatotic dermatitis Xerosis is a dry, rough quality of skin that is almost universal in the elderly and may be attributed to a subtle disturbance of epidermal maturation, such as inadequate filaggrin production[26] or altered lipid profile.[24,25] Histologic studies reveal little alteration of either the viable epidermis or the stratum corneum with age. Available data fail to demonstrate an overall decrease in stratum corneum lipids[24,90] or altered amino acid composition as etiologic factors.[91] Water content of the viable epidermis is normal, but there is some reduction in the outermost layers of the stratum corneum.[90] The surface irregularity may be attributed simply to slower transit of corneocytes through the stratum corneum, allowing accumulation of damage in situ. There is no explanation for the pruritus that often accompanies xerosis.[92] Speculations include frequent penetration of irritants through an abnormal stratum corneum and an altered sensory threshold due to subtle neuropathy.

Asteatotic eczema, a condition frequently found in the elderly during the wintertime, is a dermatitis superimposed on xerosis. It is often caused by low humidity in a heated environment. It manifests by dry, fissured skin with fine scale and is usually located to the pretibial region. This condition, which may be extremely pruritic, responds to application of medium-potency topical steroid ointments and/or liberal application of emollients.

Pruritus[92] (See also Chap. 41) Pruritus is perhaps that most common skin-related complaint of the elderly. In a majority of cases, pruritus is attributable only to xerosis, often exacerbated by low humidity, frequent bathing, or application of irritants to the skin. However, in up to 10 to 50 percent of patients in some series, pruritus may have other etiologies. These include metabolic or endocrine disorders such as diabetes mellitus, renal failure, thyroid disease, or hepatic disease, in particular the obstructive type. Pruritus can be a manifestation of a malignant neoplasm, in particular lymphoma or leukemia, or the result of a hematologic disease such as polycythemia vera. Adverse drug reactions can manifest predominantly or exclusively as pruritus and always should be considered in this segment of the population. Finally, infestations such as scabies lead to intense pruritus, and associated primary skin lesions may be overlooked. Although in the majority of cases pruritus can be managed by frequent use of moisturizers, if there is inadequate symptomatic relief, other causes should be pursued through appropriate laboratory evaluation.

INFECTIOUS PROCESSES

Bacterial[93] (See also Chap. 193) Impetigo and folliculitis in the elderly are caused by staphylococci, in contrast to impetigo in the pediatric population, which usually is caused by streptococci. Hence, in the older age group, impetigo should be treated with penicillinase-resistant semisynthetic penicillin or erythromycin until culture confirms the identity of the organism.

Cellulitis is an infectious inflammatory process that involves the subcutaneous tissue and is caused most frequently by streptococci or staphylococci. Like other inflammatory conditions, cellulitis in the elderly may present with only subtle rubor, tumor, calor, and dolor. Predisposing factors with increased prevalence in the elderly include chronic edema, compromised circulation, diabetes mellitus, surgical sites, and asteatotic eczema.

Distinct forms of cellulitis preferentially affect older individuals. These include orbital cellulitis that is caused by *Streptococcus viridans* alone or in combination with gram-negative bacteria. Another form of cellulitis that is relatively rare in the younger population is *Pseudomonas* cellulitis of the ear, an infectious process that affects elderly diabetic individuals. Erysipelas, a β-hemolytic streptococcal infection of the skin, is more common in the elderly and tends to spread more readily in this age group, creating a life-threatening situation.

Necrotizing fasciitis, caused by a strain of *Streptococcus,* is a rare cutaneous infection, but it is seen more frequently in the elderly and is associated with increased morbidity and mortality in this age group.

Parasitic[93] Scabies infestation can occur in any age group, but nursing homes provide a fertile ground for rapid spread of the infestation. In the elderly, in part because of their decreased immunity, lesions may be atypical and display less inflammation and pruritus. In addition, frequently the elderly have xerosis, and their pruritus at times may be attributed to this etiology. Treatment of scabies in the elderly is often difficult, in part because of reinfestations in nursing home environments and in part because the elderly may have difficulty in compliance. Permethrin (5%) treatment of scabies in nursing homes is safe and has the advantage of remaining on the skin surface for days, protecting the patient from reinfestation. Ivermectin, a systemic treatment that has been recommended frequently for scabies infestations of nursing homes because of its efficacy and ease of administration, has been associated with mortality in the elderly and therefore should be prescribed with caution.

Dermatophytes and yeasts[94] (See also Chaps. 205 and 206) Onychomycosis is present in approximately 40 percent of patients after age 60, and tinea pedis is present in approximately 80 percent of this patient population. Although usually present for decades, tinea pedis may exacerbate with age. Indeed, in elderly diabetic patients, interdigital tinea pedis may ulcerate and predispose to bacterial cellulitis, a presentation that is relatively rare in the young adult immunocompetent patient.

For tinea pedis without toenail involvement, topical antifungal preparations are effective. Clotrimazole, econazole, or terbinafine cream should give substantial improvement within a few weeks. However, indefinite use of a moisture-absorbing antifungal powder is required to prevent reinfection. When onychomycosis is present, oral therapy is required. Agents including terbinafine, fluconazole, or itraconazole are effective if used throughout the period required for the nail(s) to grow out (often 9 to 12 months in the elderly) but may cause hepatotoxicity or cross-react with other medications. Such concerns and frequent lack of third-party coverage for these expensive drugs have curtailed their use in the elderly.

Cutaneous infections due to *Candida albicans* are common in the elderly. When recurrent or difficult to control, candidiasis may be a sign of poorly controlled diabetes, an endocrinopathy, malnutrition, or malignancy.

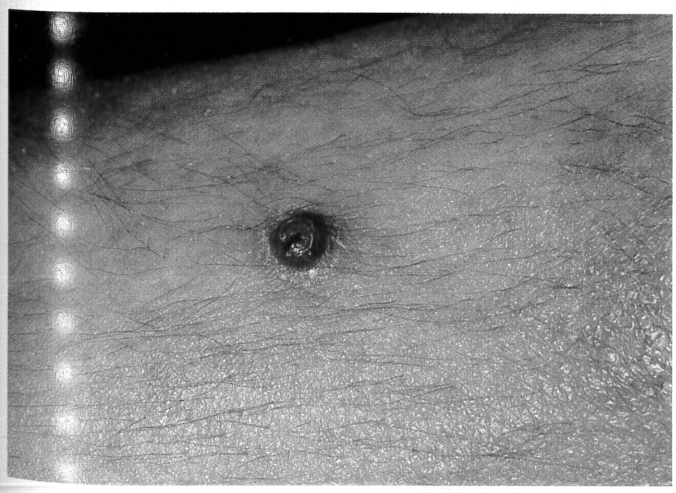
Oral candidiasis or thrush presents as white plaques on the buccal mucosa, palate and/or tongue that reveal an eroded base when scraped off. Predisposing factors include the use of broad-spectrum oral antibiotics, corticosteroids, or dentures. Systemic conditions associated with the development of thrush include diabetes, malignancies, and AIDS. Topical antimycotic agents such as nystatin and clotrimazole that are formulated for oral use usually are effective. Systemic agents that can be used to treat oral candidiasis include fluconazole, itraconazole, and ketoconazole. Angular cheilitis or perleche presents as painful, erythematous, crusted fissures at the corners of the mouth. Predisposing factors include occlusive skin folds and drooling. The condition can be treated successfully with topical antifungal preparations, but to prevent recurrence, it is important to keep the oral commissures dry.

Candidal intertrigo presents as painful erosions with peripheral scale and satellite pustules in body folds, where the moist, warm environment

Tuberculosis is the most common opportunistic infection in HIV disease in developing countries; cutaneous tuberculosis, however, is relatively uncommon. In non-HIV-infected persons with tuberculosis, the incidence of extrapulmonary tuberculosis is 15 percent; in HIV disease, 20 to 40 percent. In advanced HIV disease, the incidence of extrapulmonary disease increases to 70 percent. *Mycobacterium* spp. other than tuberculosis (MOTT) (a.k.a. environmental mycobacteria: *M. chelonae, M. fortuitum, M. kansasii, M. malmoense, M. gordonae, M. marinum,* and *M. hemophilum*) have been reported to cause cutaneous lesions in HIV disease. The most common MOTT agent in advanced HIV disease is *M. avium-intracellulare* complex (MAC); however, this rarely presents with cutaneous infection. The incidence of MAC infections has fallen with primary prophylaxis with azithromycin and, more recently, with HAART.

Bacillary angiomatosis (BA) and bacillary peliosis (BAP), caused by *Bartonella henselae* and *B. quintana,* occur most commonly in the setting of advanced HIV-induced immunodeficiency, characterized by angioproliferative lesions resembling cherry hemangiomas, pyogenic granulomas, or Kaposi's sarcoma.[52] Currently, the prevalence of BA in North America and western Europe is very low due to improved immune function with HAART and to prophylaxis given for infections such as MAC. Clinically, the cutaneous lesions of BA are red to violaceous, dome-shaped papules, nodules, or plaques resembling Kaposi's sarcoma and ranging in size from a few millimeters up to 2 to 3 cm in diameter (dermal vascular lesions with thinned or eroded epidermis) (Fig. 225-8). Less commonly, domed subcutaneous masses occur without the characteristic red color of more superficial vascular lesions.[53] Lesions are soft to firm and may be tender to palpation. The number of lesions ranges from solitary lesions to more than a 100 and, rarely, greater than 1000. Nearly any cutaneous site may be involved, but the palms, soles, and oral cavity are usually spared. Following hematogenous or lymphatic dissemination, the spectrum of internal disease caused by *B. henselae* and *B. quintana* includes soft tissue masses, bone marrow, lymphadenopathy, splenomegaly, and hepatomegaly; internal involvement can occur with or without cutaneous lesions. The course of BA is variable. In some patients, lesions regress spontaneously. BA infection may spread hematogenously or via lymphatics to involve bone marrow, bone, spleen, and liver. As with other OIs in HIV disease, BA can recur. The antibiotics of choice are erythromycin (250–500 mg PO qid) or doxycycline (100 mg bid), continued until the lesions resolve, usually 3 to 4 weeks. Secondary prophylaxis is indicated in patients with recurrent BA.

FIGURE 225-8



Bacillary angiomatosis. A vascular nodule of the shin was associated with disseminated small red papules and subcutaneous nodules in the inguinal areas bilaterally. The lesions appeared suddenly during a one-week period.

FUNGAL INFECTIONS

Cutaneous fungal infections in HIV disease occur as superficial infections (dermatomycoses), invasive cutaneous infections, or systemic fungal infection with hematogenous dissemination to the skin. HAART has markedly diminished the incidence of these infections.[54,55]

Dermatophytoses

Trichophyton rubrum causes proximal subungual onychomycosis (PSO), an infection of the undersurface of the proximal nail plate.[56] PSO occurs most often in HIV-infected individuals; the diagnosis is an indication for HIV testing. Epidermal dermatophytosis can be extensive in HIV disease. Unless immunocompromise is restored, dermatophyte infections are chronic and recurrent.

Mucocutaneous Candidiasis

Cutaneous *Candida* infections such as intertrigo are relatively uncommon in adults with HIV disease: concomitant diabetes mellitus associated with HAART may increase the prevalence. Candidiasis of moist, keratinized cutaneous sites such as the anogenital region occurs with some frequency. Candidal angular cheilitis occurs at the corners of the mouth as an intertrigo, unilaterally or bilaterally; it may occur in conjunction with oropharyngeal or esophageal disease or as the only manifestation of candidal infection. Children with HIV infection commonly experience candidiasis in the diaper area and intertrigo in the axillae and neck fold. Fingernail chronic *Candida* paronychia with secondary nail dystrophy (onychia) also is common in HIV-infected children.[57]

Candida colonization of the oropharynx is common in HIV-infected individuals, up to 60 percent in the absence of any clinical findings. *C. albicans* was the most prevalent colonizing species, but multiple species may be present. Isolation of non-*albicans* species alone correlates with advanced HIV disease and very low CD4 cell counts. Oropharyngeal candidiasis (OPC) is a marker of HIV disease progression. In a study of the onset of OPC following documented dates of HIV seroconversion, candidiasis was noted in 4 percent at 1 year after seroconversion, 8 percent at 2 years, 15 percent at 3 years, 18 percent at 4 years, and 26 percent at 5 years; the median CD4 cell count was 392 cells per microliter when OPC was first detected.[58] OPC and esophageal candidiasis (EC) have been reported to occur as a manifestation of primary HIV infection. EC, an AIDS-defining condition, occurs only with advanced CD4 count reduction (<100 cells/μL). OPC presents in four different patterns: pseudomembranous (thrush), atrophic (erythematous), hyperplastic, and as an angular cheilitis. Despite a high prevalence of candidiasis in HIV-infected individuals, disseminated candidiasis is distinctly uncommon, probably because of B cell activation and the presence of anticandidal protective antibody.

HIV-infected women with CD4 counts of 200 to 500 cells per microliter had a 33 percent incidence of vaginal candidiasis and 44 percent if the CD4 count was less than 200 cells per microliter. In a study of 117 HIV-infected women, recurrent candidal vaginitis was the most common initial clinical manifestation of HIV disease (43 of 117 women).[59] Other studies have failed to confirm an increased incidence of candidal vaginitis in HIV-infected women.

performed under local anesthesia in selected patients, when the fungal infection is of a limited extent. An affected portion of the nail plate may be removed in one session, even when the disease has reached the deeper regions of the subungual tissue beneath the proximal nail fold. Commonly, an English anvil nail splitter or a double-action bone rongeur is used for this procedure.

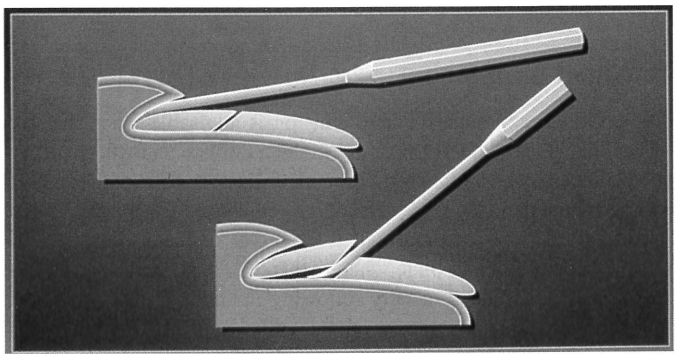
Partial surgical section of the lateral and/or medial segment of the nail plate may be sufficient for the treatment of distal lateral subungual onychomycosis. Enough normal nail is left to counteract the upward forces exerted on the distal soft tissue when walking and this will prevent the appearance of a distal nail wall.

In proximal subungual onychomycosis, removal of the nonadherent base of the nail plate, cut transversely, leaves the distal portion of the nail in place (Fig. 280-8), which decreases discomfort. Similarly, an acute paronychia that does not respond to appropriate antibiotics within 48 h should be treated surgically by removing the base of the nail plate.

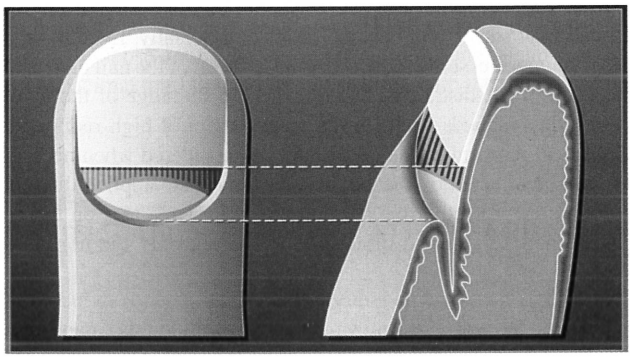
Where *Candida* infection or, more rarely, dermatophyte infection result in onycholysis, the detached portion of the nail plate should be thoroughly clipped away. This facilitates the daily application of a topical antifungal drug until nail regrowth is complete. *Candida* lateral nail edge involvement associated with paronychia should be surgically sectioned and the affected nail keratin removed. Recalcitrant *Candida* paronychia with secondary nail plate invasion may be treated by surgical excision of a crescent of thickened nail fold followed by partial or total nail avulsion.

In any type of surgically treated onychomycosis, the avulsed nail segment must always include a margin of normal nail.

FIGURE 280-8



A.



B.

A and *B*. Technique of removal of the base of the nail plate.

SURGICAL APPROACHES TO THE DIFFERENT TISSUES OF THE NAIL APPARATUS

Surgery of the Nail Matrix

When surgery involves the nail matrix, there are four primary approaches, including a reduction in its width or its length for removal of tumors, for instance, by using cold steel procedure or a 2- to 3-mm punch biopsy. In contrast to the three previously discussed procedures, complete matricectomy, that is, ablation of the nail-forming tissue, is rarely performed as the nail is permanently lost.

After reduction of the width, one is left with a narrower nail and after reduction of the length, with a diminution in the thickness of the nail. Reduction of the matrix width is a useful and/or necessary procedure in six major circumstances:

(1) lateral-longitudinal biopsy;
(2) lateral nail splitting;
(3) benign or malignant tumor in the lateral third of the nail apparatus;
(4) longitudinal melanonychia in lateral location;
(5) ingrown nail; and
(6) racquet nail.

Reduction of the matrix length has limited indications: crescent or transverse ellipse biopsy, tumors equal to or greater than 3 mm in width, and thick nails in dystrophic congenital and/or hereditary disorders.

BIOPSY[2] Biopsy of the nail matrix is performed to obtain the histopathology of any lesions or to clarify dubious clinical diagnosis.

A 3-mm punch biopsy may be performed through the nail plate into the matrix. Three millimeters is the maximum size that does not produce serious dystrophy except when it is performed in the most proximal portion of the nail matrix. When a punch biopsy is used for longitudinal *melanonychia* of less than 3 mm in width, the circumferential incision is made around the origin of the band, through the NP (Fig. 280-9). This may be distal enough to be reached by pushing back the cuticle, but if it is more proximal, the proximal nail fold (PNF) may have to be reflected using a posterolateral incision. The next step consists of removing the proximal third of the nail plate, but leaving the cylinder of tissue containing the origin of the longitudinal melanonychia still in place. This technique enables the surgeon to inspect the surrounding nail matrix and bed with a magnifying lens to determine whether pigment extends around the punch incision and to facilitate the removal of the biopsied cylinder of tissue with a Gradle scissors.

For lateral longitudinal biopsy (Fig. 280-10), an elliptical incision may be made on either side of the nail plate and proximal nail fold. For the most part, the incisions parallel the lateral edge of the nail plate. Beginning in the lateral nail groove, the incisions should include a 3- to 4-mm nail segment reaching to the bone. This ensures that a full-thickness fragment of the matrix with its lateral horn is obtained. Slightly curved iris scissors are useful for separating the tissue from the bone. Starting at the tip of the digit, one proceeds proximally while maintaining contact with the bony phalanx. Lateral longitudinal biopsy is the advised procedure when longitudinal melanonychia[3] is located in the lateral part of the nail plate.

For transverse biopsy (Fig. 280-11), two small oblique incisions are made on each side of the PNF; the fold is then reflected in order to expose the matrix area. The proximal third of the nail plate is avulsed. Then, the lesion is removed by an elliptical or a crescent-shaped wedge of tissue with the convex portion of the crescent paralleling the anterior border of the lunula. When longitudinal melanonychia lies within the midportion of the nail plate, the potential for postoperative dystrophy is great and selection of the optimal biopsy method is difficult. It is important to establish preoperatively the matrix origin (proximal or