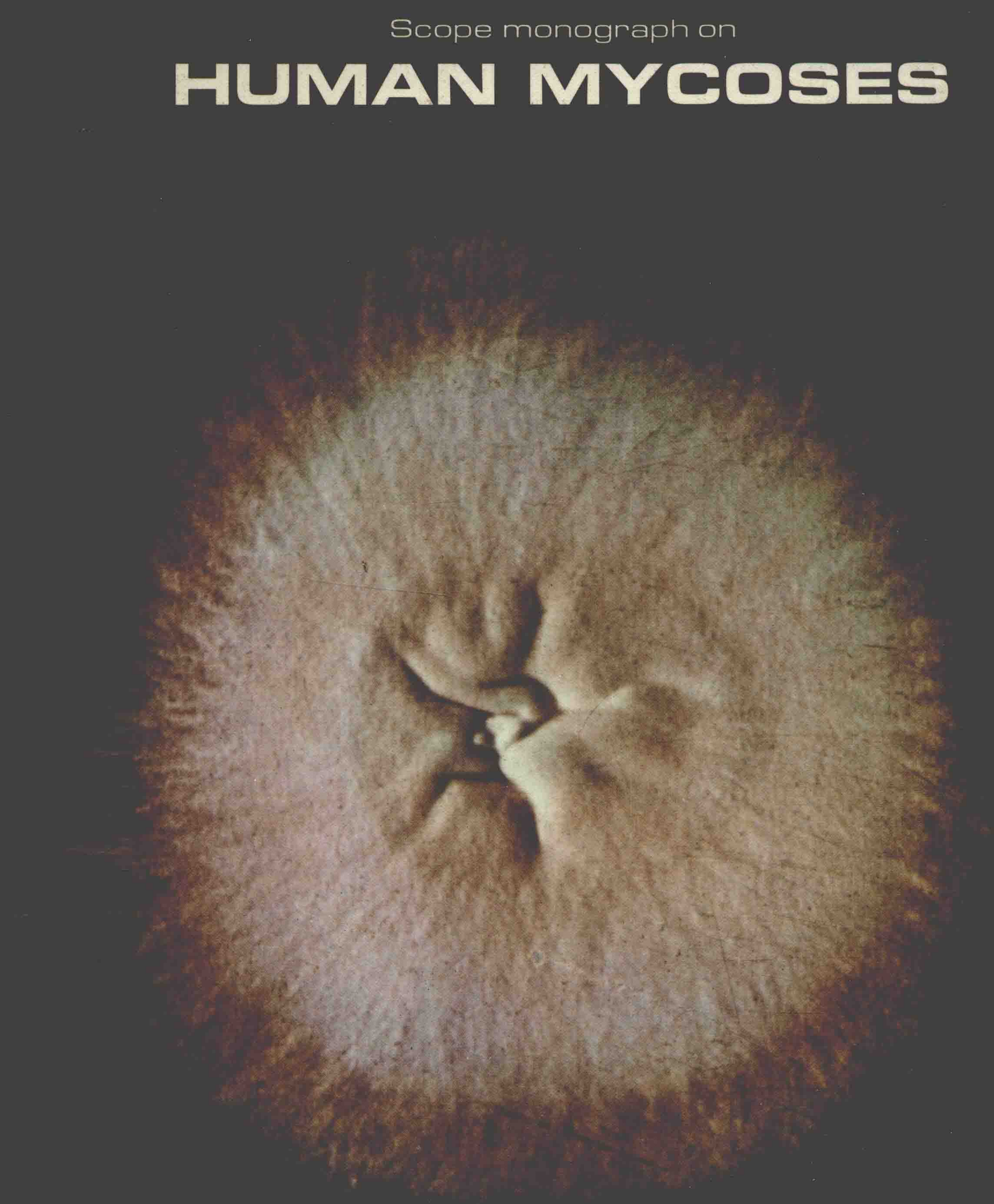
Scope monograph on

HUMAN MYCOSES



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Everett Smith Beneke, Ph.D.
Professor, Michigan State University

A visual outline of the characteristics of the dermatophytes and the deep mycoses, including the taxonomy of the various fungi involved. Published by The Upjohn Company, Kalamazoo, Michigan

Editor
Baird A. Thomas

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THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

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Readers Please Note—An extensive effort has been made by all parties associated with this monograph to verify the correctness of the dosage suggested for the treatment of each individual mycosis.

However, dosage schedules are frequently changed or altered as clinical experience accumulates.

We recommend that the approved dosage be checked with the latest product information sheet of the drug involved before it is administered or prescribed, particularly if the drug is one you haven't prescribed recently.

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Preface

THIS CURRENT EDITION of the Scope monograph on Human Mycoses is primarily intended as a guide for medical students and practitioners other than dermatologists who would appreciate a concise review of medical mycology. Because of the numerous laboratory manuals available we have not attempted to detail the laboratory tests used to identify the individual fungi but have only given their microscopic appearance in culture and in tissue as well as their cultural characteristics.

So as not to compete with the excellent mycology textbooks available, we have relied extensively on photographs, mainly in color, to characterize the various organisms included in this treatise. Arbitrarily we have divided this monograph into two sections; one deals with the common superficial fungus disease of the skin and the second with the deep or systemic mycoses. In both sections we have attempted to eliminate those organisms which were formerly thought to be fungi but are now known to be bacterial.

We wish to give special thanks to the generosity of E. S. Beneke, Ph.D., who has a dual Professorship in the Department of Botany and Plant Pathology, College of Natural Science and the Department of Microbiology and Public Health in the College of Human Medicine at Michigan State University, East Lansing, Michigan, for his many valuable suggestions in the formation of the manuscript and for providing us with a large majority of the illustrations.

We also wish to thank E. Richard Harrell, M.D., Professor and Chairman of the Department of Dermatology, The University of Michigan Medical Center, Ann Arbor, Michigan, for contributing his time and effort regarding the treatment of the diseases mentioned herein.

Miss Mary Ellen Hopper was extremely helpful in collecting and cataloging the slides of the late George Lewis, M.D., and allowing us to reproduce them in this revised monograph.

Harold Van Velsor, M.D., Wilmington, North Carolina, was very generous in providing us with excellent photographs of tinea nigra. Thomas S. Turner, Cytologist, B.P.A., of the Department of Gynecology and Obstetrics, New Jersey College of Medicine and Dentistry, Jersey City, New Jersey generously provided a slide of Hyphae and Spores of Candida Species.

Extreme thanks are due A. G. Macleod, M.D., (consultant) The Upjohn Company, Kalamazoo, Michigan, for his patience in reading the manuscript and help in arranging the illustrations.

Acknowledgment to the individual photographs can be located at the back of the book on page 46.

RELATIONSHIP OF VARIOUS CATEGORIES OF THE FUNGI

CLASS	Sub-Class, Series, or Order	Examples of Genera or Species
Myxomycetes (Slime molds)	6 Orders	
Schizomycetes (Bacteria)	Eubacterials (true bacteria)	Corynebacterium tenuis
Higher bacteria	Actinomycetales (funguslike bacteria; may branch)	Actinomyces, Nocardia, Streptomyces
Higher bacteria	Chlamydobacteriales (algalike bacteria; may be sheathed)	
Higher bacteria	Myxobacteriales (slime bacteria; slimy creeping mass)	
Higher bacteria	Spirochaetales (protozoalike bacteria)	
Higher bacteria	Rickettsiales (intracellular parasites)	
Lower fungi — **Phycomycetes** (algal fungi; nonseptate hyphae; asexual spores formed in sporangia; oöspores or zygospores formed sexually)	 Chytridiales (uniflagellate zoospores)	(?) Rhinosporidium
Lower fungi — **Phycomycetes**	 Saprolegniales—sexual: oöspores (Biflagellate zoospores)	(water molds)
Lower fungi — **Phycomycetes**	 Mucorales—sexual: zygospores (Nonmotile spores)	Rhizopus [Bread mold]—(sporangia at nodes of stolons opposite Rhizoids); Mucor—(sporangia directly on mycelium; no rhizoids); Absidia
Higher fungi — **Ascomycetes** (sac fungi; form ascospores, typically 8, sexually in an ascus or sac)	Sub-Class Hemiascomycetidae: Endomycetales (yeasts)	
Higher fungi — **Ascomycetes**	Sub-class Euascomycetidae:  Series Plectomycetes—3 orders (cleistothecia, black molds, blue molds)	Arthroderma, Nannizzia, Allescheria (Dermatophyte Perfect Stage)
Higher fungi — **Ascomycetes**	 Series Pyrenomycetes—9 orders (the perithecial fungi)	Piedraia
Higher fungi — **Ascomycetes**	 Series Discomycetes—4 orders (cup fungi, morels, and truffles)	
Higher fungi — **Form-Class Deuteromycetes** (imperfect fungi; asexual stages of Ascomycetes or rarely Basidiomycetes whose sexual stages are yet undiscovered)	 Form-Order Melanconiales (reproduce by conidia in acervuli)	
Higher fungi — **Form-Class Deuteromycetes**	 Form-Order Sphaeropsidales (reproduce by conidia in pycnidia)	
Higher fungi — **Form-Class Deuteromycetes**	 Form-Order Moniliales (reproduce by conidia borne otherwise, or by oidia, or by budding)	Aspergillus, Blastomyces, Candida, Cephalosporium, Cladosporium, Coccidioides, Cryptococcus, Epidermophyton, Fonsecaea, Geotrichum, Histoplasma, Keratinomyces, Madurella, Malassezia, Microsporum, Paracoccidioides, Phialophora, Sporotrichum, Trichophyton, Trichosporon
Basidiomycetes (produce sexual spores on a base, or basidium)	 Sub-class Heterobasidiomycetidae—3 orders (jelly fungi, rusts, smuts)	
Basidiomycetes	 Sub-class Homobasidiomycetidae—8 orders (mushrooms, puffballs, shelf, coral, and bird's nest fungi)	

Introduction

Although some changes have occurred in the classification and diagnosis of fungus diseases of the skin, the greatest change that has occurred is in the prognosis of dermatophytosis which has improved considerably in the last few years.

"Ringworm Fungi"—the dermatophytes—are widespread and stubborn pathogens, but the diseases they cause are nonfatal, are often self-limited, and are sometimes asymptomatic and consequently apt to be ignored by the patient. The fact that these diseases can be disabling under circumstances of stress, however, was demonstrated in World War II; eight per cent of all hospital admissions among the armed forces were for cutaneous diseases and of these, dermatophytosis were the second most common.

To the dermatologist, fungi are quite important like bacteria but until recently medical mycology has lagged far behind bacteriology. There was a still greater lag in the development of specific fungistatic agents until 1958 when Gentles demonstrated that oral griseofulvin cured experimental *Microsporum canis* and *Trichophyton mentagrophytes* infections in guinea pigs, by laying down in the epidermal structures just before keratinization, a barrier to prevent penetration of the dermatophytes. This was the first fungistatic agent available in addition to the array of empirically chosen remedies that have proven successful in the treatment of the dermatophytoses. The treatment of the far more serious systemic mycoses has presented a much more difficult problem in the past. There was a complete absence of antifungal antibiotics of clinical value for treating systemic fungal infections until Brown and Hazen isolated nystatin from one of the actinomycetes in 1949. In 1957 nystatin was shown by Brown and Hazen to inhibit the growth of a number of systemic mycoses including *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis* and *Candida albicans* in small mammals, and led to extensive clinical exploration. These studies established the first antifungal antibiotic of therapeutic merit, later followed by others. The most significant development after the discovery of nystatin was the discovery of amphotericin B by Gold, Stout, Pagano, and Donovick in 1956 resulting in a more satisfactory treatment for deep-seated fungal infections.

As continued advances occur in knowledge concerning such fundamental problems as what the organisms require for growth, how they survive between cases of human parasitism, how they are transmitted, how they affect human tissue biochemically as they invade it, what kind of immune response they evoke, and what metabolic, endocrinological or other kinds of factors in the host favor or resist their invasion, more successful control of fungus diseases will be developed.

The progress that has been made in medical mycology has reduced the confusion that has surrounded the clinical aspects of the mycoses and the taxonomy of the fungi. Diagnosis has been facilitated since there is now fairly general agreement on the classification of fungus diseases and on most aspects of classification of the causative organisms.

The classification system followed in this article (see page 6) is similar to that used by Constantine J. Alexopoulos in his textbook *Introductory Mycology,* the names and the synonyms for organisms (see reverse side of supplement) are those used in current references in medical mycology (see list) and the classification of diseases used throughout is in general accordance with modern dermatological usage.

Of the tens of thousands of known fungi, only about fifty-five are commonly pathogenic for man. Under certain conditions some of the other fungi, well known as saprophytes, are capable of causing diseases in man. Classification is by: Kingdom, Division, Class, Order, Family, Genus and Species. The fungi are usually separated into four classes, with the Deuteromycetes and Ascomycetes containing most of the pathogenic fungi (see inside front cover). The Deuteromycetes, the class of fungi to which most of the skin pathogens belong are by definition "imperfect" fungi whose sexual or "perfect" stage is unknown or unrecognized. Under proper environmental conditions in the laboratory the "perfect" or sexual stage of a number of the skin pathogens may be developed. If a suitable specimen of moist soil which almost always contains one of these fungi is placed in a Petri dish and sterilized hair is placed upon it, the organism will start to grow on the hair. From the hair they can be transferred to culture media and isolated for identification.

The dermatophytes are distributed throughout the world but some species are rarely reported in certain regions and commonly in others. As G. C. Ainsworth has remarked in his *Medical Mycology,* any consideration of geographic distribution of mycoses must take into account the distribution of medical mycologists. This distribution pattern may be modified as man continues to move around the world at a faster pace.

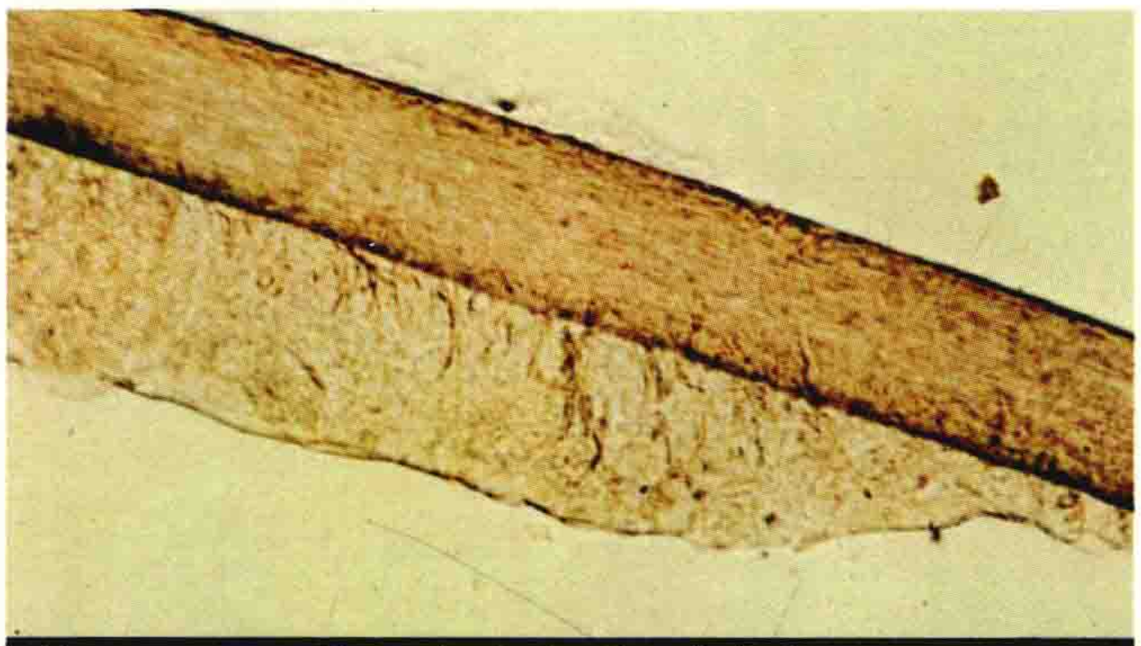
The dermatophytes invade the keratinized areas of the body such as the skin, hair and nails. The diseases incited are primarily by species of three genera: *Microsporum, Epidermophyton,* and *Trichophyton.* Cutaneous moniliasis, at times resembling the tineas is usually caused by *Candida* sp. The isolation and identification of the organisms from skin or nail scrapings, or from stubs of infected hairs are of value where difficult cases have not responded to routine treatment.

1 Piedraia hortai

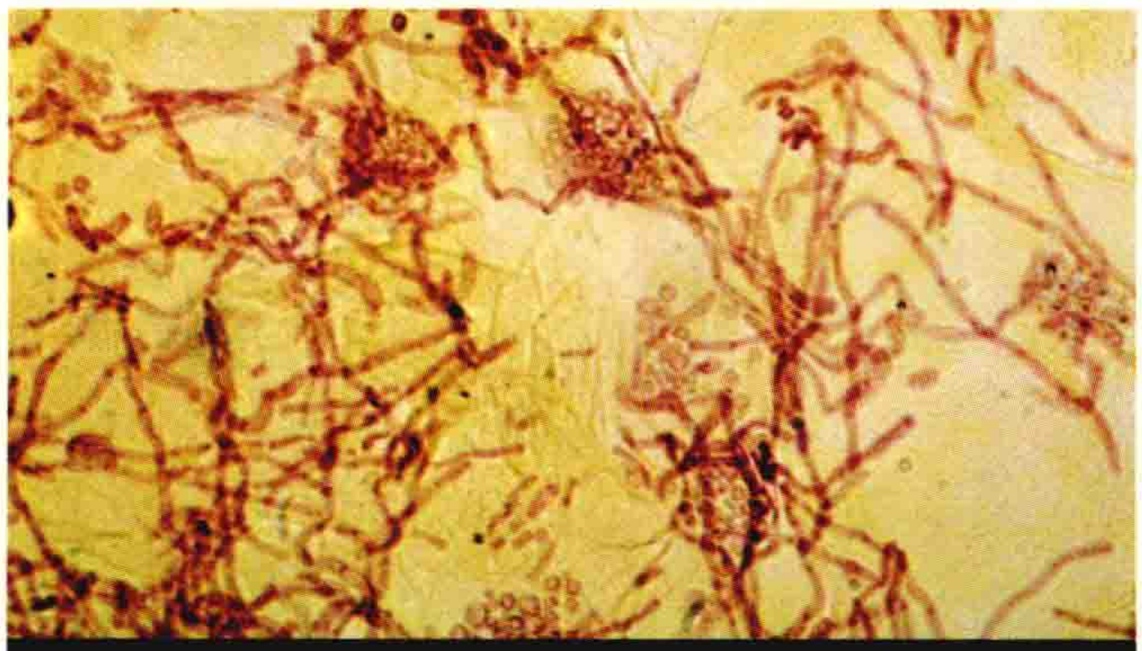
2 Piedraia hortai (hair)

3 Trichosporon beigelii

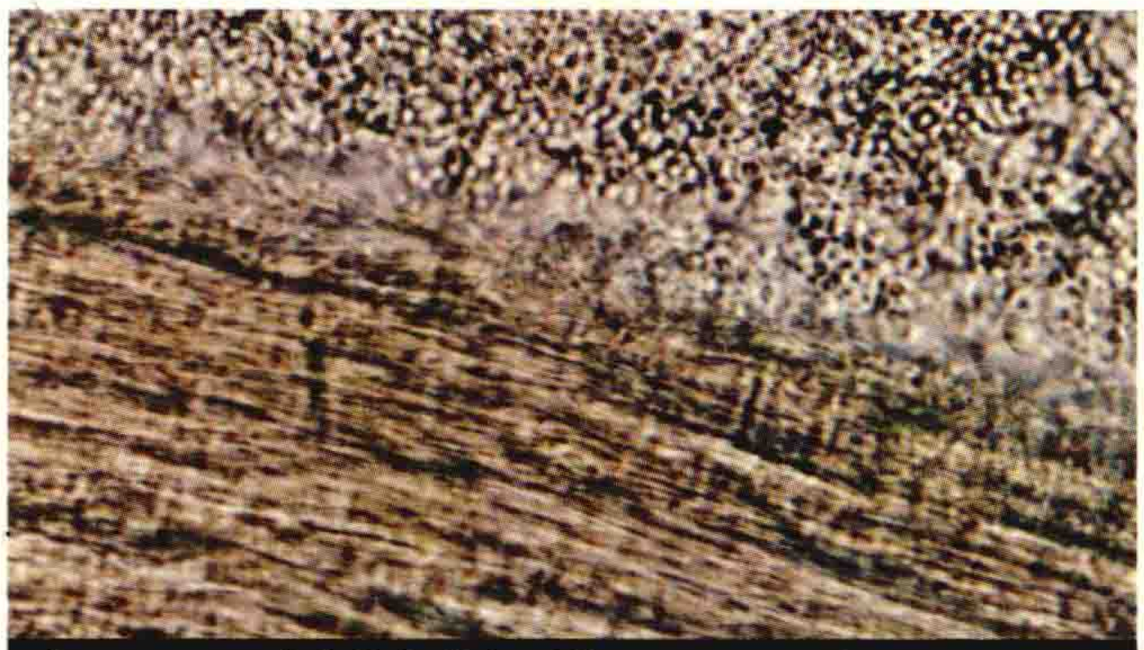
4 Trichosporon beigelii (hair)



5 Corynebacterium tenuis (hair)



6 Malassezia furfur (stained skin)

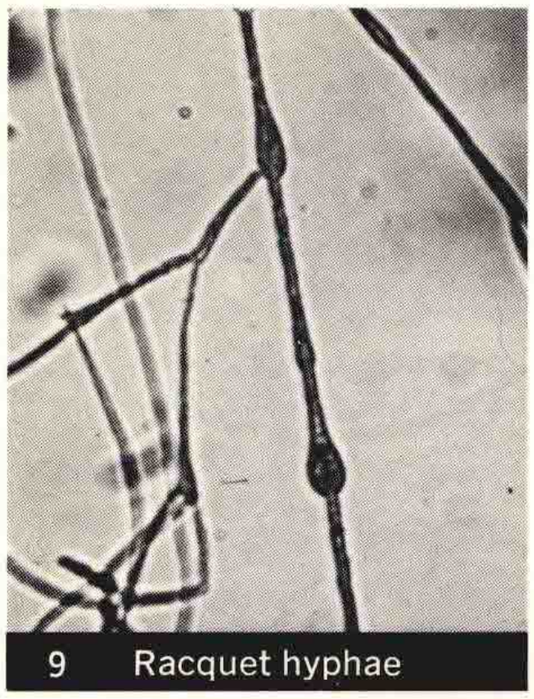


7 Ectothrix Hair—Microsporum canis

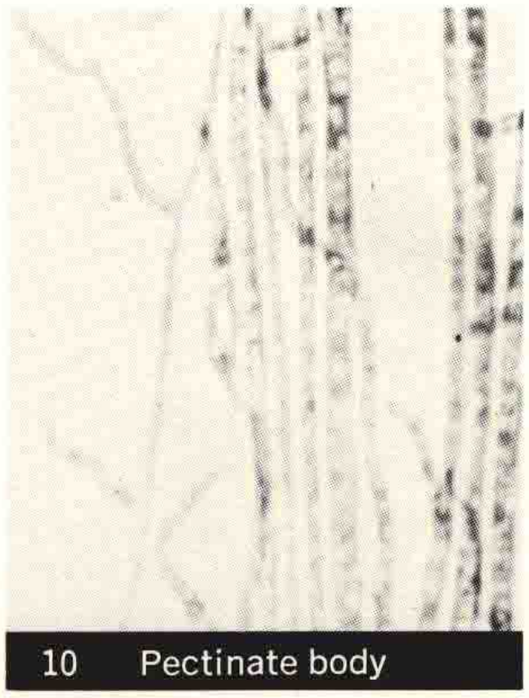
8 E. floccosum (in skin)

Superficial Infections and Clinical Examination

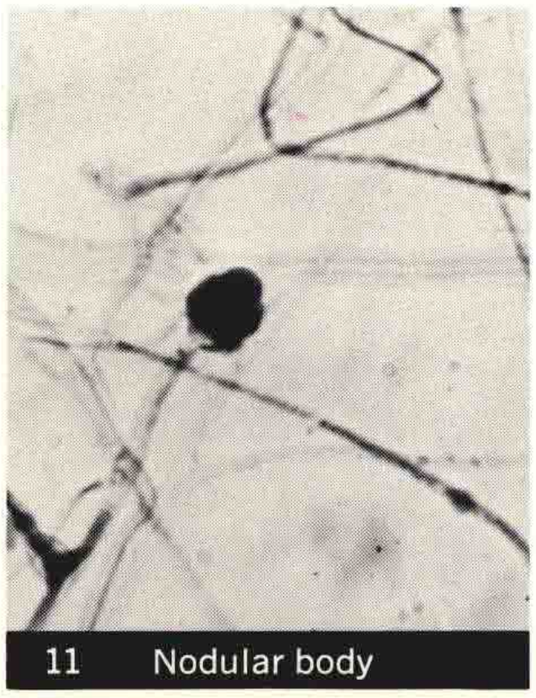
(1) Two of the three hair infections are usually cultured. *Piedraia hortai* is shown both in culture (2) and on the hair. (3) *Trichosporon beigelii* (4) has a cream colored colony, and a lighter colored nodule on the hair. (5) *Corynebacterium tenuis* is shown on the hair. (6) Skin scraping of *Malassezia furfur* stained with periodic acid-Schiff reagent. (7) The ectothrix type hair invasion of *Microsporum canis* or other species with mosaic pattern. (8) The segmented hyphae of *Epidermophyton floccosum* in the skin are similar to those seen in *Microsporum* and *Trichophyton* infections.



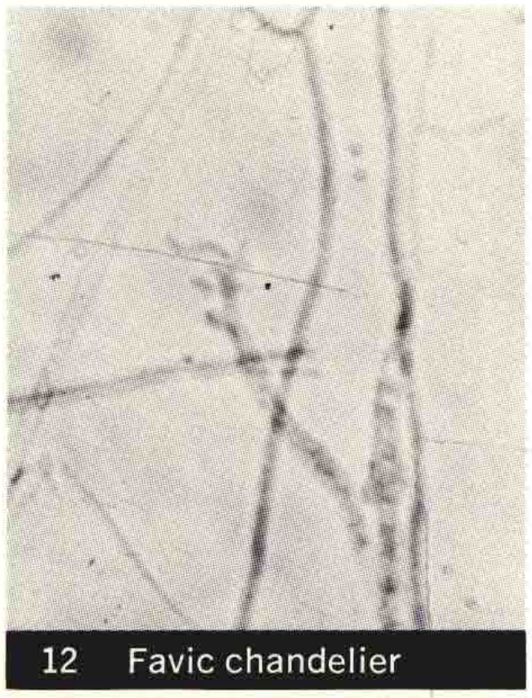
9 Racquet hyphae



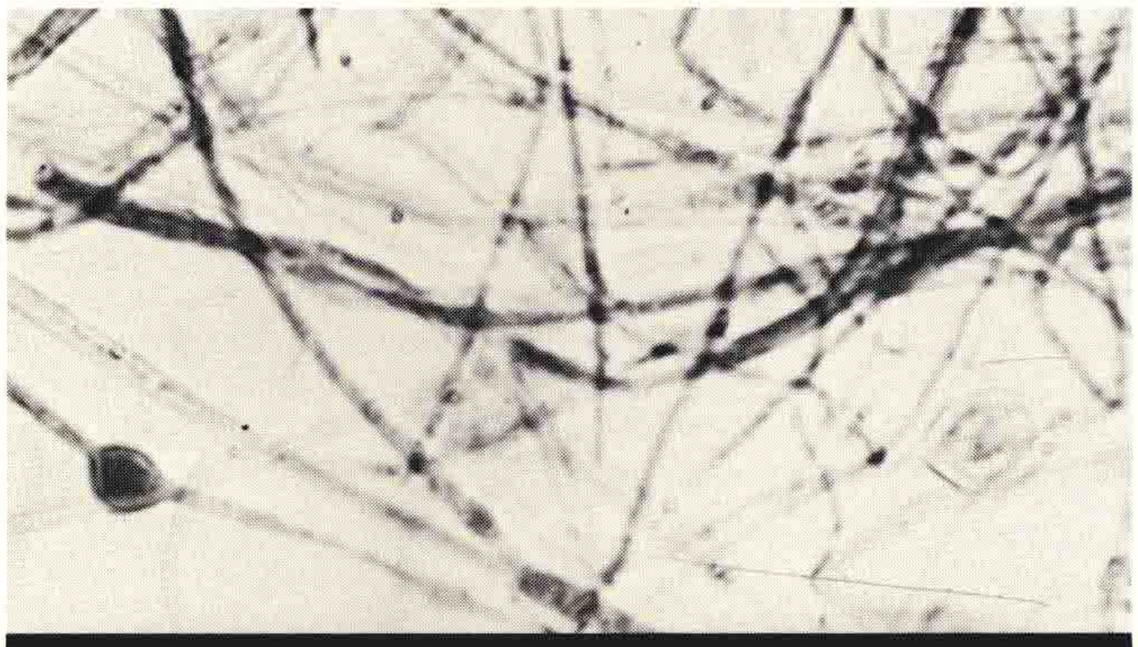
10 Pectinate body



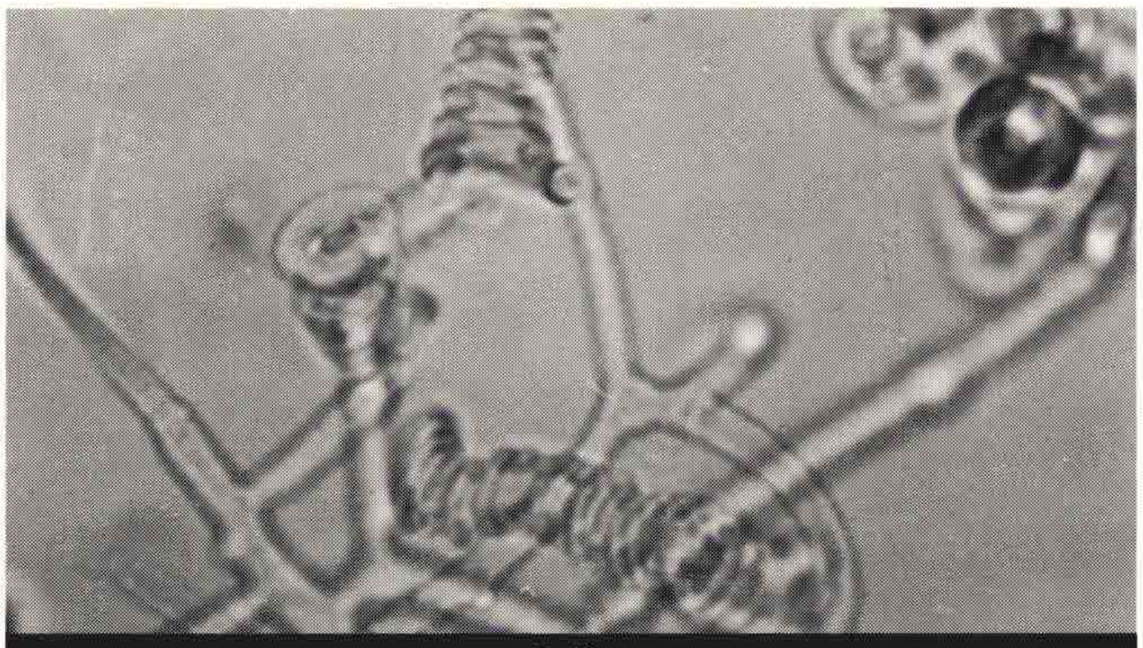
11 Nodular body



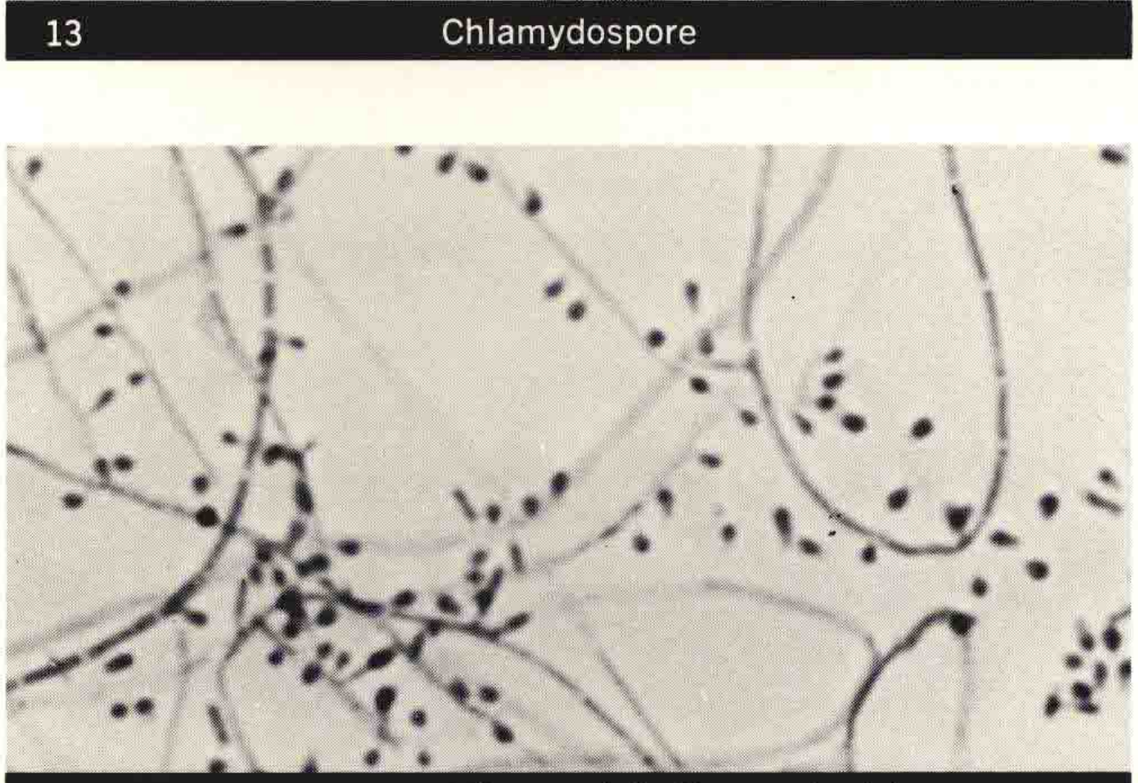
12 Favic chandelier



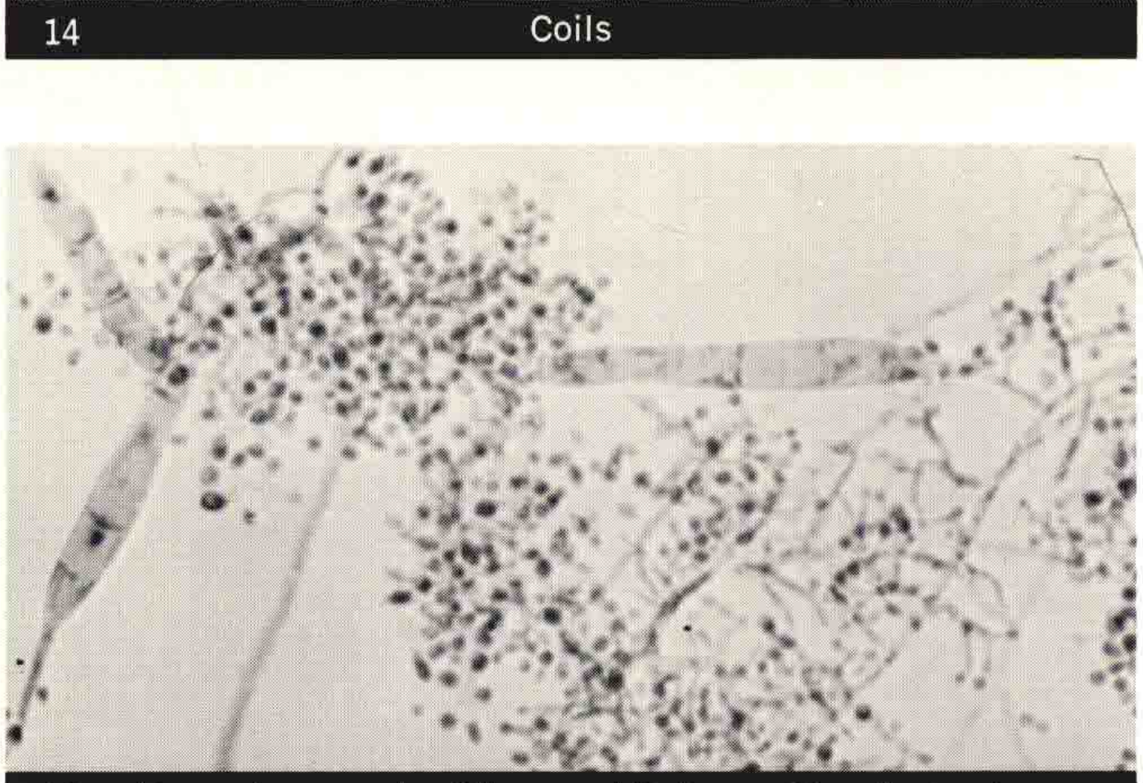
13 Chlamydospore



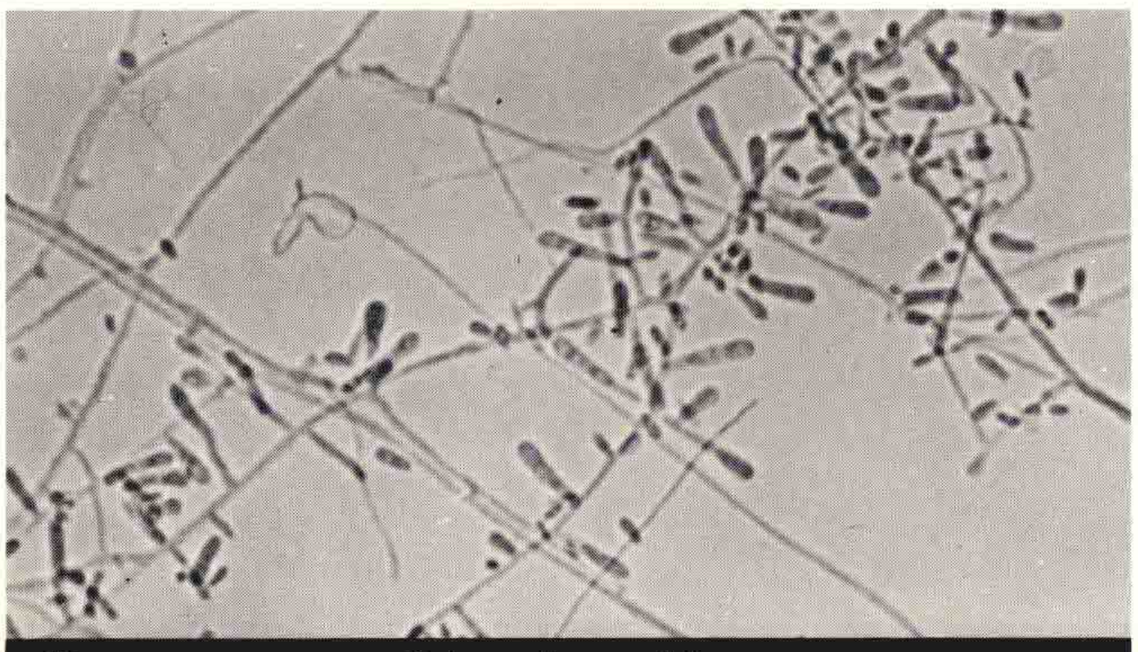
14 Coils



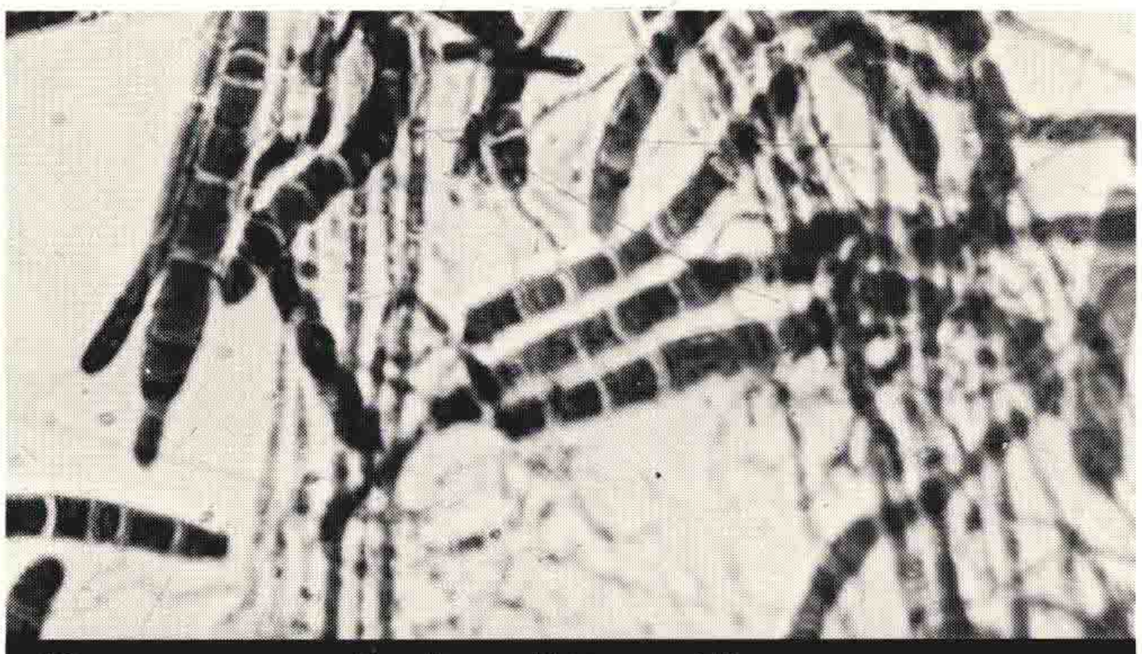
15 T. tonsurans Microconidia (borne singly)



16 T. mentagrophytes Microconidia (grapelike clusters)



17 T. terrestre conidia



18 T. rubrum Macroconidia

Microscopic Structures

Racquet hyphae (9), which are thick and club shaped, are typical of *Microsporum* and are also seen in *E. floccosum* and *Trichophyton.* The pectinate body, a curved hypha with irregular or "broken comb" projections along one side (10 left) is typical of *Microsporum* species and the various species of *Trichophyton.* The nodular body (11) a mass of closely twisted hyphae is seen in *Microsporum* and less often in *Trichophyton* and *Epidermophyton.* The favic chandelier (12) composed of knobby branching hyphae has been said to be diagnostic of *T. schoenleinii* but is also found in other *faviform Trichophytons. Chlamydospores* (13), large thick-walled resting spores are seen in most all colonies. Coils (14) are found in *Trichophyton* species. *Microconidia,* small round, oval or clavate spores borne singly (15) or in grape-like clusters (16) are numerous in some *Trichophyton* species; in others they occur rarely; a few laterally borne, are found in *Microsporum,* but none in *Epidermophyton. Macroconidia* (17 and 18), large oat-shaped spores which may be connected with hyphae or detached, are characteristic of species of *Macrosporum* (22), *Trichophyton* (18) and *Epidermophyton* (34) as described in the chart on page 27. The *conidia of T. terrestre* vary from microconidia to macroconidia in size.

FUNGUS DISEASES OF THE SKIN

TINEA CAPITIS, a fungus infection of the scalp and hair, is caused by species of *Microsporum* and *Trichophyton* and takes on various characteristics according to the species of invading organism.

Until recently *Microsporum* infections have been the most common cause of tinea capitis in children of school age, boys more often than girls. *M. audouinii* is the predominant species in most temperate countries. It is highly contagious and occurs in epidemics; likely sources of infection seem to be hair clippers and theater seats. It was reported only sporadically in the U.S. until about 1942, then widespread epidemics began to occur in the large eastern cities. The second commonest cause in the U.S. is *M. canis,* which is most often transmitted by young animals, particularly kittens. *M. gypseum,* which is rare in most parts of the world except South America, is also transmitted by young animals, more often puppies than kittens, and occurs commonly in soil.

The *Microsporum* infections begin with small, itching, scaling papules, which spread peripherally to form patches. Hairs in the path of the advancing, circular lesion lose luster and break off a few millimeters above the scalp to leave irregular grayish areas of hair stumps surrounded by spores. Since the spores are observed outside the hair shaft the infection is described as ectothrix. Fungus elements in or on the hair stumps as examined microscopically are the one certain diagnostic sign of tinea capitis, and *Microsporum*-infected hairs can be selected for study because they usually fluoresce bright green under filtered ultraviolet light (Wood's lamp).

M. audouinii infections tend to be less inflammatory than those caused by *M. canis* and particularly *M. gypseum,* which occasionally causes favus (to be discussed later). The inflammatory *Microsporum* lesions tend to be self-limited and are readily cured; the noninflammatory *M. audouinii* infections are more resistant but usually clear spontaneously at puberty if not cured before, apparently because, as demonstrated by S. Rothman et al., the sebum secreted after puberty contains fatty acids selectively fungistatic to this organism. In general, children are more susceptible to fungus infections of the scalp than adults. Albert L. Kligman, however, who experimentally inoculated human subjects in a state institution for congenital mental defectives, found that about 40 per cent of the children were resistant to scalp infections with both *M. audouinii* and *M. canis* and some adult scalps were not resistant. In all successful inoculations, some form of minor trauma was a prerequisite.

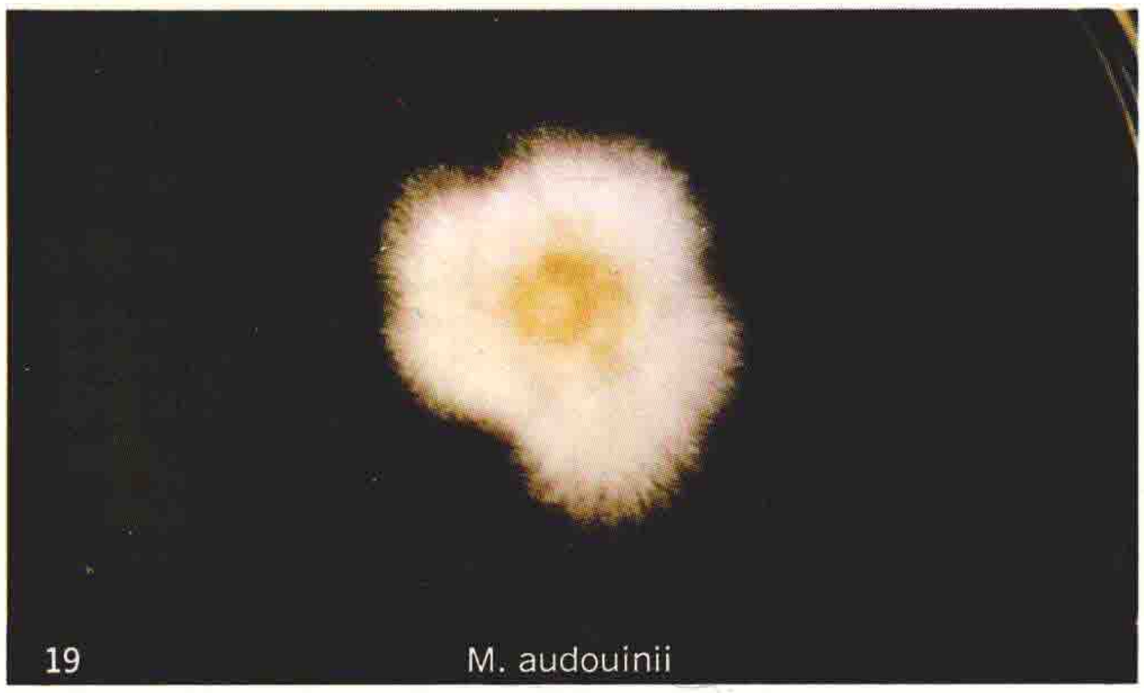
Certain *Trichophyton* infections of the scalp are rare in the U.S., particularly those caused by *T. schoenleinii, T. violaceum,* and *T. megninii.* Tinea capitis caused by *T. mentagrophytes* and *T. rubrum* occurs less rarely in this country, and an epidemic caused by *T. tonsurans* appeared in the southwestern part of the U.S., apparently spreading from Mexico. Currently, *T. tonsurans* infections of the scalp are more common in the U.S. Most Trichophyton infections are spread from man to man, directly or indirectly, but *T. mentagrophytes* and *T. megninii* both may be spread by animals.

Adult scalps do not have as much immunity to *Trichophyton* infections as to *Microsporum* infections. When the disease is acquired in childhood it tends to persist through puberty and is more resistant to treatment. *T. violaceum, T. tonsurans,* and *T. schoenleinii* produce especially refractory infections.

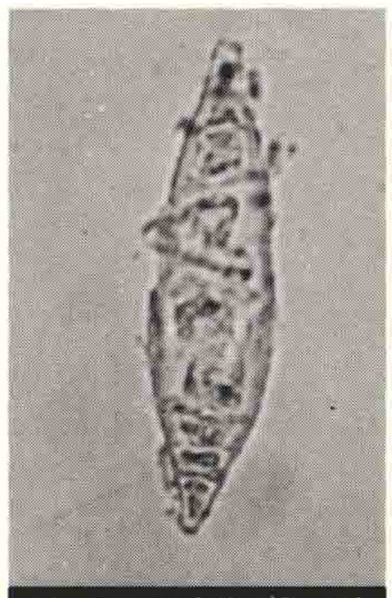
T. violaceum and *T. tonsurans* produce a "black dot" ringworm, in which the hairs, which are apparently invaded almost entirely within the shaft (endothrix infection), break off at the surface and leave stumps that look like black dots in the follicles. Detection of the disease may be difficult because it may be confused with dandruff or psoriasis. The lesions are small and chronic, only a few hairs may be infected, and these hairs, if pigmented, fluoresce little or not at all under Wood's lamp; gray, white, or blond hair may fluoresce a dead, lusterless white or, rarely a clear violet.

T. schoenleinii produces a chronic scalp infection called favus, which appears first as yellow points of fungus growth, usually penetrated by one or more hairs.

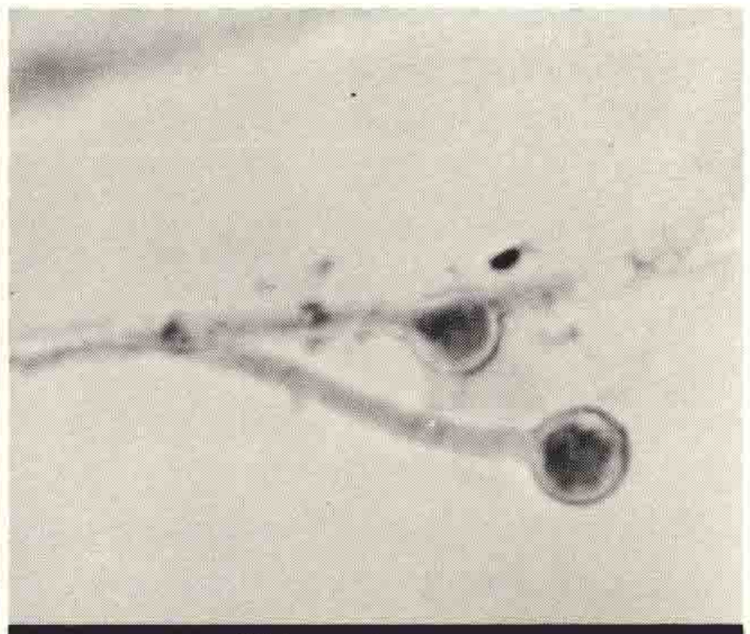
Growth and Microscopic Characteristics of
Microsporum sp. and *Epidermophyton* sp.



19 M. audouinii

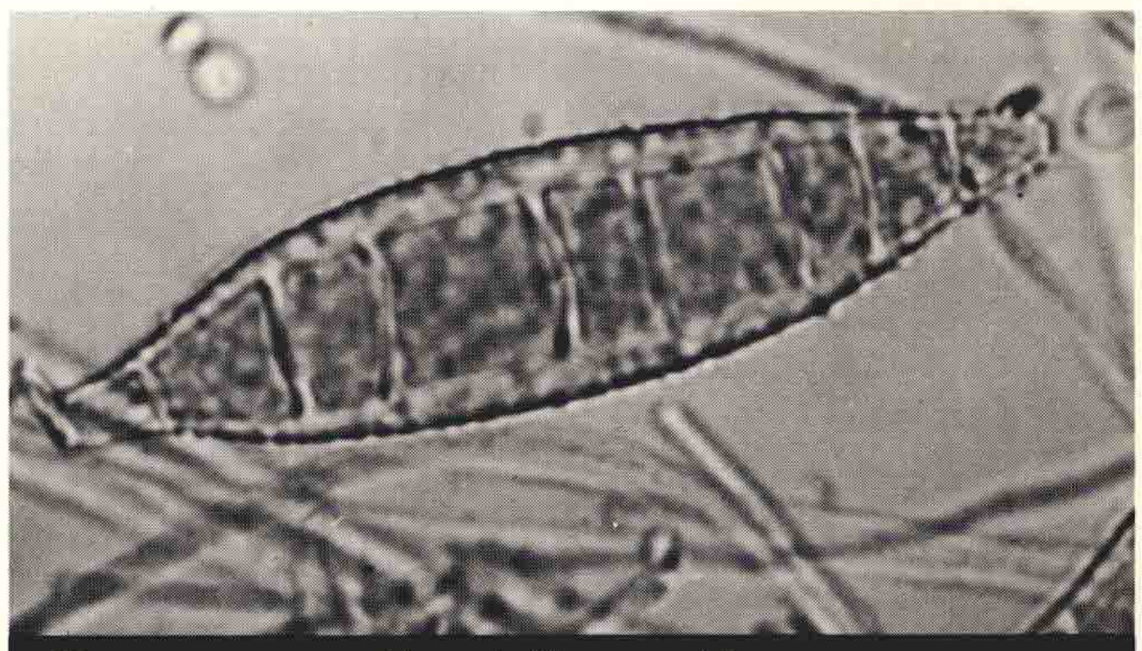


Macroconidia (Rare)
M. audouinii



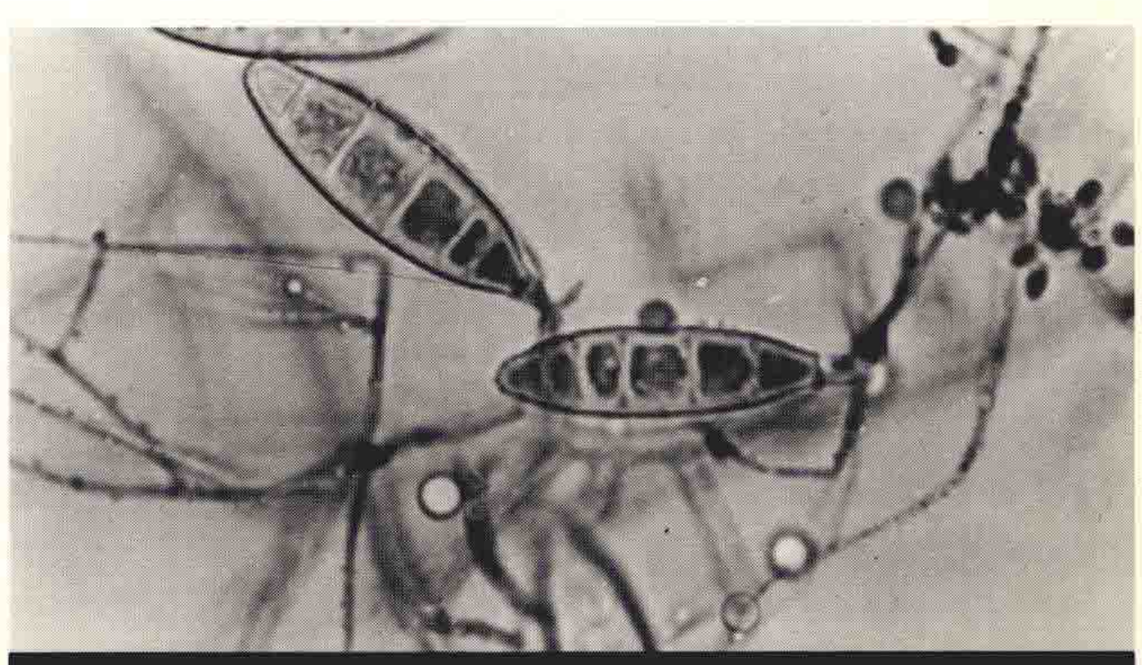
20 Chlamydospores

21 M. canis

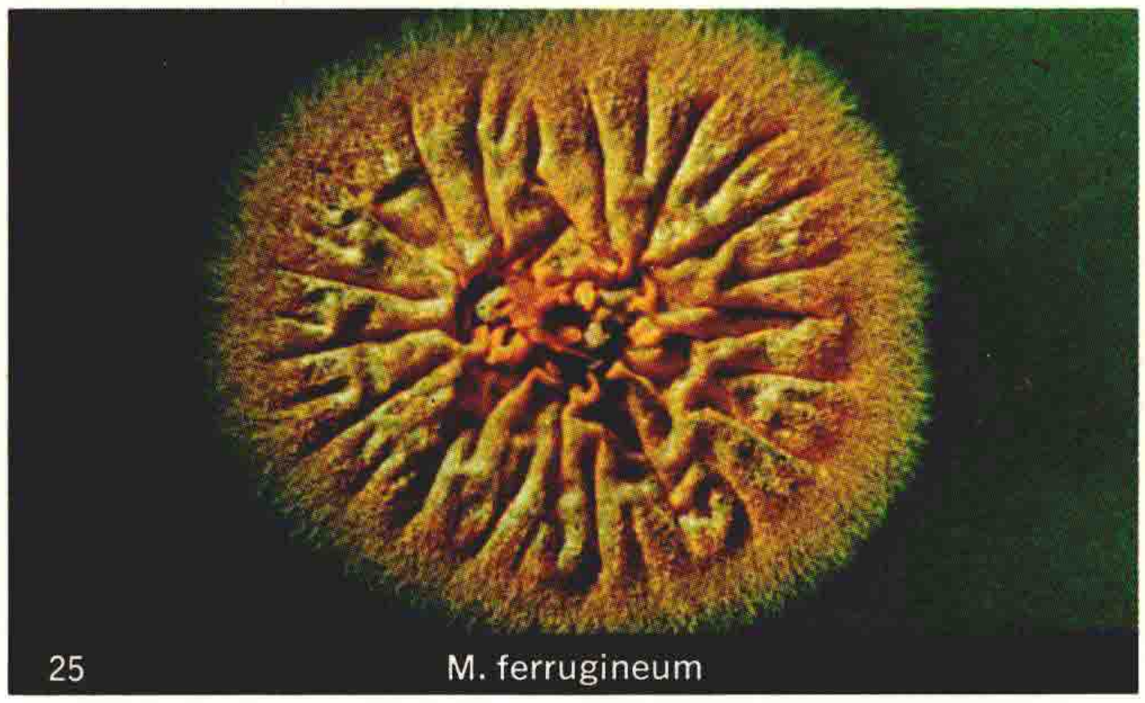


22 M. canis-Macroconidia

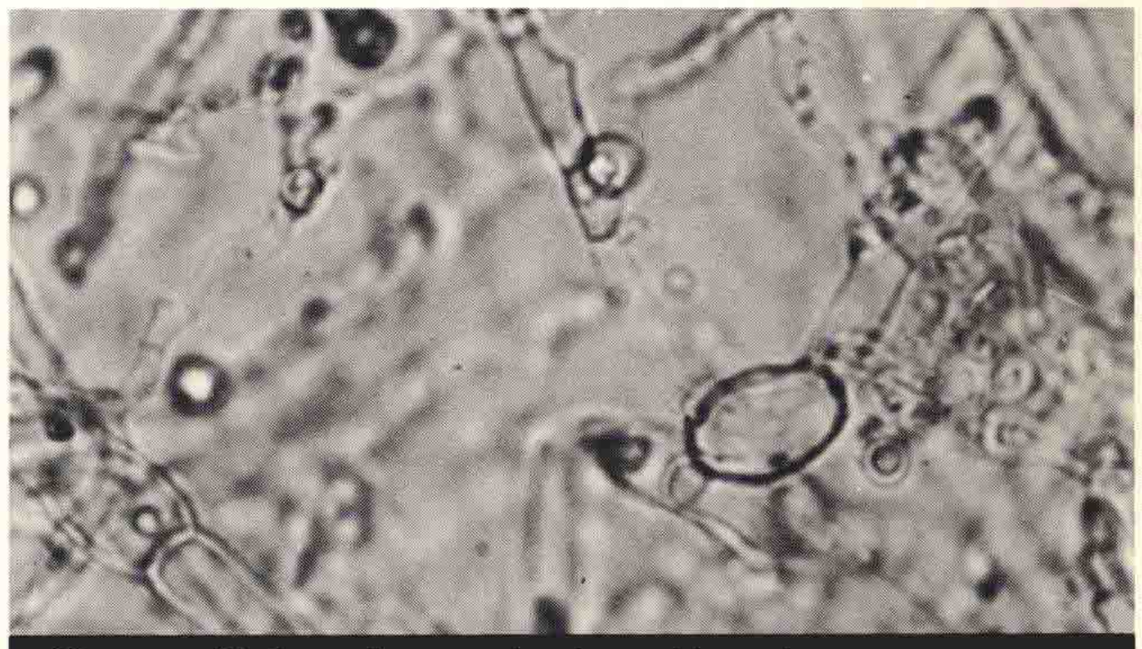
23 M. cookei



24 M. cookei-Macroconidia



25 M. ferrugineum



26 M. ferrugineum—hyphae, chlamydospores

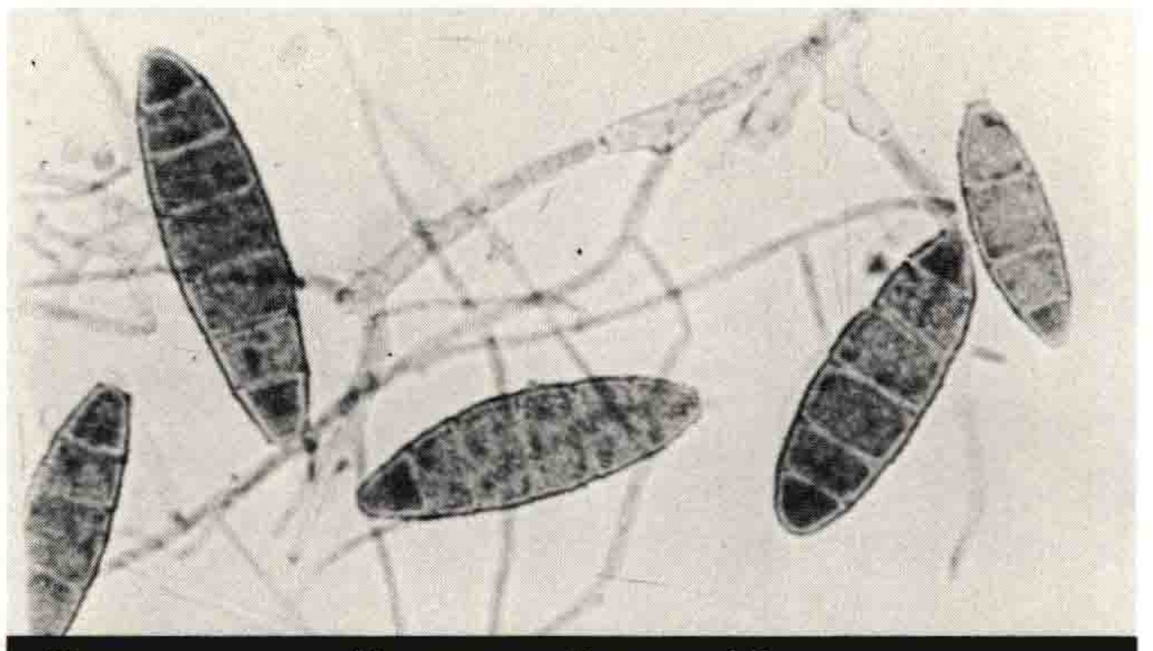
Infected hairs (endothrix) fluoresce gray-green. The points of infection develop into large elevated cup-shaped crusts called scutula, which have a peculiar mousy odor. Scutula may eventually cover the scalp; the skin then atrophies and permanent baldness results. The infection may spread to the smooth skin and nails. *T. violaceum* and, rarely, *M. gypseum* also cause favus.

T. mentagrophytes produces a violent inflammatory reaction in the scalp and frequent kerion (a boggy, pustular abscess about the hair follicles); *T. rubrum* causes milder inflammation. Inflammation tends to limit the course of the disease. Hairs do not fluoresce in these infections.

27 Microsporum gypseum

TINEA CORPORIS, sometimes known as *tinea circinata* or ringworm of the smooth skin, may be caused by many species of *Microsporum* and *Trichophyton,* and may produce lesions that vary from simple scaling to deep granuloma.

Microsporum species are the predominant cause of tinea corporis in children as they are more susceptible to these organisms than adults. *M. audouinii,* however, attacks the hair much more often than the smooth skin in temperate areas. A common cause of tinea corporis is *M. canis* and *T. mentagrophytes* in the U.S. *M. ferrugineum* is rarely reported outside Asia, Africa, and Middle Europe.



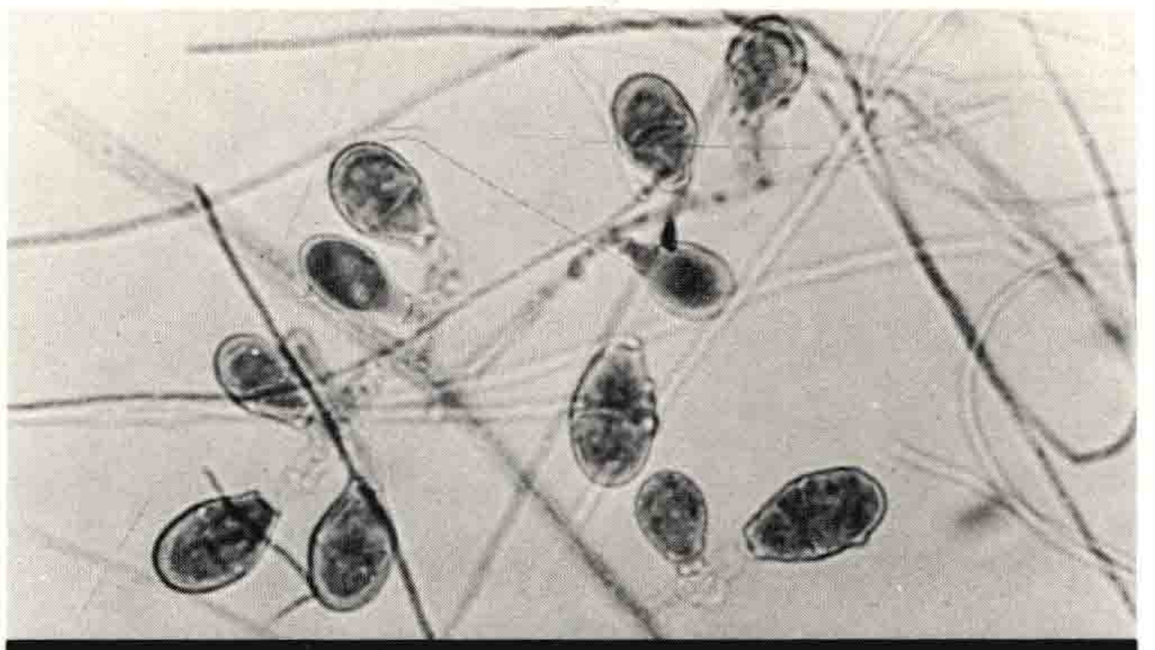
28 M. gypseum-Macroconidia

The typical lesion is annular. The center is scaly and usually tends to heal; the periphery is an advancing circle of vesicles and papules. Several lesions may become coalescent and often enlarge without central healing to form solid, papulosquamous plaques. There is often itching, especially in warm weather. Inflammatory reactions are more common in *M. canis* and *M. gypseum* infections, and lesions show less central healing.

The Trichophyton infections of the smooth skin seen most often in this country are those caused by *T. mentagrophytes* and *T. verrucosum* (both acquired from animals), *T. rubrum,* and *T. tonsurans*. Infections with *T. schoenleinii* and *T. violaceum* are seen here only occasionally: *T. concentricum* is largely confined to the tropics—Asia, certain Pacific islands, and South America. The classic lesion in trichophytosis of the smooth skin resembles that described for *Microsporum* ringworm. As in tinea capitis, however, *Trichophyton* infections are generally more resistant to treatment.

29 M. nanum

T. mentagrophytes and *T. verrucosum* produce a typical inflammatory reaction. Most cases are mild and superficial, but there are a number of recent reports of deep suppurative lesions, chiefly on the wrists and forearms, occurring among farm workers who handle cattle and other livestock. These lesions are described as



30 M. nanum-Macroconidia