CLINICAL MICROBIOLOGY REVIEWS, Oct. 2010, p. 884–928 Vol. 23, No. 4
0893-8512/10/$12.00 doi:10.1128/CMR.00019-10

Melanized Fungi in Human Disease

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INTRODUCTION

Melanin is a ubiquitous compound found in many microbes and animals. Its functions are varied but are based on the unique molecular characteristics of its structure, which make it an extremely stable molecule, resistant to a variety of destructive physicochemical processes (83, 109, 324). In recent years its pathogenic role in fungi has become well described (123, 292, 375, 460, 546). This review will focus on fungi that are considered to be melanized as a primary feature, particularly with regard to their phenotypic appearance (macroscopic and microscopic morphologies) and appearance in tissue (histology).

The terms used to describe these fungi have evolved over the

past several decades. As *Sporothrix schenckii* was one of the earliest melanized fungi described, "sporotrichoid" was often used to describe similar fungi, though currently it has been replaced by other, more useful terms. "Phaeoid," "phaeo-sporotrichose," and "dematiaceous" have also been mentioned in the literature (574). "Phaeo" comes from the Greek meaning "dark" and has been commonly used, particularly when describing infections due to these fungi as "phaeohyphomycosis," i.e., infection caused by dark-walled fungi, as suggested by Ajello et al. (12, 630). It has been suggested that the term "dematiaceous" is not appropriate given its etymologic derivation from the Greek "deme," meaning bundle, though it has become fairly entrenched in medical mycological literature and will likely persist in nomenclature (574). The term "melanized" has become more utilized recently, given its specific meaning. For the purposes of this review, however, the terms "dematiaceous," "melanized," "dark," and "phaeoid" are used interchangeably to denote fungal elements containing melanin.

The presence of melanin alone is probably not a useful criterion for inclusion in this group of clinically important fungi, as melanin has been demonstrated in practically all "nondematiaceous" clinical fungi examined in the literature, including *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Aspergillus* spp., and even *Candida albicans* (293, 521, 548, 599, 757). One might contrast the fungi discussed here as heavily melanized, with brown-pigmented hyphae in tissue often discernible without the use of any staining procedure. At present, no quantitative measure of melanin is available to distinguish dematiaceous from other fungi. In addition, *Sporothrix schenckii*, with a yeast form in tissue, is well known and well described (177) as the agent of a unique clinical entity, sporotrichosis, and only issues regarding its mycology will be discussed here.

Melanized fungi are common in the environment (see Ecology below) and are often isolated in the microbiology lab, where they may be considered contaminants. Indeed, only 10% of dematiaceous lab isolates are likely to have clinical significance (72, 607). Clinical disease due to these fungi is uncommon, with one estimate from a large metropolitan area of one case/million persons/year (617). Despite their rarity in clinical practice, melanized fungi have become increasingly recognized as important pathogens, particularly in immunocompromised patients, though individuals with apparently "normal" immune systems have also been reported to have invasive, often fatal infections (627, 628).

The clinical syndromes caused by these fungi are differentiated based on histologic findings into eumycetoma, chromoblastomycosis, and phaeohyphomycosis. Eumycetoma is a deep tissue infection, usually of the lower extremities, characterized by the presence of mycotic granules (572). It is associated with a relatively small group of fungi. Chromoblastomycosis is caused primarily by a few species of fungi that produce characteristic sclerotic bodies in tissue and is usually seen in tropical areas (501, 572). Phaeohyphomycosis is a term generally reserved for the remainder of clinical syndromes caused by melanized fungi (623, 630). For the purposes of this review, these will be arbitrarily divided into allergic disease, superficial and deep local infections, pulmonary disease, central nervous system (CNS) infection, and disseminated disease. We do not aim to review every publication regarding melanized fungi, but rather we seek to provide a broad, yet in-depth overview of the field as it currently stands, recognizing that it will continue to evolve and expand with our increasing knowledge of and experience with these clinically important fungi.

ECOLOGY

Melanized or dematiaceous fungi as defined above are frequently considered ubiquitous saprobes inhabiting living and dead plant material and, for the most part, residing in the soil. We now know, however, that these generalized assumptions are incorrect for the group as a whole, as several etiologic agents occupy specific ecological niches or microenvironments, and the knowledge of their natural ecology contributes to our understanding of their opportunistic/pathogenic potential (175, 177, 606, 779). It has been suggested (175) that our use of the term "dematiaceous" be restricted to those ubiquitous, mostly plant-associated hyphomycetous fungi with brown hyphae (220, 221), such as *Alternaria*, *Bipolaris*, *Curvularia*, and *Exserohilum* in the order *Pleosporales*. The natural ecology of melanized fungi in several other orders is more restricted (187). For example, fungi in the order *Calosphaeriales* belong mostly to woody-plant- or wood-inhabiting genera such as *Phaeoacremonium*, *Phialemonium*, and *Pleurostomophora*, whereas some genera in the order *Chaetothyriales*, such as *Exophiala*, may have specific microenvironments and are characterized as "microextremophiles." The ability of some species in this genus, such as *E. xenobiotica*, to grow in high concentrations of xenobiotics (606) such as xylene, toluene, or creosote-treated utility poles, as well as to cause human disease, is truly remarkable. Species in the genus *Exophiala* and related genera are frequently referred to as the "black yeast-like fungi" and are so named because of their ability to produce budding, yeast-like cells at some point in their life cycle as well as dark hyphae. The ecology of *Pseudallescheria* and *Scedosporium* was also recently investigated by examining the occurrence of these species in natural and human-dominated environments (393). These findings demonstrated increasing environmental recovery with increasing human habitation and a concomitant elevation in nitrogen concentrations. Another genus defined by its residence in a particular environmental niche is the halophilic genus *Hortaea* in the order *Capnodiales*. *Hortaea werneckii*, the agent of tinea nigra, is found in subtropical saltwater habitats and is manifested by its opportunistic adherence to the dead, salty keratin layers of the human hand (87). Thus, while several genera are considered "ubiquitous," many prefer well-defined microenvironments which, for some genera, predispose them to causing disease where similar conditions exist in the host.

In addition, there are species that appear to be geographically restricted, such as *Rhinocladiella mackenziei*, which has been seen primarily in patients from the Middle East (726). While *Scedosporium prolificans* has been reported from many locations, most clinical cases originate from Australia and Spain, for unclear reasons (76, 336). This may be due to environmental features that preferentially support specific fungal species.

CLASSIFICATION, TAXONOMY, AND NOMENCLATURE

Classification of fungi is simply their assignment into defined categories. A classification system is composed of hierarchical

groups which may be further subdivided to indicate degrees of relationships. The basic unit of classification is the species, although there is currently no universally acceptable definition for this unit. Taxonomy is the arrangement of these fungi into a classification. With multilocus sequencing providing classification insights unavailable to the phenotypic systematists (those who study the relationships and classification of organisms and the processes by which they have evolved), new phylogenetic classification schemes have emerged. Taylor et al. have provided an excellent treatment of the phylogenetic concepts underlying the definition of species in fungi (737). The abbreviated classification scheme to the ordinal level for ascomycetous melanized fungi covered in this review is based upon the most recent work of Hibbett et al. (340) and the Myconet "Outline of Ascomycotya" (463).

Kingdom: Fungi
- Phylum: *Ascomycota*
  - Subphylum: *Pezizomycotina*
    - Class: *Dothideomycetes*
      - Orders: *Capnodiales*, *Dothideales*, *Pleosporales*, *Botryosphaeriales*
    - Class: *Eurotiomycetes*
      - Order: *Chaetothyriales*
    - Class: *Sordariomycetes*
      - Orders: *Microascales*, *Sordariales*, *Calosphaeriales*, *Ophiostomatales*

As seen above and in Table 1, clinically significant melanized fungi span several ascomycetous orders in the kingdom Fungi.

Nomenclature refers to assigning formal scientific names. This process is regulated by the International Code of Botanical Nomenclature (ICBN) (http://www.bgbm.org/iapt/nomenclature/code/default.htm) to facilitate a stable naming system and to avoid and reject names which are in error or are ambiguous (789). Lack of adherence to these requisites often invalidates a taxon name and results in multiple names for the same organism. Other reasons for name changes include the placement of fungi into new genera as determined by phylogenetic studies, which frequently occurs within this heterogeneous group of fungi. When this occurs, the species epithet is retained, but it may require modification in keeping with the rules of Latin grammar. An example of recent changes for melanized fungi include the movement of *Phialophora richardsiae* to *Pleurostomophora richardsiae* and of *Phialophora parasitica* to *Phaeoacremonium parasiticum.* Discovery of a previously unrecognized teleomorph (sexual or meiotic state) may also precipitate a name change. A recent example is found in the discovery of the teleomorph for *Scedosporium apiospermum*, which was incorrectly thought to be *Pseudallescheria boydii.* We now know through the work of Gilgado et al. that the teleomorph for *S. apiospermum* is the heterothallic ascomycete *Pseudallescheria apiosperma*, as evidenced by the production of cleistothecia (round sexual structures containing asci and ascospores) and ascospores (the sexual reproductive propagules) between compatible mating strains of *S. apiospermum* (283). As the teleomorph name takes precedence over the anamorph (asexual, mitotic) name, the correct binomial would be the sexual state. Whether this name would be adopted by clinicians in everyday usage remains problematic.

Also confusing for clinicians and laboratorians alike is the naming convention that permits the use of more than one name for the same fungus. This is allowed when a particular form of the fungus is the one more commonly seen in the laboratory. Fungi recovered in culture commonly display only an anamorphic state. They may be either heterothallic isolates with no known teleomorph or homothallic strains failing to produce their sexual state *in vitro*. A few clinically significant homothallic melanized fungi do form both anamorphs and teleomorphs in culture. In this situation, as mentioned above, the teleomorph name takes precedence over the anamorph name, e.g., *Pseudallescheria boydii* rather than *Scedosporium boydii* and *Microascus cinereus* rather than *Scopulariopsis cinerea.* Additionally, in some genera, such as *Pseudallescheria*, two separate anamorphs which are distinctively different microscopically may be produced, and these are referred to as synanamorphs (another asexual form of the same fungus). Some homothallic strains, however, lack anamorphs and are known only by the name of the sexual state. Examples would include members of the genus *Chaetomium.* The advent of sequencing characterization has provided the tools necessary to reevaluate the evolutionary relationships of these black molds, and today multilocus molecular phylogenetic studies are clearly redefining previously described entities, uncovering new species and varieties, and correlating these with their natural habitats.

IDENTIFICATION OF ETIOLOGIC AGENTS

Over 150 species and 70 genera of dematiaceous fungi have been implicated in human and animal disease (Table 2). As the number of patients immunocompromised as a result of diseases and medical therapy increases, additional species are being reported as causes of human disease, expanding an already long list of potential pathogens. Identification of melanized etiologic agents known to cause human or animal disease has traditionally been based upon phenotypic features of the isolate observed in culture (175, 177, 220, 221). This practice continues to be the mainstay of fungal identification in most routine settings. More recently, molecular techniques employed for classification purposes and those provided by research facilities have provided additional tools for the characterization of these molds. Extensive sequencing for some genera has illustrated the concept of "species complexes," or the inclusion of several separate species into what was formerly referred to as a single species. This has been clearly demonstrated in the genera *Exophiala* (825), *Scedosporium* (281–283), and *Phaeoacremonium* (525). The "splitting" of these species into separate taxa has of necessity changed our reporting practices. As an example, laboratories previously comfortable with discriminating only between *Exophiala* (*Wangiella*) *dermatitidis* and *E. jeanselmei* are now aware of several other clinically significant species that are not easily separated by phenotypic features alone (177, 184, 825) and that *E. jeanselmei* is in fact one of the less frequent agents of disease. Therefore, species other than *E. dermatitidis* are best reported as an *Exophiala* sp., not *E. dermatitidis*, unless sequencing has provided a species identification. These "new and improved" reporting techniques, however, must be communicated to clinicians in a manner consistent with their understanding of current organism terminology and the associated mycoses.

TABLE 1. Salient features of selected clinically significant dematiaceous fungi[a]

Genus type	Order	Genus or species	Salient phenotypic and/or diagnostic features[b]
Anamorphic (asexual) hyphomycete (conidia borne free)	*Capnodiales*	*Hortaea werneckii*	Colonies olivaceous to black, mucoid to yeast-like, restricted; broad hyphae, wide annellated zones produce pale brown 1- to multicelled annelloconidia
		Cladosporium spp.	Colonies olivaceous to black, velvety; conidiophores simple or branched, with or without nodes or swellings; ramoconidia ("shield cells") give rise to branching chains of fragile, dark, mostly 1- or 2-celled conidia with prominent attachment scares (hila)
	Dothideales	*Aureobasidium pullulans*	Colonies of *A. pullulans* var. *pullulans* mucoid, cream to pink initially and later brown to black, while those of *A. pullulans* var. *melanigenum* black at the outset; hyaline blastoconidia borne synchronously from hyaline hyphae; dark, thick-walled chlamydospores; DNA sequencing necessary for reliable differentiation of *A. pullulans* and *H. dematioides*
		Hormonema dematioides	Colonies similar to those seen in *A. pullulans*; hyaline blastoconidia produced asynchronously by percurrent proliferation from hyaline and dark hyphae
	Pleosporales	*Alternaria* spp.	Colonies woolly, pale to olivaceous to black, with rapid growth; large, dark, euseptate[c], muriform conidia in chains; *A. infectoria* conidia may be sparse and have long apical beaks serving as secondary conidiogenous cells
		Bipolaris spp.	Colonies woolly, gray to black, with rapid growth, bipolar germination, geniculate conidiophores, flattened hilum; *B. spicifera* has 3 distosepta[d] and 4 cells, while *B. hawaiiensis* has predominately 5 distosepta and 6 cells
		Curvularia spp.	Colonies woolly, gray to black, with rapid growth; geniculate conidiophores; conidia euseptate and curved (pronounced to subtle) due to swollen middle cell which is darker in *C. lunata*; *C. lunata* var. *aeria* produces large stroma visible with the naked eye
		Exserohilum spp.	Colonies woolly, gray to black, with rapid growth; geniculate conidiophores, truncate protruding hilum; *E. rostratum* has 7-9 distosepta; 8-10 cells; prominent dark basal and distal septa; *E. longirostratum* has longer conidia with central curvature; *E. mcginnisii* has subtle warty projections on conidia
	Chaetothyriales	*Exophiala* spp.	Colonies mucoid initially, later more filamentous; conidiogenous cells predominately annellidic; phialides sometimes present; annellated black yeast synanamorph often present; many species very similar microscopically; nitrate positive; DNA sequencing of ITS region facilitates species identification; maximum temp varies; most frequently seen clinical species include *E. xenobiotica*, *E. oligosperma*, *E. lecanii-corni*, and *E. phaeomuriformis*
		Exophiala dermatitidis	Colonies black, mucoid; nitrate negative; growth at 40°C; black yeast *E. exophialae* synanamorph present; most common clinical *Exophiala* species; accurately identified by phenotypic features; obsolete name *Wangiella dermatitidis*
		Cladophialophora spp.	Colonies black, velvety; growth rates and temperatures vary for individual species; microscopically similar to *Cladosporium* spp. but lack conidiophores, "shield cells," and prominent hila; conidia are nonfragile (remain intact in chains); neurotropic species include *C. bantiana* and *C. modesta*; other human pathogenic species include *C. arxii*, *C. boppii*, *C. carrionii*, *C. devriesii*, *C. emmonsii*, *C. mycetomatis*, *C. samoënsis*, and *C. saturnica*
		Fonsecaea spp.	Colonies olivaceous to black, velvety; conidia formed from swollen denticles giving rise to secondary and tertiary conidia in chains of up to four conidia; conidia also formed on sympodial conidiophores like in *Rhinocladiella* and occasionally from discrete phialides like in *Phialophora; F. pedrosoi* an agent of chromoblastomycosis, *F. monophora* an agent of both chromoblastomycosis and cerebral phaeohyphomycosis
		Ochroconis gallopava	Colonies are brownish, velvety, with a maroon diffusing pigment; 2-celled, clavate conidia borne from denticles; growth at 45°C; no growth on media containing cycloheximide; neurotropic; obsolete names *Dactylaria gallopava*, *D. constricta* var. *gallopava*
		Phialophora spp.	Colonies olivaceous to black, velvety; three species are clinically significant; *P. verrucosa* has dark, funnel-shaped collarettes; *P. americana* has deep, vase-shaped collarettes; the slow-growing *P. europaea* has very short collarettes
		Rhinocladiella spp.	Colonies olivaceous to black, velvety; long, erect, brown, unbranched sympodial conidiophores; 1-celled pale ellipsoidal conidia borne on crowded denticles; an *Exophiala* yeast synanamorph may be present; *R. mackenziei* is a neurotropic species in the genus with relatively few conidia per fertile part of the geniculate conidiophore; conidia 1-celled, pale brown, ellipsoidal with a prominent truncate hilum; poor growth at 25°C, good growth at 40°C; obsolete name *Ramichloridium mackenziei*; other pathogenic species include *R. aquaspersa* and *R. similis*
		Veronaea botryosa	Colonies gray to blackish-brown, woolly; long, brown conidiophores; pale brown, 2-celled conidia with a rounded apex and truncate base borne from closely spaced intercalary conidiogenous cells
	Microascales	*Scedosporium* spp.	Colonies pale to yellowish-gray to darker gray, some with orange reverse, woolly; conidiogenous cells annellidic; some species produce a *Pseudallescheria* teleomorph and a *Graphium* synanamorph; similar human pathogenic species in the *Pseudallescheria boydii* species complex as defined by recent molecular studies include *S. apiospermum*, *S. boydii*, *S. aurantiacum*, and *S. dehoogii*; *S. prolificans* (obsolete name *S. inflatum*) possessing inflated annellidic conidiogenous cells, is unrelated to members of the *P. boydii* species complex
		Scopulariopsis spp.	Colonies gray to olivaceous-brown, woolly; conidiogenous cells annellidic; several very similar dark species are anamorphs of various *Microascus* spp.

	Sordariales	*Madurella mycetomatis*	Colonies very slow growing and often heaped; dark brown to black; diffusible brown pigment; unlike *M. grisea*, *M. mycetomatis* grows at 40°C and fails to assimilate sucrose; precise identification facilitated by ITS sequencing
		Myceliophthora thermophila	Colonies light brown, powdery; ill-defined margin; conidia borne from ampulliform swellings are hyaline and smooth initially becoming rough and brown at maturity; growth at 48°C
		Acrophialophora fusispora	Colonies centrally dark front and reverse; unbranched, erect, brown, echinulate conidiophores are anchored by a foot cell; chains of conidia with fine or coarse spirals produced from apex of brown conidiophores and inflated phialides on hyaline hyphae; growth at 40°C
	Calosphaeriales	*Phialemonium* spp.	Colonies buff to gray to yellow; conidiogenous cells phialides and adelophialides (reduced phialides lacking a basal septum); *P. obovatum* has obovate conidia and a green diffusing pigment; sporodochia-producing isolates of *P. curvatum* have been reported
		Phaeoacremonium spp.	Colonies range from buff to pale yellow to pale or dark pink to various shades of brown; hyphae brown; conidiophores often have small warts (exudates); three distinct types of phialides may be present (types I, II, and III); polyphialides may also be present; 1-celled conidia aggregate at apices of phialides and are commonly reniform (kidney shaped) to allantoid (sausage shaped); human pathogenic species that grow at 40°C include *P. parasiticum* (obsolete name *Phialophora parasitica*), *P. rubrigenum*, *P. alvesii*, *P. amstelodamense*, *P. krajedenii*, *P. tardicrescens*, and *P. venezuelense*
		Pleurostomophora spp.	Colonies of *P. richardsiae* (obsolete name *Phialophora* richardsiae) dark brown, velvety; phialides with prominent flaring collarettes bear globose, brown conidia while phialides with indistinct collarettes bear pale allantoid to cylindrical conidia; colonies of *P. repens* (obsolete name *Phialophora repens*) pale brown, phialides lack flaring collarettes, and conidia are pale, allantoid to cylindrical
	Coniochaetales	*Lecythophora* spp.	Colonies moist, salmon to orange; conidiogenous cells primarily adelophialides; conidia aggregate at apices of conidiogenous cells; *L. mutabilis* distinguished from *L. hoffmannii* by dark chlamydoconidia
	Ophiostomatales	*Sporothrix* spp.	Colonies initially cream-colored, moist, with a finely wrinkled surface, becoming brownish-grayish with the production of dark sessile conidia; hyaline, budding cigar-shaped yeast cells present in host and at 35°C; *S. schenckii* is a species complex as determined by calmodulin sequencing; human pathogenic species include *S. schenckii* (sessile conidia triangular to oval); *S. globosa* (sessile conidia globose, no growth at 37°C); *S. brasiliensis* (sessile conidia subglobose, geographically restricted to Brazil); *S.luriei* (dark sessile conidia absent)
Anamorphic (asexual) coelomycete (conidia borne within enclosed or semienclosed structures; organisms treated here have pycnidial conidiomata; frequently acquired by traumatic implantation)	*Pleosporales*	*Phoma*, *Pleurophoma*, *Pleurophomopsis* spp.	Colonies pale to light brownish-gray to darker gray, woolly; pycnidia brown to black; conidia small (4-6 μm), oblong, sometimes slightly curved, hyaline, often guttulate (containing small droplets); species are very similar and best differentiated by ITS sequencing
		Coniothyrium, *Paraconiothyrium*, *Microsphaeropsis* spp.	Colonies pale gray to grayish-brown to brownish-black, some producing dark diffusible pigments into the agar, woolly; pycnidia brown to black; conidia mostly oblong of various sizes, pale brown to dark; species are very similar and best differentiated by ITS sequencing
		Pyrenochaeta spp.	Colonies olivaceous to gray-black, restricted, velvety; pycnidia brown to black with setae surrounding the ostiole; conidia 1-celled, hyaline
	Botryosphaeriales	*Lasiodiplodia theobromae*	Colonies grayish-black, woolly; pycnidia ostiolate, sometimes with setae; conidiogenous cells annellidic; large conidia 20-30 by 10-15μm, initially aseptate and hyaline; 1 septate, dark, longitudinally striate at maturity; obsolete name *Botryodiplodia theobromae*
		Neoscytalidium dimidiatum	Colonies woolly, black, with rapid growth, filling plate within a few days; an otherwise similar hyaline variant is also referred to as *N. dimidiatum*; 1- and 2-celled, dark or hyaline arthroconidia not separated by disjunctor cells; thin hyaline and wide (10-12 μm) dark or hyaline hyphae; multilocular pycnidial coelomycetous synanamorph requires several weeks to mature on plant-based media and produces versicolored conidia (middle cell darker); no longer referred to as *Nattrassia mangiferae* as this organism is an unrelated fruit pathogen now known as *Neofusicoccum mangiferae*
		Macrophomina phaseolina	Colonies gray, woolly, with a dark diffusing pigment and small black dots representing immature/mature sclerotia; pycnidia and conidia usually not formed in culture; identification by sequencing
	Sordariales	*Phomopsis* spp.	Colonies pale to light brown or gray, woolly; pycnidia brown to black, may be multilocular; conidia of two types, alpha conidia ellipsoidal while beta conidia long, filamentous, curved
Teleomorphic (sexual) (produce ascomata, asci, and ascospores in culture)	*Sordariales*	*Chaetomium* spp.	Colonies olivaceous to grayish-brown, woolly; ascomata perithecial (opening at top) and covered with setae (hairs); large, reddish-brown elliptical ascospores; *C. globosum*, setae coiled, ascospores subglobose, growth at 35°C, no growth at 42°; *C. atrobrunneum*, neurotropic, setae mostly straight, ascospores narrowly fusoidal, growth at 42°C; *C. perlucidum*, neurotropic, very similar to *C. atrobrunneum* in colony morphology setae, and ascospore size; growth at 42°C

Continued on following page

TABLE 1—*Continued*

Genus type	Order	Genus or species	Salient phenotypic and/or diagnostic features[b]
		Achaetomium strumarium	Colonies pale to light brown with reddish-brown diffusing pigment after 2 weeks, woolly; ascomata perithecial with long, slightly curved setae; ascospores hyaline to dark, 13-17.5 by 8.5-11 μm, fusoidal; neurotropic species with growth at 40°C
	Pleosporales	*Leptosphaeria* spp.	Colonies dark, velvety to slightly woolly, slow-growing; ascomata cleistothecial (no opening); ascospores hyaline, mostly with 4-6 septa; *L. senegalensis* and *L. thompkinsii* distinguished by ascospore features
	Microascales	*Microascus* spp.	Colonies initially white to gray to brownish; ascomata perithecial, developing as black dots in concentric rings on the agar, and may exude a cirrhus of red ascospores at maturity; species treated here have very similar, dark *Scopulariopsis* anamorphs; *M. cinereus*, short perithecial necks and orange-segment-shaped ascospores; *M. cirrosus*, longer perithecial necks with heart-shaped ascospores; *M. trigonosporus*, longer perithecial necks with triangular ascospores
		Pseudallescheria spp.	Colonies pale to yellowish gray to gray to brownish, woolly; ascomata cleistothecial; *Scedosporium* and *Graphium* anamorphs present; human pathogenic species as defined by recent molecular studies are *Pseudallescheria boydii* (anamorph *Scedosporium boydii*), *Pseudallescheria apiosperma* (anamorph *Scedosporium apiospermum*, heterothallic, does not form a teleomorph in culture, D-ribose negative), *P. ellipsoidea*

[a] Adapted from Table 14-1 from reference 724 with permission. This list is not all inclusive. Pictures of all organisms are available at doctorfungus.org or on the CD-ROM of the *Atlas of Clinical Fungi*, pilot version of 3rd ed. (174).
[b] On potato flake agar at 25°C.
[c] True septa continuous with outer wall.
[d] Pseudosepta where only inner walls are involved.

Phenotypic Identification

The level to which black molds can or should be identified in the routine laboratory may depend on several factors, such as the genus of the organism recovered, whether or not an epidemiologic investigation is warranted, and/or the level of identification required for appropriate patient management. The phenotypic identification of black molds is based primarily upon their macroscopic morphology (color, growth rate, and growth characteristics on standardized media), their microscopic morphology (hyphae, conidiogenous cells [specialized cells that produce the conidia], conidia [asexual reproductive propagules], etc.), and a limited number of physiologic features (primarily cycloheximide tolerance, nitrate assimilation, urea hydrolysis, and growth at various salt concentrations). Only genus-level identification may be possible or required for genera with several similar, closely related species, such as described above for *Exophiala.* In some other genera, certain species are clearly associated with a particular type of mycosis, and a combination of morphologic features, temperature, and physiology can provide a species-level identification. This is the case for the agent of cerebral phaeohyphomycosis, *Cladophialophora bantiana.*

Macroscopic morphology. The medium (see "Isolation Procedures and Culture" in Diagnosis below) is an important consideration in the identification of melanized fungi. The use of a medium that promotes growth most consistently matching the original description of the organism is preferred, and this typically is a plant-based medium. The most commonly used is potato dextrose agar (PDA) or variations thereof. It provides colony colors that are close to those originally described, and it is usually adequate for conidiation. Other plant-based media include malt extract agar, V-8 juice agar, cereal agar, carnation leaf agar, cornmeal dextrose agar, and others. A more complete list of media and reagents may be found in the *Manual of Clinical Microbiology*, 9th ed. (441), and in the *Atlas of Clinical Fungi*, 2nd ed. (175). Phaeoid molds vary considerably in their colony colors. Although this characteristic is highly dependent upon environmental conditions, it is one that can be useful in the initial separation of genera/species. While most species are various shades of pale gray to dark gray to black, others may be brown or very pale or may turn darker only with the production of certain structures. Others may be some shade of purple or distinguished by diffusible pigments. Etiologic agents which are typically brown on PDA include *Ochroconis gallopava*, *Pleurostomophora richardsiae*, *Pleurostomophora repens*, some *Phaeoacremonium* species, *Wallemia sebi*, *Myceliophthora thermophila*, and *Veronaea botryosa.* The "pale list" includes fungi which seldom turn dark, such as *Phialemonium* species. *Lecythophora mutabilis* remains lightly colored until the production of dark chlamydospores. *Ochroconis gallopava* exudes a wine-red pigment into the agar (more pronounced on Sabouraud dextrose agar [SDA]), and several *Phaeoacremonium* species exhibit purple to lavender colonies.

Microscopic morphology and pleomorphism. Variable microscopic morphology in the same fungus, also referred to as pleomorphism or pleoanamorphism, is another feature useful in the phenotypic identification of black molds. Some fungi may display more than one form, such as yeast-like growth initially and more filamentous growth subsequently. This is

TABLE 2. Melanized fungi in human disease[a]

Genus	Species
Achaetomium[d]	*A. strumarium*
Acrophialophora[b]	*A. fusispora*
Alternaria[b]	*A. alternata*, *A. chlamydospora*, *A. dianthicola*, *A. infectoria*, *A. longipes*, *A. tenuissima*
Anthopsis[b]	*A. deltoidea*
Arnium[d]	*A. leporinum*
Arthrinium[b]	*A. phaeospermum*
Ascotricha[d]	*A. chartarum*
Aureobasidium[b]	*A. pullulans*
Bipolaris[b]	*B. australiensis*, *B. hawaiiensis*, *B. papendorfii*, *B. spicifera*
Botryomyces[b]	*B. caespitosus*
Chaetomium[d]	*C. atrobrunneum*, *C. funicola*, *C. globosum*, *C. murorum*, *C. perlucidum*
Cladophialophora[b]	*C. arxii*, *C. bantiana*, *C. boppii*, *C. carrionii*, *C. devriesii*, *C. emmonsii*, *C. modesta*, *C. mycetomatis*, *C. saturnica*, *C. samoënsis*
Cladorrhinum[b]	*C. bulbillosum*
Cladosporium[b]	*C. cladosporioides*, *C. herbarum*, *C. oxysporum*, *C. sphaerospermum*
Colletotrichum[c]	*C. coccodes*, *C. crassipes*, *C. dematium*, *C. gloeosporioides*, *C. graminicola*
Coniothyrium[b]	*C. fuckelii*
Corynespora[b]	*C. cassiicola*
Curvularia[b]	*C. brachyspora*, *C. clavata*, *C. geniculata*, *C. inequalis*, *C. lunata*, *C. pallescens*, *C. senegalensis*, *C. verruculosa*
Cyphellophora[b]	*C. laciniata*, *C. pluriseptata*
Dichotomophthora[b]	*D. portulacae*
Dichotomophthoropsis[b]	*D. nymphaearum*
Dissitimurus[b]	*D. exedrus*
Drechslera[b]	*D. biseptata*
Exophiala[b]	*E. asiatica*, *E. attenuata*, *E. bergeri*, *E. castellanii*, *E. dermatitidis*, *E. jeanselmei*, *E. lecanii-corni*, *E. moniliae*, *E. oligosperma*, *E. phaeomuriformis*, *E. pisciphila*, *E. salmonis*, *E. spinifera*, *E. xenobiotica*
Exserohilum[b]	*E. longirostratum*, *E. mcginnisii*, *E. rostratum*
Fonsecaea[b]	*F. monophora*, *F. pedrosoi*
Hormonema[b]	*H. dematioides*
Hortaeae[b]	*H. werneckii*
Lasiodiplodia[c]	*L. theobromae*
Lecythophora[b]	*L. hoffmannii*, *L. mutabilis*
Leptosphaeria[d]	*L. senegalensis*, *L. thompkinsii*
Macrophomina[c]	*M. phaseolina*
Madurella[b]	*M. grisea*, *M. mycetomatis*
Microascus[d]	*M. cinereus*, *M. cirrosus*, *M. trigonosporus*
Monilliella[b]	*M. suaveolens*
Microsphaeropsis[c]	*M. arundinis*, *M. olivacea*
Myceliophthora[b]	*M. thermophila*
Mycocentrospora[b]	*M. acerina*
Mycoleptodiscus[b]	*M. indicus*
Neoscytalidium[c]	*N. dimidiatum*
Neotestudina[d]	*N. rosatii*
Nigrospora[b]	*N. sphaerica*
Ochrocladosporium[b]	*O. elatum*
Ochroconis[b]	*O. gallopava*, *O. humicola*, *O. tshawytschae*
Oidiodendron[b]	*O. cerealis*
Phaeoacremonium[b]	*P. alvesii*, *P. amstelodamense*, *P. griseorubrum*, *P. krajdenii*, *P. parasiticum*, *P. rubrigenum*, *P. sphinctrophorum*, *P. tardicrescens*, *P. venezuelense*
Phaeosclera[b]	*P. dematioides*
Phaeotrichoconis[b]	*P. crotalariae*
Phialemonium[b]	*P. curvatum*, *P. obovatum*
Phialophora[b]	*P. americana*, *P. bubakii*, *P. europaea*, *P. reptans*, *P. verrucosa*
Phoma[b]	*P. cruris-hominis*, *P. dennisii* var. *oculo-hominis*, *P. eupyrena*, *P. glomerata*, *P. herbarum*, *P. minutella*, *P. minutispora*, *P. sorghina*
Piedraia[d]	*P. hortae*
Pleurophoma[c]	*P. cava*
Pleurophomopsis[c]	*P. lignicola*
Pleurostomophora[b]	*P. repens*, *P. richardsiae*
Pseudochaetosphaeronema[b]	*P. larense*
Pseudomicrodochium[b]	*P. suttonii*
Pyrenochaeta[b]	*P. mackinnonii*, *P. romeroi*, *P. unguis-hominis*
Rhinocladiella[b]	*R. aquaspersa*, *R. basitona*, *R. mackenziei*, *R. similis*
Sarcinomyces[b]	*S. phaeomuriformis*
Scedosporium[a]	*S. prolificans*
Scopulariopsis[b]	*S. asperula*, *S. brumptii*, *S. fusca*
Sphaeropsis[c]	*S. subglobosa*
Stenella[b]	*S. araguata*
Taeniolella[b]	*T. stillbospora*
Tetraploa[b]	*T. aristata*
Thermomyces[b]	*T. lanuginosus*
Ulocladium[b]	*U. chartarum*
Veronaea[b]	*V. botryosa*

[a] Some doubtful cases have been omitted; the list may not be all inclusive. Some genera that are outside the taxonomic orders discussed in the text but that contain melanized structures are included. Adapted from reference 493 with permission of the publisher.

[b] Anamorphic hyphomycete.

[c] Anamorphic coelomycete.

[d] Teleomorphic ascomycete.

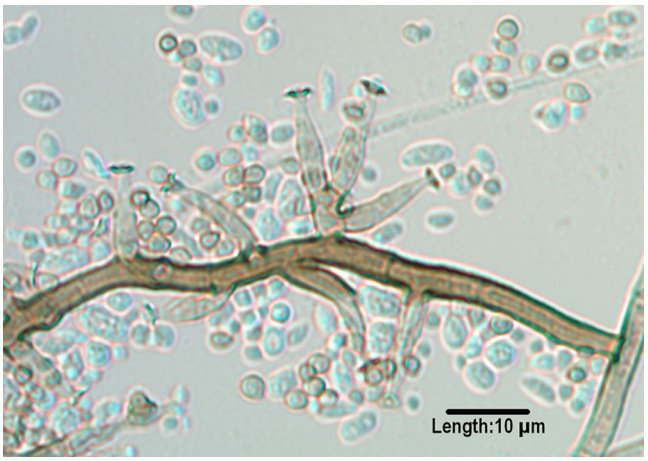

FIG. 1. Conidiogenous cells of *Pleurostomophora richardsiae*, demonstrating prominent flaring collarettes as well as the two types of conidia (oval and globose) produced by this species. (Unless otherwise noted, in this and subsequent figures light microscopy photomicrographs of conidiogenous cells and/or conidia were taken from slide culture preparations grown on potato flakes agar for 7 days at 25°C.)

common in the black yeasts such as *Exophiala* and related genera. Pleoanamorphism may also be exhibited by different types of anamorphic structures (synanamorphs), such as the *Graphium* state in *Pseudallescheria* or variably shaped conidia in *Pleurostomophora richardsiae* (Fig. 1). Identification of homothallic ascomycetes is typically based on the type of ascomata produced (primarily cleistothecia [round, closed structures containing asci and ascospores] or perithecia [round to pear-shaped structures with an opening or ostiole containing asci and ascospores], as in *Pseudallescheria* or *Chaetomium*/*Achaetomium*/*Microascus*, respectively) and differences in ascospore morphology. Ascospores may be of various sizes, shapes, colors, and ornamentations. The bulk of clinical black molds, however, are heterothallic ascomycetes. These mitosporic fungi are identified mostly by their methods of conidiogenesis and the morphology of their conidia. The majority of mitosporic isolates are hyphomycetes with their conidia borne free in the aerial mycelium. Also seen are coelomycetes, whose conidia are borne within asexual structures known as conidiomata. The methods of conidiogenesis (blastic [blown-out = blastoconidia, as seen in many genera] or thallic [formed from preexisting hyphae = arthroconidia, as in *Neoscytalidium*]), the types of conidiogenous cells (primarily annellidic [*Scedosporium*, *Scopulariopsis*, and *Hortaea*] or phialidic [many genera]), and the morphology of the conidia are taken in aggregate to form the basis for a morphologic identification. Annelloconidia are formed from percurrent, indeterminate conidiogenous cells that produce rings or annellations and become longer and narrower with the production of conidia, while phialoconidia are formed from conidiogenous cells with collarettes that may be quite distinct or subtle, and the conidiogenous cell remains the same size and shape with conidial production. It should be pointed out, however, that these morphologic features used to identify anamorphic species lacking teleomorphs are strictly phenotypic and do not define their phylogenetic placement within the order (157).

Physiologic features. Physiologic characteristics may also assist in separation of various genera/species. However, only those that are available in routine laboratories are widely employed. The ability or inability of isolates to grow on media containing cycloheximide (referred to as cycloheximide tolerance), nitrate assimilation, urease activity, and salt tolerance, particularly for halophilic strains, are all useful adjuncts to the morphologic examination. Larger reference labs and research facilities also may use a battery of carbon assimilation profiles. Temperature tolerance is also useful in segregating potential pathogens. Those that fail to grow at 35°C are more likely to be recovered from superficial sites, while those capable of growth at this temperature have the potential for more invasive human disease. Several clinically significant dematiaceous molds are thermotolerant to thermophilic, with maximum growth temperatures to 45°C and beyond. A partial listing of these potentially neurotropic species includes *E. dermatitidis*, *O. gallopava*, *C. bantiana*, *C. modesta*, *C. emmonsii*, *R. mackenziei*, *Acrophialophora fusispora*, *Fonsecaea monophora*, and some aggressive *Achaetomium* and *Chaetomium* species.

Molecular Characterization

Molecular characterization of fungi is a mature discipline in the molecular systematics arena, with multilocus datasets, extensive taxon sampling, and rigorous analytical methods being the norm (340). Its use in the clinical laboratory, however, is mostly restricted to epidemiologic studies and to identification of unusual/uncommon or difficult-to-identify isolates. Molecular identification of most species relies on sequencing of ribosomal genes and comparison with published databases, notably those in GenBank; however, over 10% of these deposits may be erroneous (176). Private databases are also sometimes utilized for particular genera; however, these are difficult to access and may also contain incorrect deposits. Also, various methods and genes or gene regions such as the internal transcribed spacer regions ITS1 and ITS2, the D1/D2 domains, β-tubulin, actin, calmodulin, manganese superoxide dismutase, ATPase subunit 6, chitin synthase, mitochondrial small-subunit (SSU) rRNA, translation elongation factor 1α, and others are utilized, so that interlaboratory standardization of sequencing is lacking. Several International Society for Human and Animal Mycology (ISHAM) working groups are addressing standardization of fungal sequencing (58) as is the Clinical and Laboratory Standards Institute (CLSI) (146). Genera for which substantial sequencing data are available and for which species distinction appears to be satisfactory include those known as black yeasts, i.e., *Exophiala* and related genera (ITS) (825), *Sporothrix* species (calmodulin) (480), *Phaeoacremonium* species (β-tubulin and actin) (525), and *Pseudallescheria*/*Scedosporium* species (ribosomal DNA [rDNA] gene cluster, β-tubulin, calmodulin, and translation elongation factor 1α) (330). Molecular characterization should always be evaluated in light of phenotypic features, and sequence data for uncommon and/or potentially new species should be compared with those for ex-type strains.

ANAMORPHIC HYPHOMYCETE GENERA

Capnodiales

Hortaea. *Hortaea werneckii* is the etiologic agent of tinea nigra, an asymptomatic, superficial mycosis causing hyperchromic plaques without keratinolysis in the dead keratin layers of the skin (186, 685) and mostly restricted to the palms of the hands (tinea nigra palmaris) and soles of the feet (tinea nigra plantaris) (87). It is a halophilic organism whose natural habitat is in tropical and subtropical hypersaline environments (823), and it is thought be acquired through superficially abraded skin (186). Colonies are restricted, black, moist, and yeast-like initially, later becoming filamentous. Wide hyphae are densely septate, thick walled, and brown. Intercalary or lateral annellidic conidiogenous cells produce brown, two-celled ellipsoidal conidia with a darkened central septum. ITS sequencing facilitates molecular identification (823) and clearly distinguishes *H. werneckii* from other closely related halophilic and acidophilic (*H. acidophila*) nonpathogenic species (347).

Cladosporium. The genus *Cladosporium* has recently undergone molecular and morphologic scrutiny (157), with many organisms being reassigned to other genera. One example is the transfer of *Cladosporium elatum* to *Ochrocladosporium elatum*. The genus is extremely ubiquitous, and although it is an agent of allergic disease in indoor settings, few species are documented to cause disease. The species complexes *Cladosporium cladosporioides* and *C. oxysporum* are the ones most commonly cited in cases of cutaneous and subcutaneous disease (313, 586, 641, 776) and occasionally deeper infections (396, 429); however, they are commonly contaminants, making the nature of reports doubtful. The inability of *Cladosporium* species to grow on media containing cycloheximide, their prominent "shield cells," and conidia that are fragile (easily detached) and possess dark hila (attachment scars) are all features distinguishing *Cladosporium* from the unequivocally pathogenic *Cladophialophora* species.

Dothideales

Aureobasidium. Recent molecular characterization of *Aureobasidium pullulans* and closely related organisms by multilocus sequence analysis (ITS, partial 28S rDNA, β-tubulin, translation elongation factor 1α, and elongase), expanding the work of de Hoog and Yulova and of Yulova et al. (173, 820), has shown that the genus *Aureobasidium* contains a single species and several varieties containing differing amounts of melanin and having various salt (820, 823) and temperature (824) tolerances. The mode of conidiogenesis is primarily synchronous rather than percurrent, as in *Hormonema*; however, features of conidiogenesis are difficult to ascertain with certainty. Sequencing is usually required for a definitive identification. Two varieties are human pathogens, *A. pullulans* var. *pullulans*, and *A. pullulans* var. *melanigenum.* In the former, colonies remain pink for approximately 1 week, tolerate 15% salt, and have a maximum temperature of 30°C, while in the latter, colonies are black at the outset, tolerate 10% salt, and have a maximum temperature of 35°C. *Aureobasidium* is an opportunistic pathogen of humans and animals recovered in cases of catheter-related septicemia (117, 360), disseminated infections (344, 663), chromoblastomycosis (616), and peritonitis (144, 367).

Hormonema. As noted above, *Hormonema* species are phenotypically similar to *Aureobasidium pullulans*; however, conidiogenesis is primarily percurrent rather than synchronous. There are rare reports of cutaneous phaeohyphomycosis (149) and fungal peritonitis (690) due to this organism, both of which were reported prior to molecular characterization.

Pleosporales

Alternaria. *Alternaria* is a large genus of plant pathogen species that are only occasionally implicated in opportunistic human disease. Cutaneous and subcutaneous phaeohyphomycosis in immunosuppressed individuals is the most common presentation (275, 577, 587, 798). Organ transplantation (280) and Cushing's syndrome appear to be major risk factors for cutaneous/subcutaneous disease, while bone marrow recipients are at risk for sinusitis (577). Ocular disease in individuals exposed to soil and garbage (577) is the next most common presentation, while onychomycosis is rarely reported. There are also occasional reports of allergic fungal sinusitis (67). While several species, such as *A. chlamydospora* (65, 703), *A. longipes* (275), and *A. tenuissima* (124, 642, 644), have been reported, most clinical isolates have been shown to be either *A. alternata* (176, 497, 710) or *A. infectoria* (99, 551, 648). ITS region sequences have demonstrated that *A. longipes* and *A. tenuissima* cannot be distinguished from *A. alternata.* Conidial production by *Alternaria infectoria* is sparse, and colonies may be pale.

Bipolaris. The most common mycosis attributed to *Bipolaris* spp. is allergic fungal sinusitis (125, 246, 417, 444, 508, 580). Other disease associations include subcutaneous lesions, keratitis, and peritoneal dialysis-associated peritonitis (508). Extension to the central nervous system via the nasal sinuses highlights the neurotropic potential of the genus, though this is very rare (260, 817). Clinically significant species inciting human disease include *B. spicifera*, *B. hawaiiensis* (Fig. 2), and *B. australiensis*. They are differentiated morphologically by conidial size and the number of distoseptations (pseudosepta where only inner walls are involved) (20). Conidia demonstrate bipolar germination, hence the genus name "*Bipolaris*."

Curvularia. Curvularia species are common in dead plant material and may cause a variety of human mycoses, including fungal keratitis, invasive sinusitis (215), onychomycosis, black grain eumycotic mycetoma (378), endocarditis (104), subcutaneous disease (813), and peritonitis (98, 241, 631) as well as systemic infections (175, 177). Additional reports involved fatal cerebral phaeohyphomycosis in an immunocompetent individual (121), endophthalmitis (579), and contaminated saline-filled breast implants (392). Clinical isolates include *C. geniculata*, *C. lunata*, *C. pallescens*, *C. senegalensis*, *C. brachyspora*, *C. clavata*, *C. verruculosa*, and *C. inaequalis* (Fig. 3) (598). *C. lunata* is the most common clinical species, and *C. lunata* var. *aeria* (Fig. 4) may produce large, upright stroma in culture that are visible with the naked eye.

Exserohilum. Three *Exserohilum* species recovered from humans are *E. rostratum*, *E. longirostratum*, and *E. mcginnisii*, although molecular studies suggest that they may be the same species (175, 177). The genus is characterized by its long,

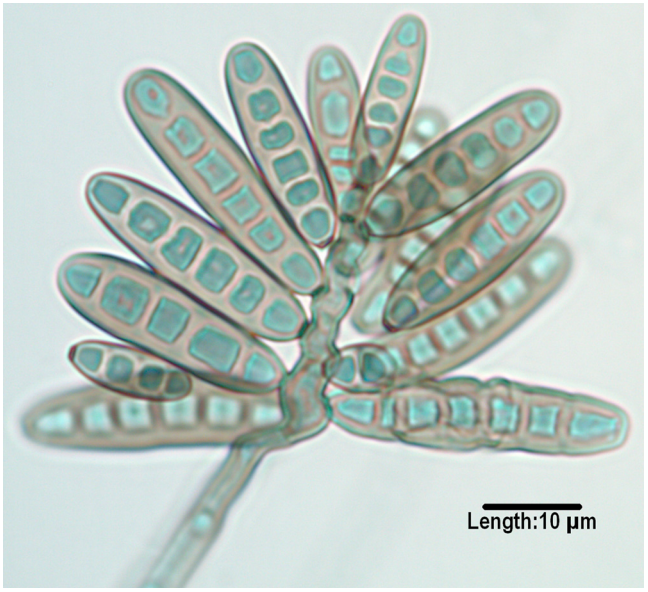

FIG. 2. Conidia of *Bipolaris hawaiiensis*, demonstrating mostly five distosepta and six cells being borne from a geniculate conidiophore/conidiogeous cell.

multidistoseptate conidia and a protruding hilum. *E. rostratum* exhibits darkened basal and distal septa, and *E. longirostratum* has conidia that are noticeably longer and centrally curved (Fig. 5), while *E. mcginnisii* has conidia with warty projections on their outer walls. Not all authorities agree that *E. rostratum* and *E. longirostratum* are separate species. Species are opportunistic and are etiologic agents of sinusitis (566), which may extend to the central nervous system (46), and keratitis (488), as well as cutaneous and subcutaneous mycoses (359, 508, 580). A fatal disseminated case was reported in a patient with aplastic anemia (37).

FIG. 3. Conidia of *Curvularia inaequalis* with mostly five septa and six cells borne from a geniculate conidiogenous cells.

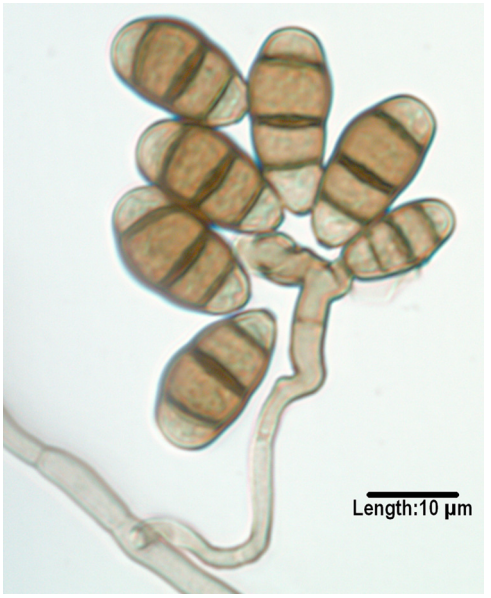

FIG. 4. Conidia of *Curvularia lunata* var. *aeria* borne from a geniculate conidiogenous cell. Note that the middle cell is slightly enlarged, and septa are eusepta (true septa continuous with the outer wall).

Chaetothyriales

***Exophiala*.** Species in the genus *Exophiala* are frequently referred to as "black yeasts" due to the ability of several species to form a budding yeast-like synanamorph as well as hyphal forms. Colonies are olivaceous-black with a black reverse and are initially moist or yeast-like, later becoming velvety at maturity. Asexual replication is by annellidic conidiogenous cells, and conidia are formed in clusters both from intercalary

FIG. 5. Multidistoseptate conidia of *Exserohilum longirostratum*, demonstrating a prominent basal septum (true septum) and a protruding hilum.

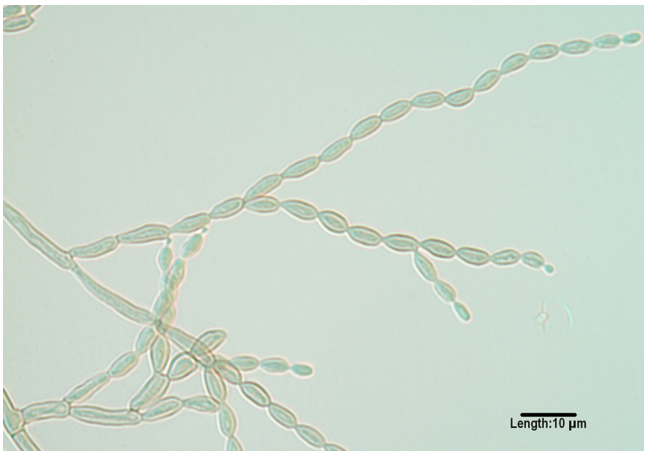

FIG. 6. Long, nonfragile chains of conidia as seen in *Cladophialophora bantiana*.

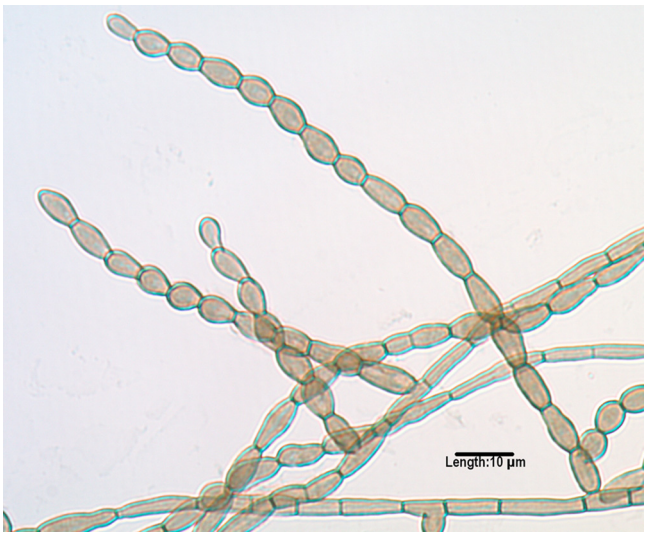

FIG. 7. Long, nonfragile chains of conidia produced by a less common species of *Cladophialophora*, *C. emmonsii.* Note that conidiophores and prominent hila (attachment scars) are absent.

conidiogenous loci and at the tips of annellides. Some species may occasionally form conidia in chains (182) (catenate) on nutritionally deficient media or display phialides as well as annellides (183). Species are very similar microscopically, and unequivocal differentiation is facilitated by physiologic features such a temperature tolerance and nitrate assimilation and by molecular characterization. Some waterborne psychrophilic species such as *E. pisciphila* are pathogens of fish (436, 438), while others such as *E. mesophila* are found in dental unit water lines (604) and municipal drinking water (300). The most clinically important species are thermotolerant (719). In a recent study of U.S. clinical isolates, reidentification of strains by ITS sequencing showed the most common species to be *E. dermatitidis* (29%), *E. xenobiotica* (20%), and *E. oligosperma* (19%) (94, 825). While many clinical isolates are reported as *E. jeanselmei*, which has been regarded as a major agent of subcutaneous phaeohyphomycosis, this species made up only 8% of the isolates, and molecular studies clearly showed *E. jeanselmei* to be a heterogeneous complex of species (184, 780). *Exophiala jeanselmei* has been redefined clinically as an agent of traumatic cutaneous infection eventually leading to eumycetoma (27, 52, 683). *Exophiala dermatitidis* is distinguished phenotypically by its mostly mucoid colonies, ability to grow at 40°C, lack of nitrate assimilation (569), and yeast cells surrounded by capsules (819), which it shares with another aggressive species, *E. spinifera* (180, 214, 536, 699). The range of mycoses incited by *E. dermatitidis* include neurotropic infections in young, immunocompetent individuals (restricted to Asia) (138, 345, 492, 494), systemic lymphadenitis (13), cutaneous and subcutaneous infections in mostly immunocompromised individuals (346, 492), colonization of airways in cystic fibrosis patients (597), and mycoses related to continuous ambulatory peritoneal dialysis (CAPD) (783). It is also an opportunist in lungs of cystic fibrosis patients (320, 355) and may be recovered from the stool in patients with diarrhea (178). It has been recovered from Turkish steam baths (489) and associated with free-living amoebae in hospital water (128). *E. phaeomuriformis*, which is similar in morphology to *E. dermatitidis*, can grow at a maximum temperature of 38°C (490). *Exophiala spinifera* and the similar *E. attenuata* (780) have long, spine-like conidiophores. *E. spinifera* is an agent of serious disseminated mycoses in adolescents (180) and of cases of subcutaneous phaeohyphomycosis (327, 699). *E. xenobiotica*, which is capable of growing in the presence of high concentrations of xenobiotics such as xylene, toluene, or creosote-treated utility poles, was the agent of subcutaneous phaeohyphomycosis in a non-Hodgkin lymphoma patient (36). *E. asiatica* is a newly described species causing a fatal, disseminated cerebral phaeohyphomycosis in China (452).

Cladophialophora. *Cladophialophora* species, although morphologically similar to *Cladosporium* species, are differentiated by belonging to a different order, the *Chaetothyriales* rather than the *Capnodiales*; by lacking conidiophores, "shield cells," or prominent hila (attachment points); by their ability to grow on media containing cycloheximide; and by having dry, nonfragile chains of conidia. The genus has recently been reevaluated by multilocus sequencing and currently contains seven species associated with humans (51). *C. bantiana*, (Fig. 6), previously characterized at the molecular level (279), is a neurotropic species with growth at 40°C and is the causative agent of numerous cases of cerebral phaeohyphomycosis (204, 272, 353, 395, 628, 733), many of which occur in immunocompetent individuals and most of which are fatal. The species has also been reported as an agent of eumycetoma (89), along with *Madurella mycetomatis* (51). Less common species occasionally incriminated in deep and superficial mycoses include *C. modesta*, *C. arxii*, *C. devriesii*, *C. emmonsii* (Fig. 7), *C. boppii*, and *C. saturnica* (47, 51, 295, 505, 516, 568, 748). *C. carrionii* and the recently described *C. samoënsis* are agents of chromoblastomycosis (51, 229, 446, 610, 826). *C. yegresii* is considered a closely related environmental sister species to *C. carrionii* (181, 782).

Fonsecaea. The genus *Fonsecaea* is comprised of two species (174, 533). *F. pedrosoi* is known almost exclusively as an agent of chromoblastomycosis (45, 515, 610, 695), while the newly described *F. monophora* (Fig. 8) is known as an agent of chromoblastomycosis (808, 809, 810) and subcutaneous disease

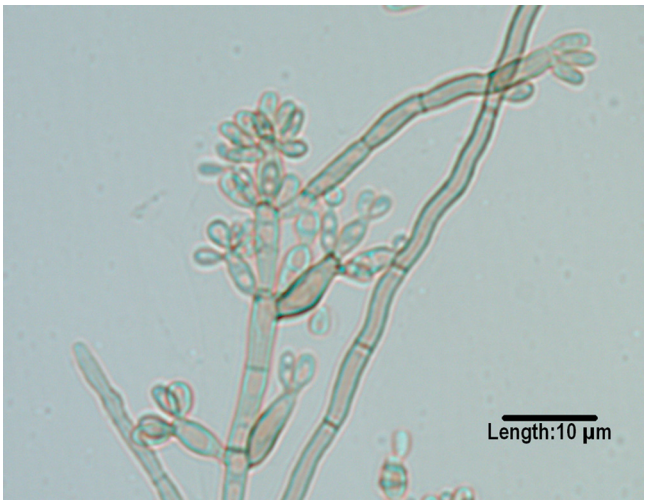

FIG. 8. Conidial formation in *Fonsecaea monophora.* Conidia are formed from swollen denticles which give rise to secondary and tertiary conidia in chains of up to four conidia. The same type of conidiogenesis occurs in *F. pedrosoi*.

FIG. 9. Two-celled, clavate (club-shaped) conidia of *Ochroconis gallopava* borne on long, thin denticles.

and, more recently, cerebral phaeohyphomycosis (721, 733). Prior reported cases of central nervous system and/or other deep tissue infections (520, 545, 701) should most likely be attributed to *F. monophora.* A murine model of disseminated infection with *F. monophora* was recently reported (113). Both species form conidia from swollen denticles which give rise to secondary and tertiary conidia in short chains of up to four conidia. Conidia may also be formed from sympodial conidiophores, as in *Rhinocladiella*, and in balls from discrete phialides with collarettes, as in *Phialophora.* Molecular characterization is required for unequivocal differentiation.

Ochroconis. *O. gallopava* was initially observed to cause central nervous system disease in poultry (354). It has subsequently been shown to be an etiologic agent of neurotropic infections in immunocompromised humans (692) as well as pulmonary infections in immunocompetent hosts (348, 554). *O. gallopava* has colonies that are brownish rather than gray or olivaceous, produces a maroon diffusing pigment more pronounced on SDA than on PDA, grows at 40°C, fails to grow on media containing cycloheximide, and displays clavate, two-celled, hyaline conidia borne on long denticles (Fig. 9).

Phialophora. Some human pathogens with phialidic conidiogenesis previously assigned to *Phialophora* (263) have been moved to other genera, namely, *Phaeoacremonium* (525) and *Pleurostomophora* (777), leaving only those species that are filamentous throughout their life cycle. Both *P. verrucosa* and *P. americana* produce their conidia from phialides with conspicuous darkened collarettes; these are funnel shaped and vase shaped in *P. verrucosa* (Fig. 10) and *P. americana* (Fig. 11), respectively. Sequencing has demonstrated a close relatedness, suggesting that the species may be synonymous (185, 811). *P. verrucosa* is primarily an agent of chromoblastomycosis (257, 770), although other reported infections include endocarditis, keratitis, and osteomyelitis (209, 760). A recently described species implicated in superficial infections, *P. europaea*, has very short collarettes (179).

Rhinocladiella. Four species of *Rhinocladiella* are known agents of human disease. *R. mackenziei* (formerly *Ramichloridium mackenziei* and also thought to be synonymous with *Ramichloridium obovoideum*, which is now unrelated in the genus *Pleurothecium* as *P. obovoideum*) (43) is a frequently fatal neurotropic organism previously thought to be restricted to individuals residing in or immigrating from Middle Eastern countries (114, 394, 726). It has now been reported as the etiologic agent of a brain abscess in a man from India, an area where it is not endemic, who reported no travel outside the country (48). *R. aquaspersa* is an occasional agent of chromoblastomycosis (39, 589, 693). *R. basitona* was recovered from subcutaneous lesions in a man from Japan (43). *R. similis* (184) appears to be the agent reported under the name *R. atrovirens* in cases of mycetoma (535) and cerebral phaeohyphomycosis in an AIDS patient (193).

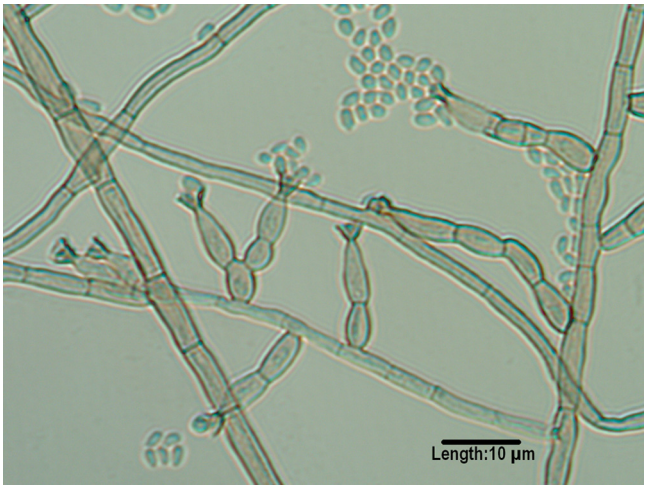

FIG. 10. Dark, funnel-shaped collarettes at the tips of the conidiogenous cells (phialides) in *Phialophora verrucosa.* Also note the oval-shaped conidia.

FIG. 11. Deep, dark, vase-shaped collarettes in *Phialophora americana*.

***Veronaea*.** Initial reports of infection due to *Veronaea botryosa* were clustered in China; however, a more global distribution is now recognized, with cases seen in Libya, Philippines, an island in the Indian Ocean, and the United States. Two cases are noteworthy as agents of subcutaneous disease in heart (725) and liver (251) transplant recipients. The genus has recently been reexamined at the molecular level by Arzanlou et al. (43).

Microascales

***Scedosporium*.** The genus *Scedosporium* and its associated teleomorph *Pseudallescheria* were extensively reviewed by Cortez et al. in 2008 (153); therefore, the information provided here will augment that previously published and/or highlight new taxonomy, distribution, and disease. *Scedosporium prolificans*, which is closely related but not a member of this complex, appears to occupy a more restricted geographic range, with infections occurring mainly in Australia, Spain, and the United States (747). Clinical discussion (see Clinical Syndromes and Their Management below) will be limited to *S. prolificans*, as related species have been extensively reviewed elsewhere (153) and may not reveal phaeoid hyphae in tissue, in contrast to the case for *S. prolificans*. Infection with this organism is of major concern in all settings due to its refractoriness to antifungal therapy and associated high mortality (18, 29, 76, 96, 119, 153, 312, 475, 538, 664, 802, 806). A recent review of 162 cases reported in the literature summarizes major risk factors as malignancy (46%), cystic fibrosis (12%), and solid organ transplantation (9%) and chief clinical presentations as disseminated infection (44%) and pulmonary mycoses (29%), followed by bone and joint infections (10%) (638). All disseminated infections were in individuals with underlying disease, primarily hematological malignancies; 70% of these had positive blood cultures, and mortality in this group was 88%. Molecular characterization by ITS, D1/D2, translation elongation factor 1α, and the chitin synthase genes for 20 cases of *S. prolificans* infection occurring in Germany between 1993 and 2007 suggests the possibility of two or three distinct genotypes (747). This finding may further our understanding of the epidemiology of this organism. Multiple genotypes were previously suggested by inter-simple-sequence-repeat (ISSR) fingerprinting (708). Increased numbers of infections with *S. prolificans* have also been reported from France (304) and Australia (190). Inflated annellides, a key microscopic feature in the identification of this organism, may be subtle in some isolates and easily overlooked. However, the colony color of *S. prolificans* is always darker than for other *Scedosporium* species.

***Scopulariopsis*.** The genus *Scopulariopsis* is unusual in containing both hyaline and dark species. Most pigmented species associated with disease are anamorphs of various *Microascus* species detailed in Teleomorphic Genera below. *Scopulariopsis* shares an annellidic method of conidiogenesis with *Scedosporium* species but can be differentiated from this genus by conidial formation in chains rather than in clumps.

Sordariales

***Madurella*.** An agent of dark grain mycetoma primarily in West Africa, *M. mycetomatis* has recently been proven to be a member of the *Sordariales* (172), unlike *M. grisea*, which resides in the *Pleosporales.* Isolates are very slow growing, produce a brown diffusible pigment, grow at 40°C, and frequently remain sterile in culture; however, lateral phialides and globose conidia are occasionally produced. Precise identification is facilitated by DNA sequencing. Molecular characterization of 38 different *M. mycetomatis* isolates from Sudan has shown them to have identical DNA patterns, suggesting that host susceptibility rather than differential virulence is the determining factor in clinical presentations (10).

***Myceliophthora*.** *Myceliophthora thermophila* is a thermophilic fungus common in high-temperature areas such as compost and exhibits growth at 50°C. Colonies are pale brown, and conidia are borne from ampulliform swellings. Reports suggest that its recovery from tissue, even with a heavy fungal burden, may be difficult (196). The organism is also uncommonly seen in the laboratory and may provide identification challenges. It has been fatal in a disseminated case (95) and in a patient with aortic involvement with medial necrosis (234). A severe case of osteomyelitis was also reported following extensive injury to a knee and distal femur following a barnyard pitchfork injury (196).

***Acrophialophora*.** *Acrophialophora fusispora* is an uncommonly seen agent occasionally microscopically misidentified as *Scedosporium prolificans.* The two species have similarly inflated conidiogenous cells, although they are phialidic versus annellidic and conidia are produced in chains rather than clusters in *A. fusispora* and *S. prolificans*, respectively. The organism grows at 40°C, colonies display a striking darkening centrally (both front and reverse), and it produces finely echinulate conidia demonstrating various degrees of spiral banding. It has been reported as an agent of cerebral phaeohyphomycosis in a leukemic child (24), as an agent of keratitis (691), and as an agent of keratouveitis in association with a retained intraocular lens (41).

Calosphaeriales

***Phialemonium*.** The genus *Phialemonium* was initially described to accommodate organisms closely resembling *Acremonium* spp. but containing pigmentation, although colonies of-

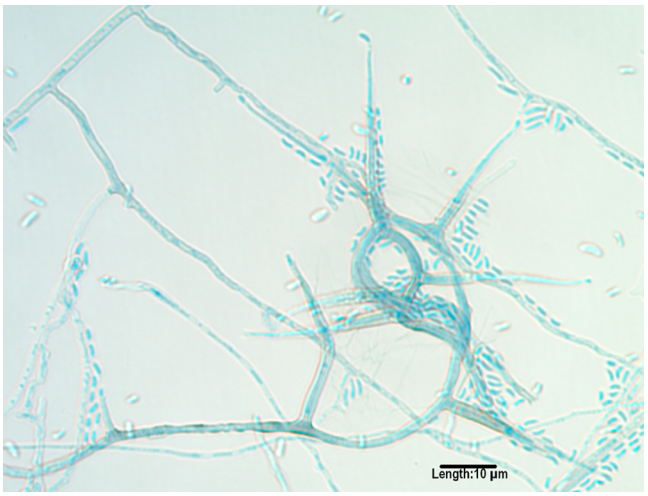

FIG. 12. Melanized hyphae, demonstrating warts (bottom), long robust phialides, and allantoid (curved) conidia of *Phaeoacremonium parasiticum*.

ten remain pale (264). Colonies are typically moist to slightly filamentous, and conidiogenous cells are a mixture of medium-length phialides and adelophialides (short phialides lacking a basal septum). The genus currently contains two species of clinical interest, *P. obovatum* and *P. curvatum. P. obovatum* produces a green, diffusible pigment; has obovate conidia (like an upside-down egg); and has been reported as an agent of fatal endocarditis in a neonate (273). *P. curvatum* isolates range from cream to yellowish to pale brownish and have allantoid (curved) conidia. Infections attributed to *P. curvatum* include cutaneous and subcutaneous disease, disseminated infection, endophthalmitis, peritonitis, arthritis, and fungemia (167, 264, 308, 793). Also reported are cases of hemodialysis-associated endovascular infections (608) and endocarditis (561), with some cases linked to intracavernous penile injections in men frequenting impotence clinics (717). Several recent cases have demonstrated sporodochial formation in *P. curvatum*, a feature not previously seen in this species (167, 608, 793). Rivero et al. have recently reviewed published *Phialemonium* cases (634).

***Phaeoacremonium*.** The genus *Phaeoacremonium* initially accommodated isolates with features similar to those seen in both *Acremonium* and *Phialophora* (159). It differs from the former by having pigmented hyphae and conidiophores and from the latter by having indistinct collarettes and warty conidiogenous cells. A recent morphologic and molecular characterization of the genus using β-tubulin sequences (525) has more clearly defined the genus and provided differential features for clinically significant species. Human pathogens include *P. parasiticum* (obsolete *Phialophora parasitica*) (Fig. 12) (335), *P. alvesii* (567), *P. amstelodamense*, *P. griseorubrum*, *P. krajdenii* (525), *P. rubrigenum* (491), *P. tardicrescens*, and *P. venezuelense* (309, 525). Infections caused by *P. parasiticum* include subcutaneous abscesses (245), thorn-induced arthritis (651), and disseminated infection (54). Colony colors may range from yellowish brown to orange-brown to brown to lavender.

***Pleurostomophora*.** Clinically significant species in the mostly wood-inhabiting genus *Pleurostomophora* include *P. richardsiae* (obsolete *Phialophora richardsiae*) and *P. repens* (obsolete *Phialophora repens*), and individuals acquiring these mycoses are commonly immunocompromised (369, 601, 815). Species are anamorphs of the genus *Pleurostoma. P. richardsiae* is characterized microscopically by distinctive flaring collarettes (Fig. 1) and both globose and oval conidia. The colonies of both species tend to be brown rather than gray or olivaceous. Human infections include subcutaneous cases (311) and bone disease (761).

Coniochaetales

***Lecythophora*.** Two *Lecythophora* species, *L. mutabilis* and *L. hoffmannii*, are of clinical significance. Both produce orange, moist colonies initially, with central darkening in *L. mutabilis* as pigmented chlamydospores are produced. Organisms are agents of endophthalmitis (677), sinusitis (485), and prosthetic valve endocarditis (207). Recent large-subunit rDNA sequencing confirms the association of *Lecythophora* species with teleomorphs in the genus *Coniochaeta* (792) in the order *Coniochaetales* (361).

Ophiostomatales

***Sporothrix*.** Sporotrichosis occurs worldwide, with the primary agent of disease being *Sporothrix schenckii.* The disease is commonly acquired by implantation of the fungus from various types of woody/plant material. Lymphocutaneous lesions are the norm; however, pulmonary disease and disseminated infections may occur in patients with underlying diseases (177). As a dimorphic fungus, it exhibits cigar-shaped yeasts in tissue and at 35°C and filamentous growth in culture. Only the sessile conidia borne along the sides of the hyphae are melanized. In a recent study characterizing the genus by calmodulin sequencing (480) and critically reviewing morphologic/physiologic features, these sessile conidia were shown to vary according to species within the *S. schenckii* species complex (479). They are elongate to triangular in *S. schenckii* and globose to subglobose in *S. brasiliensis* and *S. globosa.*

ANAMORPHIC COELOMYCETE GENERA

Pleosporales

***Phoma* and *Phoma*-like pycnidial coelomycetes.** Several genera of morphologically similar pycnidial coelomycetes are occasionally recovered in cases of human subcutaneous disease (307, 585, 704), endophthalmitis (685), and deep tissue infection (411); however, their documentation and reporting as etiologic agents is limited by a lack of adequate identification (727). They include *Phoma*, *Pleurophoma*, *Pleurophomopsis*, and *Pyrenochaeta* species, with small, hyaline, typically one-celled conidia, and *Coniothyrium* (411, 704), *Paraconiothyrium* (773), and *Microsphaeropsis* species (307, 585, 685), with pale brown to dark, one-celled conidia (Fig. 13). The morphologic features of species within several sections in the genus *Phoma* have been detailed by Boerema et al. (84). Species in these similar genera are best differentiated by ITS sequencing.

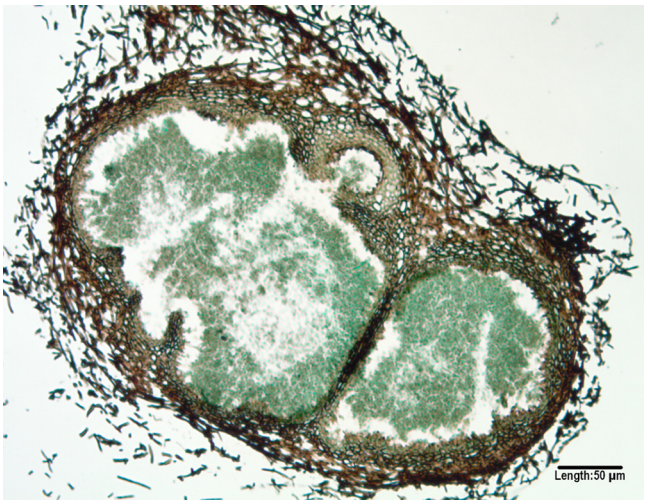

FIG. 13. A GMS-stained cross section of a multilocular pycnidium of a *Microsphaeropsis* species produced on carnation leaf agar after 5 weeks of incubation at 25°C.

Botryosphaeriales

Lasiodiplodia. *L. theobromae* is a pycnidial coelomycetous organism incriminated in cases of subcutaneous disease (720), pneumonia in a liver transplant recipient (805), and ocular infections (615, 705). Conidia may take several weeks to mature and are distinctive, large (20 to 30 by 10 to 15 μm), and hyaline and single celled initially, becoming dark, striated, and two celled at maturity. The organism was formerly known as *Botryodiplodia theobromae*.

Macrophomina. *Macrophomina phaseolina* has been recently reported as an agent of disseminated disease in a renal transplant recipient (735) and as an agent of a cutaneous infection in a child with acute myeloid leukemia (714). The species is difficult to identify without sequencing, as the isolate typically remains sterile in culture, producing only sclerotia (sterile hard masses of hyphal elements).

Neoscytalidium. *Neoscytalidium dimidiatum*, previously known as *Scytalidium dimidiatum* (518, 519) is a rapidly growing, black, woolly, arthroconidia-producing mold. Microscopically similar hyaline variants lacking melanin, formerly referred to as *Scytalidium hyalinum* (639), should also be referred to as *N. dimidiatum.* The species may also produce a coelomycetous pycnidial synanmorph with extended incubation on appropriate media. The name *Nattrassia mangiferae* has now been placed in the new genus *Neofusicoccum* (158, 735). This organism is a plant pathogen, and the name should not be used for human isolates. *N. dimidiatum* primarily produces infections mimicking those caused by dermatophytes on skin and nails (218, 459), although there are occasional reports of ocular infections (26) and deep mycoses in immunocompromised individuals (73, 476, 694, 801).

Sordariales

Phomopsis. There are only rare reports of *Phomopsis* species in human disease. Similarly to *Phoma* and related genera, they are rarely identified beyond the genus level. They are recognized by their black, pycnidial conidiomata (globose to subglobose structures lined with conidiogenous cells) that produce hyaline alpha (ellipsoidal) and beta (long, filamentous, curved) conidia. One report concerns a case of osteomyelitis of the finger in a diabetic patient (727).

TELEOMORPHIC GENERA

Sordariales

Chaetomium* and *Achaetomium. Two ascomycetous genera known to produce their sexual state in culture are *Achaetomium* and *Chaetomium.* The fruiting body in both is a perithecium (a flask-shaped ascoma with an apical opening). Rarely are conidia produced. Species are differentiated mostly phenotypically by the size and shape of ascomata and the type of setae they possess, the size and shape of their brownish ascospores, and temperature tolerance. Most species fail to grow at 35°C and above and are common degraders of various organic compounds. The human pathogen *C. globosum* grows at 35°C but not 40°C, and reports of invasive disease due to this and other, unidentified species (34, 449, 742, 814) are inadequately documented and most likely due to neurotropic species. *Chaetomium atrobrunneum* (314) and *C. perlucidum* do grow at 40°C, are neurotropic (64), and should be considered in the differential diagnosis of CNS fungal disease. A key for identification of clinically significant species has been published by Barron et al. (64). The closely related *Achaetomium strumarium* is pale in culture and produces a reddish-purple diffusible pigment, ascospores similar to those of pathogenic *Chaetomium* spp., and occasional lateral, sessile conidia. It is also neurotropic and an agent of CNS phaeohyphomycosis with growth at 40°C (1, 40).

Pleosporales

Leptosphaeria. *Leptosphaeria senegalensis* and the related *L. tompkinsii* are agents of black grain mycetoma mostly restricted to northern West Africa and India (177). In culture, colonies are slow growing and woolly, and black closed ascomata (cleistothecia) are immersed in the agar. Maturation of ascomata and ascospores is facilitated on plant-based media, and species are differentiated by ascospore features (216, 217).

Microascales

Microascus. Several pigmented *Scopulariopsis* species go on to produce their *Microascus* perithecial teleomorphs in culture. Several of these species have been documented as agents of fatal disease, particularly in transplant recipients. *M. cinereus* caused a brain abscess in a bone marrow transplant recipient (53), suppurative cutaneous granulomata in a patient with chronic granulomatous disease (483), and endocarditis of a prosthetic valve (129). *M. cirrosus* was the etiologic agent of disseminated disease in a pediatric bone marrow recipient (424), and *M. trigonosporus* was reported in a fatal pneumonia in another bone marrow transplant recipient (517). *Microascus* species are differentiated primarily by the size/shape of the perithecia, the length of the perithecial necks (Fig. 14), and the size and shape of the reddish-brown ascospores, which are

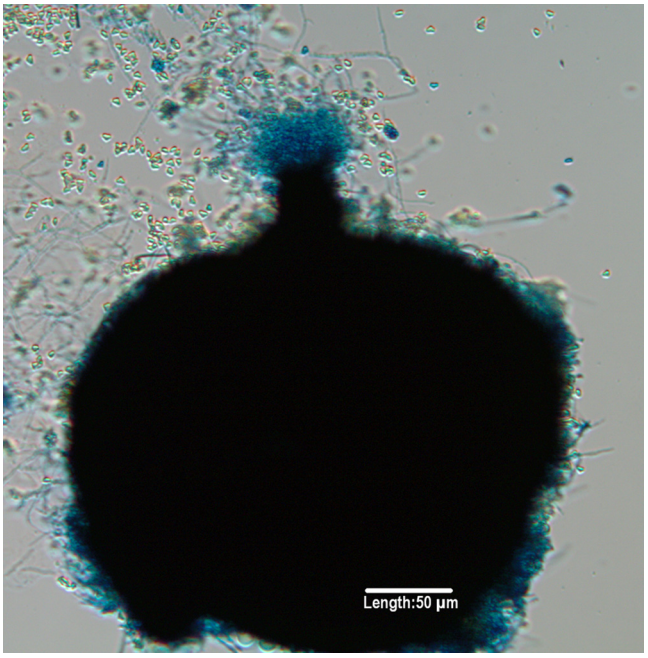

FIG. 14. Perithecium of *Microascus trigonosporus* formed on potato flake agar after 3 weeks of incubation at 25°C. Note ascospores being released from the ostiole in the neck of the perithecium.

orange section shaped in *M. cinereus*, heart shaped in *M. cirrosus* (Fig. 15), and triangular in *M. trigonosporus* (Fig. 16).

***Pseudallescheria*.** As discussed above for the anamorphic genus *Scedosporium*, Cortez et al. extensively reviewed *Pseudallescheria*/*Scedosporium* in 2008 (153), and so only subsequent taxonomic changes will be discussed here. The human pathogenic species as defined by recent molecular studies are as follows: *Pseudallescheria boydii* (anamorph *Scedosporium boydii*), *Pseudallescheria apiosperma* (anamorph *Scedosporium apiospermum*, heterothallic, not forming its teleomorph in culture, and D-ribose negative), and *Pseudallescheria ellipsoidea* (281–283). Other species of clinical interest in the *P. boydii* species complex include *S. aurantiacum* (190, 281) and *S. dehoogii* (282).

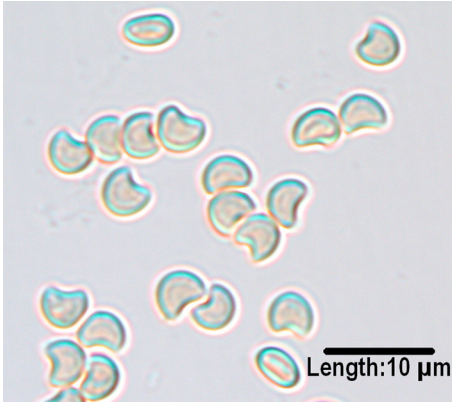

FIG. 15. Heart-shaped ascospores of *Microascus cirrosus* produced on potato flake agar after 3 weeks of incubation at 25°C.

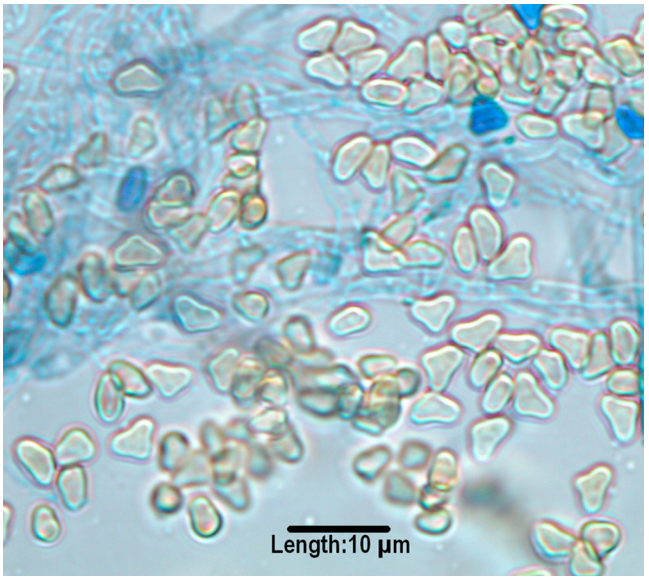

FIG. 16. Triangular ascospores of *Microascus trigonosporus* produced on potato flake agar after 3 weeks of incubation at 25°C.

PATHOGENESIS

Surveys of outdoor air for fungal spores routinely show dematiaceous fungi (687). This suggests that all individuals are exposed, though few develop disease. Exposure is primarily from inhalation or minor trauma, which is frequently not even noticed by the patient. Relatively little is known regarding the pathogenic mechanisms by which melanized fungi cause disease, particularly in immunocompetent individuals.

Role of Melanin

One of the likely virulence factors is the presence of melanin in the cell wall, which is common to all dematiaceous fungi, though relatively few species have been studied (439, 522, 573, 666). Melanin in fungi is derived primarily from either dihydroxyphenylalanine (L-DOPA) or dihydroxynaphthalene (DHN) (437). Dematiaceous fungi contain only DHN melanin; L-DOPA melanin has not been described to our knowledge (122, 274, 439, 766). It is generally localized to the cell wall, though the exact mechanism of its production is poorly understood. In the species *F. pedrosoi*, melanin is produced in melanosomes associated with Fe^{2+} and Ca^{2+} and then transported to the cell wall (253). Melanin is extremely resistant to a variety of physicochemical agents, including free radical compounds, toxic metals, desiccation, and even ionizing radiation (165, 249, 331, 795). A species of *Chaetomium* was isolated from grass that had been frozen in a glacier for over 5,000 years (331).

Considerable work has been done to elucidate the virulence potentials of several fungi (dematiaceous and nondematiaceous) that contain melanin, notably *Aspergillus fumigatus*, *Cryptococcus neoformans*, *E. dermatiditis*, and *S. prolificans* (123, 134, 201, 203, 205, 284, 428, 549, 573, 653, 671, 730, 756). There are multiple proposed mechanisms by which melanin may act as a virulence factor (109, 324, 375). It may confer a protective advantage by scavenging free radicals and hypochlorite that are produced by phagocytic cells in their oxidative

burst and that would normally kill most organisms (376, 671). In addition, melanin may bind to hydrolytic enzymes, thereby preventing their action on the plasma membrane, and to antifungal drugs, preventing their action (370, 375, 547, 768). There is also evidence that certain melanized fungi are less susceptible to phagocytosis and killing by neutrophils and macrophages (334, 584). These multiple functions may help explain the pathogenic potential of some dematiaceous fungi, even in immunocompetent hosts. Specifically, in *E. dermatitidis*, disruption of melanin production leads to markedly reduced virulence in animal models and restriction of hyphal growth (103, 201, 203, 428). However, hyphae of *S. prolificans* were found to be more susceptible to damage from neutrophils than *A. fumigatus* (284). Melanin has also been shown to reduce the susceptibility of *M. mycetomatis* to ketoconazole and itraconazole by binding these drugs (766). Though only a minority of dematiaceous fungi have been studied, it is likely that melanin plays a critical role in pathogenesis for clinically important species.

Other Putative Virulence Factors

It is interesting to note that most allergic disease and eosinophilia is caused by three genera, *Alternaria*, *Bipolaris*, and *Curvularia* (622). The virulence factors in these fungi that are responsible for eliciting allergic reactions are not well understood, though *Alternaria* was found to stimulate the degranulation of eosinophils, possibly due to an aspartic protease (372, 496). These organisms are very common in the environment, so exposure is practically universal, though the incidence of allergic disease is relatively low, suggesting that host factors may play a role. A study by Schubert et al. found that HLA-DQB1*03 was associated with allergic fungal sinusitis (676). Further studies are needed to better delineate the importance of virulence factors other than melanin.

DIAGNOSIS

The timely and accurate diagnosis of fungal infections by melanized fungi consists of a multifaceted approach. With the exponential increase in immunocompromised individuals, particularly those in tertiary care cancer centers (72), this becomes imperative to prevent potentially fatal outcomes. Standard conventional diagnostic procedures include direct microscopy, histopathological stains to document tissue invasion, radiographic and computerized tomography (CT) findings, and isolation procedures to recover the fungus and identify the etiologic agent. The clinical presentation and diagnostic findings segregate these infections into the major categories of eumycetoma, chromoblastomycosis, and phaeohyphomycosis. Phaeohyphomycosis maybe further delineated depending upon whether infections are superficial or deep, by their anatomic location, and by the host's response. The microscopic features seen in phaeohyphomycosis, however, are similar regardless of the anatomic site. The confusion surrounding the placement of members of the *Sporothrix schenckii* and *Pseudallescheria boydii* species complexes within the dark molds is related to their tissue presentation as yeast cells and hyaline hyphae, respectively. As the term phaeohyphomycosis is commonly used to describe fungi with dark hyphae in tissue, these organisms would be excluded; however, both produce melanized conidia in culture. As a thorough review of infections caused by *Pseudallescheria*/*Scedosporium* species has recently been published (153), this paper will concentrate on taxonomic changes and new species documented as etiologic agents subsequent to that review.

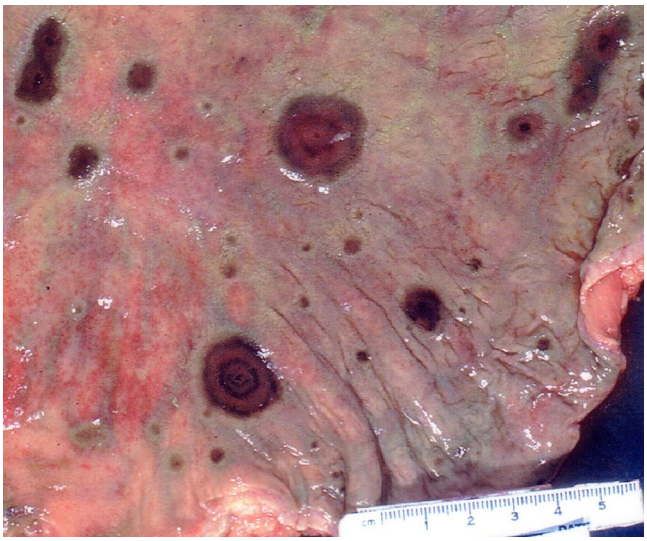

FIG. 17. *Bipolaris spicifera* colonies in stomach mucosa of patient with disseminated disease (autopsy). (Reproduced from reference 624 [original Fig. 15-6A] with kind permission of Springer Science and Business Media.)

Initial Specimen Processing

The appropriate specimen collection, transport, and processing procedures are important considerations in the demonstration of melanized fungi in tissue and their recovery in culture. The most useful diagnostic specimens are those collected at the source of infection; however, specimens peripheral to the site of infection, such as blood cultures in hematogenously disseminated disease, may also be diagnostic in the absence of focal manifestations or when foci are not easily accessible. Appropriate specimens for the recovery of fungi are detailed elsewhere in several reference works (723). Specimens commonly obtained for recovery of melanized fungi include tissue biopsy specimens, aspirates, and body fluids. Surgically obtained specimens should always be cultured as well as processed for histopathology, and the inoculum should be finely sliced or minced rather than ground (as in the case for recovery of *H. capsulatum*). Gross examination may occasionally reveal evidence of melanized fungi as well (Fig. 17). Small volumes of sterile body fluids may also be concentrated by syringe filtration (0.2 μm). Several blood culture systems are available, and the maximum amount of blood recommended should always be used. Swab cultures from superficial sites are usually not representative of the disease process, frequently contain indigenous contaminating mycobiota, and should generally be avoided. Grains or granules should also be washed several times in antimicrobial-containing saline to avoid bacterial overgrowth (504). Also compromising etiologic agent recovery is a delay in specimen transport. Optimally, most specimens

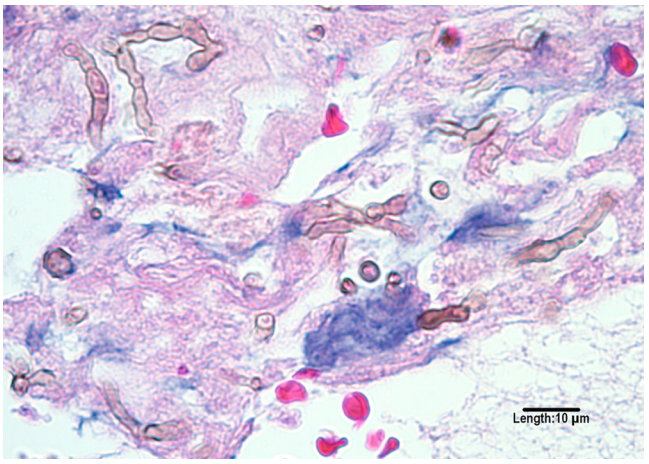

FIG. 18. H&E stain of melanized, moniliform hyphal elements of *Cladophialophora bantiana* from a brain abscess.

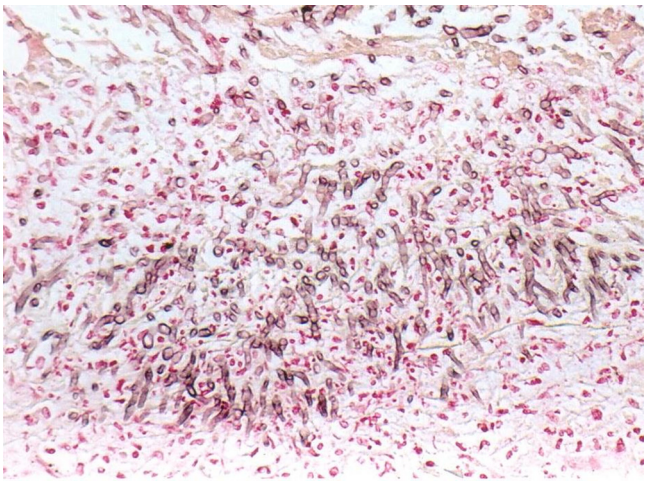

FIG. 19. *Bipolaris spicifera* in lung tissue (Fontana-Masson stain; magnification ×100). (Reproduced from reference 624 [original Fig. 15-13B] with kind permission of Springer Science and Business Media.)

should be processed within 2 h of collection, and cerebrospinal fluid should never be refrigerated (723).

Guidelines regarding the handling of potentially infectious fungi in the laboratory setting are available. It is suggested that cultures of certain well-known pathogenic fungi, such as *Coccidioides immitis/posadasii* and *H. capsulatum*, be worked with in a biosafety level (BSL) 3 facility, which requires a separate negative-pressure room, though clinical samples may be handled under BSL 2 conditions (130). Recently, certain agents of phaeohyphomycosis, in particular *C. bantiana*, have been included in the list of fungi that should be kept under BSL 2 containment (130), and in Europe this mold is considered a hazard category 3 agent (one that can cause severe human disease) (231). This seems reasonable given its propensity, albeit rare, for causing life-threatening infection in healthy individuals.

Direct Microscopy

Due to the ubiquitous nature of melanized fungi, examination of direct specimens is critical, as the finding of fungal elements within tissue is required to document a black mold as the etiologic agent when recovered in culture. It should also be noted that in individuals receiving antifungal therapy, hyphae seen in tissue may be the only evidence of disease, as growth in culture may be severely suppressed or absent. Conversely, recovery in culture without visualization in tissue should be interpreted with caution. Isolation of the same organism multiple times or from multiple sites also supports its role in disease when microscopic evidence is lacking. Commonly used methods for the direct examination of specimens include the Gram stain, several different concentrations of KOH preparations (with or without the incorporation of mycological stains), and the fluorescent calcofluor white stain (652). The Gram stain and KOH preparations are rapid, easily performed tests that should not be overlooked when making an initial assessment of fungal disease with appropriate clinical specimens. Each is described in detail in various microbiology texts (441, 591). Calcofluor and related fluorochromes that bind to cellulose and chitin in fungal cell walls provide another rapid stain for demonstrating fungi by utilizing fluorescence (326). A fluorescence microscope with broadband excitation filters in the range of 300 to 412 nm (322) and eye barriers are required (441). Diagnostic structures seen by direct microscopy also vary according to the clinical presentation. In cases of eumycetoma incited by dark fungi, the demonstration and appearance of pigmented grains or granules (bundles of hyphae often embedded in a cement-like matrix) from pus, exudates, bandage gauze, and biopsied tissue are highly significant and narrow the potential etiologic agents to a limited number of black molds known to cause mycetoma. Members of the *Pseudallescheria boydii* species complex and *Phaeoacremonium* species, however, produce pale grains in tissue (159, 503). Fungi responsible for grains or granules expressed from draining sinus tracts are best visualized in permanent histopathological preparations, as are sclerotic bodies seen in chromoblastomycosis. Fungal elements seen in phaeohyphomycosis are frequently detected by direct microscopy; however, tissue invasion is best documented by permanent histopathological stains. The Gram stain may also be useful in some settings with fungi often demonstrating variable staining. Note that the hyphae are often Gram negative while the conidia are Gram positive; however, either structure may be Gram variable.

Histopathology and Special Stains

Several histopathological stains are useful for the demonstration of melanized fungi (670). The most frequently used hematoxylin-and-eosin (H&E) stain demonstrates pigmentation in hyphae that are strongly melanized (Fig. 18). In fungi that are only lightly pigmented, hyphae may be misidentified as hyaline rather than dark. The melanin Fontana-Masson stain (Fig. 19) is useful in these situations to visualize the phaeoid nature of hyphae in tissue, though other molds may occasionally stain strongly as well (414). An additional stain useful for dark hyphae is the periodic acid-Schiff (PAS) stain (Fig. 20). It

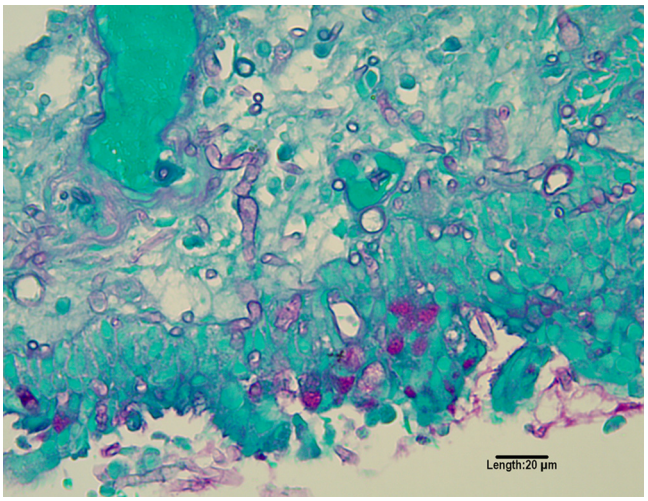

FIG. 20. PAS stain of *Ochrocladosporium elatum*, formerly *Cladosporium elatum*, from sinus tissue.

is frequently preferred over H&E due to the more vivid colors of hyphae, which stain a bright pink-purple against a green background; however, it may overshadow the melanin when present. For practically all fungal histopathology, a Gomori methenamine silver (GMS) stain is ordered. Its utility is in the dramatic visualization of hyphae as dark elements against a green background; however, it fails to discriminate between pigmented and nonpigmented fungal elements (Fig. 21). Note that in Fig. 19 and 21 many of the fungal elements are either short stubby hyphae, pseudohyphae, or moniform (bead-like) hyphae. This is not an uncommon tissue presentation with several dematiaceous genera and is quite different from that seen in aspergillosis, fusariosis, or zygomycosis. Chromoblastomycosis (Fig. 22) presents in tissue as brown, compact muriform hyphal elements with horizontal and vertical cross walls variously referred to as sclerotic bodies, Medlar bodies, or "copper pennies" (610).

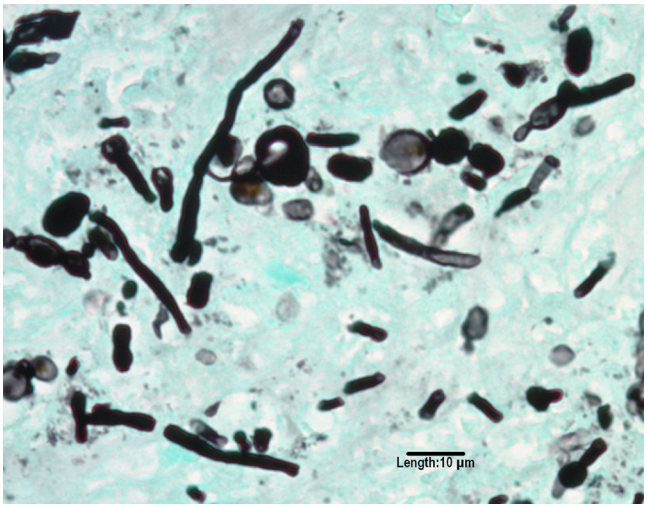

FIG. 21. GMS stain of *Rhinocladiella mackenziei* from a brain abscess. Note the many moniform hyphal elements often seen with melanized fungi.

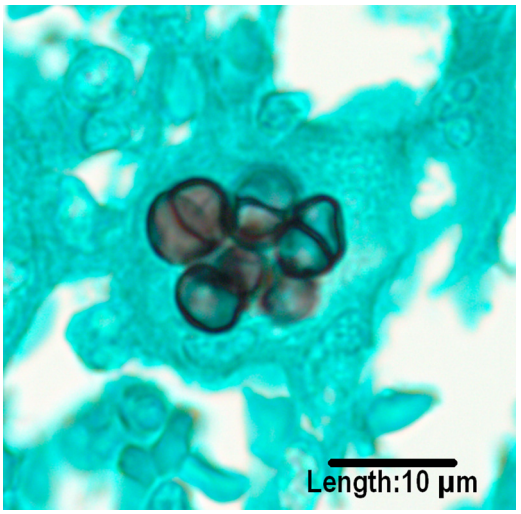

FIG. 22. GMS stain of sclerotic bodies produced by *Fonsecaea pedrosoi.*

Isolation Procedures and Culture

These ubiquitous fungi can be contaminants in cultures, making the determination of clinical significance problematic. A high degree of clinical suspicion as well as correlation with appropriate clinical findings is required when interpreting culture results. The recovery of dematiaceous fungi from clinical specimens requires the appropriate media and incubation conditions. Various references list suggested schemes for primary isolation media (722, 723). A common approach is to include nonselective as well as selective media, such as those containing cycloheximide, media enriched for fastidious organisms such as brain heart infusion agar (BHI) and inhibitory mold agar (IMA), and also media containing antimicrobial agents to suppress bacteria in specimens collected from nonsterile sites. A nonselective medium frequently employed is SDA. While growth is adequate, the color of the colonies is often cream to pale orange or light brown, making their recognition as phaeoid genera difficult. When these same isolates are transferred to plant-based media, they assume their more typical olivaceous to dark brown to black color. The additional time required for these subcultures can have potentially devastating consequences in the profoundly compromised individual, and therefore the use of a plant-based medium initially, such as PDA, is highly recommended. Cultures are commonly incubated at 30°C; however, room temperature at or near 25°C may also be used. Cultures should be examined every day for the first 3 days and twice a week thereafter. Most phaeoid molds are recovered within a week, and incubation of negative cultures beyond 3 weeks is seldom necessary (430). Substantially longer incubation, however, may be required for development of diagnostic structures in some isolates, particularly for coelomycetes or homothallic ascomycetes. All filamentous organisms should be manipulated and examined under a certified biological safety cabinet.

Radiology

There are few radiologic features that distinguish melanized fungi from other molds as causes of infection. The "dot-in-circle" sign has been noted to be specific for the finding of eumycetoma in magnetic resonance imaging (MRI) studies (141). This is felt to be due to the low signal intensity produced by the fungal grains in tissue.

Antigen Testing and Serology

There are no widely available serologic or antigen tests available to specifically detect melanized fungi in blood or tissue. However, serum antigen testing for 1,3-β-D-glucan (primarily for *Candida* spp.) and galactomannan (primarily for *Aspergillus* spp.) may cross-react with melanized fungi, though usually with low levels (164, 419). However, in immunocompromised patients with cultures positive for dematiaceous fungi, a positive serum galactomannan test may indicate concomitant infection with *Aspergillus*; careful clinical correlation is advised (71). Further studies are needed to better understand the nature and likelihood of cross-reactivity. Serum enzyme-linked immunosorbent assays (ELISAs) for *F. pedrosoi* and *C. carrionii* have been developed to aid in the diagnosis of chromoblastomycosis, though relatively low sensitivity and specificity have limited their usefulness, and only small numbers of patients have been studied (552, 775, 778).

Molecular Diagnostics

In an effort to improve the rapidity with which invasive fungal infections are detected as well as the sensitivity and specificity of diagnostic tests, recent assays have focused on nonculture methods, in particular nucleic acid-based methods, such as PCR assays. Despite advances in the direct diagnosis of other, more common genera such as *Candida*, *Aspergillus* and *Fusarium*, the direct diagnosis of infections incited by melanized species remains a challenge. However, studies have begun to examine the potential of identifying species within this diverse group of fungi using PCR of highly conserved regions of ribosomal DNA (2). A panfungal PCR assay described by Lau et al. targeting the ITS1 region was able to detect several species of dark molds from fresh, formalin-fixed, or paraffin-embedded tissue specimens, including *S. prolificans*, *Exophiala* spp., *Exserohilum rostratum*, and *Microsphaeropsis arundinis* (445). In a real-time PCR assay targeting part of the 28S large-subunit rRNA gene, Vollmer et al. were able to amplify *Aureobasidium pullulans* in clinical specimens from intensive-care patients with either artificial respiration or infective endocarditis (785). While these methods and those to be refined in the foreseeable future will provide a more rapid diagnosis for some agents of phaeohyphomycosis, the diversity of black molds increasing in immunocompromised individuals makes their identification from direct materials a daunting task. Currently, a greater utility of molecular methods is in the identification, taxonomy, and phylogenetic placement of these melanized fungi.

IN VITRO ANTIFUNGAL SUSCEPTIBILITY

In vitro antifungal susceptibility testing has advanced considerably in the past several years, especially when one considers that a standardized method for testing yeasts was not available until 1997 (534), the first standardized method for filamentous fungi was not available until 2002, and both were updated in 2008 (147, 148). Due to the relatively recent development of antifungal susceptibility testing, the available *in vitro* data for dematiaceous fungi are relatively sparse, and often rely on small numbers of isolates per species. An important issue is that much of the older literature is often inconsistent with regard to methodology, making reliable observations difficult. In addition, as defined interpretive breakpoints are not available for any of the molds, guidelines for interpreting *in vitro* data frequently rely on close approximations to breakpoints for *Candida* species, as well as achievable concentrations of the drug using standard dosing regimens. A MIC of ≤ 1 μg/ml is often used as an indicator of potential susceptibility for most drugs used to treat black molds, excluding flucytosine (5-FC) (<50 μg/ml), recognizing that there are significant differences in pharmacological properties between the various agents as well as differences in drug concentrations tested. Lower MICs typically suggest better activity. The *in vitro* activities of several antifungal agents against a variety of dematiaceous fungi are presented in Table 3. The data are from a compilation of the current literature (49, 50, 161–163, 224–228, 250, 266, 294, 315, 382–384, 391, 532, 553, 625, 781, 782); however, clinical correlates are not available. Antifungal susceptibility testing of etiologic agents, when warranted, may assist in appropriate patient management.

Polyenes

Amphotericin B. Amphotericin B generally has good *in vitro* activity against most clinically important dematiaceous fungi. However, some species have been consistently resistant (MICs of ≥ 2 μg/ml) *in vitro*, including *S. prolificans* and *S. brumptii* (507), while other species have occasionally been found to be resistant, including *Curvularia* spp., *Exophiala* spp., and *R. mackenziei* (507, 726). Significant toxicity often limits use of the standard formulation, primarily due to renal insufficiency, electrolyte disturbances, and infusion-related side effects. However, nephrotoxicity has been significantly reduced by the development of lipid-associated formulations (339). Use of these preparations allows for much higher doses than possible with standard amphotericin B, which may improve their efficacy against these fungi. In addition, lipid amphotericin B preparations may achieve higher concentrations in brain as well (407).

Natamycin. Natamycin is a polyene antifungal used exclusively as topical therapy in eye infections, particularly keratitis. It has broad spectrum of activity against most relevant molds (*Aspergillus* and *Fusarium*) and is available in concentrations of up to 5%, which is generally well tolerated (478, 650). Data for susceptibility against common dematiaceous fungi are very limited, though one study did show activity against *Curvularia* (800).

TABLE 3. *In vitro* activities of antifungal agents against selected melanized fungi[a]

Species	Activity[b]											
	AmB	Itra	Vori	Posa	Isavu	Ravu	Keto	Terb	5-FC	Casp	Mica	Anid
Alternaria spp.	+	++	+	++	+			+	−	+		+
Aureobasidium pullulans	+	++	++									
Bipolaris spp.	+	++	++	++	+	+		+		+		+
Chaetomium spp.	+	++	++			++	+		−			
Cladosporium spp.	+	++	++					++	+		+	
Cladophialophora bantiana	++	++	++	++			+	+	+	+	++	+
Curvularia spp.	+	++	++	++	+	+		+		+		
Exophiala spp.	+	++	++	++	+	+		+	+	+		+
Exophiala dermatitidis	++	++	++	++		+	+	+	+		+	+
Exserohilum spp.	++	++	++			+		+				
Fonsecaea pedrosoi	++	++	++			+	++	++	+	+	+	+
Lasiodiplodia theobromae								+				
Madurella mycetomatis	+	++	++				++	+	−			+
Ochroconis gallopava	+	++	+									
Phialemonium spp.	+	+	+									
Phialophora spp.	+	++		++		+		+	+	+		+
Rhinocladiella spp.	+	++	++			+			+			
Rhinocladiella mackenziei	+	+	+	+	+				+	−		−
Scedosporium/*Pseudallescheria* spp.	−	+	++	+								
Scedosporium prolificans	−	−	−	−				−		−	−	−
Scopulariopsis brumptii	−	−		−								−
Veronaea botryosa		+	+									
Wallemia sebi	+	+	+	+				+	−		+	

[a] Adapted from reference 625 with permission of Expert Reviews Ltd.

[b] Abbreviations: AmB, amphotericin B; 5-FC, flucytosine; Keto, ketoconazole; Itra, itraconazole; Vori, voriconazole; Posa, posaconazole; Ravu, ravuconazole; Casp, caspofungin; Mica, micafungin; Anid, anidulafungin; Terb, terbinafine; Isavu, isavuconazole. ++, good activity suggested based on consistently low MICs and testing against at least five isolates of a particular genus or species; +, potential/marginal activity suggested based on inconsistent MICs or very few isolates of a particular genus or species; −, no significant activity suggested based on consistently high MICs. The results do not represent formally defined CLSI breakpoints.

Azoles

The triazole agents itraconazole, voriconazole, and posaconazole demonstrate the most consistent *in vitro* activity against dematiaceous fungi, except against *S. prolificans* and *S. brumptii*, which are resistant to all azoles (120, 227, 507, 509). Only voriconazole is available as an intravenous (i.v.) formulation. All of these agents have significant drug interactions that must be considered during therapy (310). In addition, therapeutic drug monitoring is becoming increasingly utilized as data correlating serum levels with clinical response and toxicity accumulate (706).

Other azoles have a limited role in the therapy of these infections. Ketoconazole was the first oral azole and has a relatively broad spectrum. However, a number of side effects have significantly limited its current use with the availability of newer agents that are much better tolerated. Sparse *in vitro* data are available for dematiaceous fungi, but good activity is noted for the most common fungi causing chromoblastomycosis and mycetoma (35, 767). Fluconazole has negligible activity against dematiaceous molds (132, 259) and essentially no role in therapy given the variety of other options available, though anecdotal success has been reported (198).

Itraconazole. Though itraconazole was the first oral azole with significant activity against dematiaceous fungi and has had the most clinical use in therapy, concerns over adverse effects and the lack of an intravenous formulation have reduced its use in recent years. For itraconazole, the capsule form requires an acidic environment for absorption, while the suspension with cyclodextrin does not, being more consistently absorbed. Itraconazole demonstrates good activity against the vast majority of dematiaceous fungi tested (226–228, 506, 507). MICs generally are $\leq$0.125 μg/ml for this group of fungi.

Voriconazole. Voriconazole has become the treatment of choice for invasive aspergillosis, supplanting amphotericin B for this indication (385, 745). It has also become a commonly used agent for treating many other invasive mold infections, especially those caused by dematiaceous fungi. The i.v. form is particularly useful in critically ill patients. It is generally well tolerated, though visual side effects are common but rarely limit therapy (745). In addition, like itraconazole, it has a broad spectrum of activity that includes most dematiaceous fungi (227, 228, 507). However, MICs may be slightly higher for voriconazole, though the clinical significance of this is unclear.

Posaconazole. Posaconazole is the most recently released azole and has the broadest spectrum of any oral agent (338, 401, 707). It is currently available only orally, though an i.v. formulation is being developed. It is generally very well tolerated. Oral absorption is significantly improved if it is administered with food, particularly food with a high fat content. The published *in vitro* data are relatively limited for dematiaceous fungi, but good activity is demonstrated against most species tested, including *Bipolaris* spp., *C. bantiana*, and *R. mackenziei* (14, 52, 224, 592). Posaconazole may be useful in cases of CNS disease, even that due to refractory molds (600).

Investigational azoles. Isavuconazole is a broad-spectrum azole with both oral and i.v. forms that has not been approved for use at this writing. Limited *in vitro* data exist for dematiaceous fungi (294, 532). Ravuconazole is another investigational azole with activity against a wide variety of molds (259).

Flucytosine

Flucytosine (5-FC) is unique in its mechanism of action, inhibiting DNA and RNA synthesis (252, 774). In the United States it is available only in oral form. The development of resistance during monotherapy has resulted in its use in combination therapy for systemic mycoses, most notably cryptococcal meningitis (774). *In vitro* studies with dematiaceous fungi are limited, though activity against *C. bantiana*, *Exophiala* spp., and *Fonsecaea* (*F.*) *pedrosoi*, the major etiologic agent of chromoblastomycosis, has been shown (111, 202).

Allylamines

Allylamines, like the azoles, also inhibit ergosterol synthesis, but they act on squalene epoxidase, an enzyme two synthetic steps before the target of azoles. Their clinical role has been limited to treatment of dermatophyte infections, though there has been recent interest in potentially expanding their clinical spectrum (333, 626). Terbinafine is the only oral allylamine available for systemic use. However, its extensive binding to serum proteins and distribution into skin and adipose tissue have diminished enthusiasm for its use in treating serious systemic fungal infections (356, 381, 468, 655). *In vitro* studies against dematiaceous fungi are emerging, and broad-spectrum activity has been seen, including against *Alternaria*, *Curvularia*, and *Bipolaris* and agents of chromoblastomycosis (35, 382, 506). The *in vitro* testing range for this agent is typically between 0.004 and 2 μg/ml.

Echinocandins

The echinocandins are the latest group of antifungal agents to be developed and have a unique mechanism of action, inhibiting 1,3-β-D-glucan synthesis and thereby disrupting the fungal cell wall (118). Caspofungin, micafungin, and anidulafungin are available only in an intravenous formulation and are generally well tolerated and, notably, have very few significant drug interactions (145). They are generally considered therapeutically equivalent, based on studies conducted on invasive *Candida* infections. *In vitro* studies with dematiaceous fungi are limited, with variable activity noted against many dematiaceous fungi, including *Curvularia*, *Bipolaris*, and *F. pedrosoi* (224, 225). *S. prolificans* appears to be resistant (225, 509). Micafungin may have lower MICs for *C. bantiana* than other echinocandins (225). In general, MICs for dematiaceous fungi are higher than those for *Aspergillus* spp.

Other Agents

A variety of drugs have been explored for activity against these fungi, given their refractory nature. Miltefosine, a drug originally developed as an anticancer drug and found to be effective in leishmaniasis, has antifungal activity against a variety of dematiaceous fungi, including *S. prolificans* (797). Nikkomycin, a chitin synthase inhibitor with activity against *Coccidioides immitis*, was found to have relatively poor activity against dematiaceous fungi (454).

Antifungal Combinations

Uses of antifungal combinations are being increasingly studied as strategies for treatment of refractory fungal infections, though not extensively for dematiaceous fungi. However, for *C. bantiana* and *S. prolificans*, the most common fungi causing CNS and disseminated diseases, respectively, novel approaches are needed to improve therapy, and a variety of combinations have been studied *in vitro* and *in vivo* (see Animal Models of Infection below). In a murine model of *C. bantiana*, combination therapy was found to be superior to monotherapy for all agents tested (481).

Given that no single antifungal agent has significant activity against *S. prolificans*, numerous combinations have been studied to improve efficacy. The combination of itraconazole and terbinafine has been studied against *S. prolificans*, which is otherwise generally resistant to all agents. *In vitro*, synergistic activity against most isolates of this species was found, and no antagonism was noted (511). Voriconazole and terbinafine also display similar synergy *in vitro* (510). The mechanism is presumably potent inhibition of ergosterol synthesis at two different steps of the pathway by these agents. However, this should be interpreted with caution, as terbinafine is not recommended for systemic infections. The combination of voriconazole with micafungin and amphotericin B was found to be synergistic *in vitro* against *S. prolificans*, though double combinations also lowered individual MICs (637). Other reports suggest synergy against *S. prolificans* with voriconazole and caspofungin or with micafungin and amphotericin B (160, 716, 821). Importantly, antagonism was not observed with any of these combinations. Gil-Lamaignere et al. showed a synergistic effect of voriconazole or posaconazole with neutrophils *in vitro* against hyphae of *S. prolificans* (285). Older literature also suggests synergy with ketoconazole and 5-FC for a variety of dematiaceous fungi (152). This may be applicable to other azoles as well.

ANIMAL MODELS OF INFECTION

There are relatively few animal studies with dematiaceous fungi. One of the earliest studies was a murine model of infection with *E. dermatitidis* and *F. pedrosoi* (603). Amphotericin B and 5-FC were active alone or in combination, though ketoconazole was not. In another study, 5-FC had the broadest activity against *C. bantiana*, *O. gallopava*, and *E. dermatitidis* in mice, followed by amphotericin B and fluconazole (despite resistance *in vitro*) (202). Terbinafine was ineffective *in vivo*, despite good *in vitro* activity (202).

More recent studies have focused on therapy with posaconazole in refractory mycoses due to *R. mackenziei*, *C. bantiana*, and *E. dermatiditis*. Al-Abdely et al. found posaconazole to be more effective than amphotericin B or itraconazole in murine models of central nervous system infection with *R. mackenziei* and *C. bantiana* (14, 15). Posaconazole was also found to be effective in a model of disseminated *E. dermatiditis* infection (301). In another murine model of *C. bantiana* infection, posaconazole and flucytosine improved survival alone, though the combination of posaconazole, flucytosine, and micafungin yielded the greatest benefit (481). In a recent murine model of *F. monophora*, posaconazole was associated with significantly better survival than amphotericin B or itraconazole (113).

TABLE 4. Clinical syndromes, associated dematiaceous fungi, and suggested therapy[a]

Clinical syndrome	Commonly associated fungal genera or species	Therapy[b]
Eumycetoma	*Madurella*, *Pyrenochaetae*, *Leptosphaeria*	Azole ± Terb
Chromoblastomycosis	*Fonsecaea* (*F. pedrosoi*), *Phialophora*, *Rhinocladiella*	Azole ± Terb
Phaeohyphomycosis		
Allergic fungal sinusitis	*Bipolaris*, *Curvularia*	Surgery + steroids ± Itra
Allergic bronchopulmonary mycosis	*Bipolaris*, *Curvularia*	Steroids ± Itra
Onychomycosis	*Alternaria*, *Scopulariopsis*	Itra or Terb ± topical agents
Tinea nigra	*Hortaea werneckii*, *Stenella araguata*	Topical agents
Subcutaneous nodules	*Alternaria*, *Exophiala*, *Phialophora*	Surgery ± azole
Keratitis	*Curvularia*, *Bipolaris*, *Exserohilum*	Topical natamycin ± topical azole
Bone and joint infection	*Scedosporium prolificans*, *Alternaria*	Vori ± Terb
Peritonitis	*Curvularia*, *Exophiala*, *Alternaria*	Catheter removal ± AmB or azole
Pneumonia	*Ochroconis*, *Exophiala*, *Chaetomium*	Vori (L-AmB if severe)
Brain abscess	*Cladophialophora bantiana*, *Rhinocladiella mackenziei*, *Ochroconis*	Azole + L-AmB or echinocandin ± 5-FC (see text)
Disseminated disease	*Scedosporium prolificans*, *Bipolaris*, *Exophiala*	Vori + Terb ± echinocandin, Vori ± echinocandin or L-AmB (see text)

[a] Adapted from reference 625 with permission of Expert Reviews Ltd.
[b] Abbreviations: Vori, voriconazole; Itra, itraconazole; Terb, terbinafine; L-AmB, lipid amphotericin B; 5-FC, flucytosine; azole, voriconazole, posaconazole, or itraconazole; +, with; ±, with or without.

Posaconazole was associated with improved survival compared with amphotericin B or caspofungin in a murine model of *Exophiala* infection (633).

S. prolificans was studied in a murine model, and the combination of micafungin with either voriconazole or amphotericin B was associated with improved survival, though the triple combination of all three agents was not more effective (637). Posaconazole with granulocyte-macrophage colony-stimulating factor (GM-CSF) against *S. prolificans* did not improve survival in one study (698), though liposomal amphotericin B with G-CSF did improve survival in a murine model (560).

CLINICAL SYNDROMES AND THEIR MANAGEMENT

A wide variety of clinical syndromes have been associated with melanized fungi, reflecting their diverse nature (Table 4). The number of published articles relating to these fungi has risen steadily in recent years. They may be considered opportunists or true pathogens, and many of the various clinical presentations can occur in both healthy and immunocompromised individuals. In reviewing the literature, it is seen that case reports often lack crucial details of medical history, diagnostic studies, therapy, and especially clinical follow-up. This limits their usefulness in determining the efficacy of the therapy. However, since randomized trials are not practical given the rarity of these infections, we are left to manage with the available data.

Eumycetoma

Mycetoma is one of the oldest infections described in recorded writings, being mentioned as "pada valmikam" (anthill foot) in the ancient Vedic hymns of India (455). Eumycetoma is due to fungi and accounts for one-third to one-half of all cases of mycetoma (473). The first report in the modern medical literature was in 1846 by Godfrey (289). It is a chronic subcutaneous infection caused by a small group of fungi and characterized by the presence of grains, or sclerotia, in tissue (502). These grains are usually white or black, depending on the fungal species involved, and are composed of fungal cells surrounded by a dense extracellular matrix containing a melanin compound, which gives it a dark color and likely has a role in protecting the organism from host defenses (9). Eumycetoma is common in many tropical and subtropical areas of the world. The species involved are often associated with a particular geographic region. *M. mycetomatis* is one of the most common species, particularly in Africa and India (9). Many other species have been implicated, including *Pyrenochaeta romeroi* (South America), *Leptosphaeria senegalensis* (Africa), *E. jeanselmei*, *Curvularia* spp., and *P. verrucosa* (9).

In contrast to chromoblastomycosis and subcutaneous phaeohyphomycosis, which may be cured with surgical techniques alone, eumycetoma almost always requires prolonged systemic antifungal therapy in addition to surgery due to the extensive and deep tissue involvement. The most experience has been with ketoconazole and itraconazole, though itraconazole appears to have more consistent clinical activity (9, 27, 30, 116, 127). Recently, reports of success using voriconazole and posaconazole have been published (431, 447, 462, 537). Therapy generally is continued for at least 3 months, though courses of 6 to 24 months or longer are often required. In refractory cases, combination therapy has also been used, adding either flucytosine or terbinafine to an active triazole (350, 447). Surgery can help to reduce disease burden and occasionally cure small, localized lesions that do not involve bone (30). Amphotericin B is largely ineffective and impractical given the duration of therapy that is often required (632).

Chromoblastomycosis

Chromoblastomycosis is a slowly progressive, chronic subcutaneous mycosis that is seen predominantly in tropical areas (610). Pedroso was one of the first to report of this disease in 1920 (581). The term chromoblastomycosis was introduced by Terra et al. in 1922 (739). Minor trauma typically precedes the

lesions, though many patients do not recall this. Nodular lesions can progress over years to form large, verrucous plaques. Histopathology is characterized by the presence of muriform sclerotic bodies (Medlar bodies or "copper pennies") in tissue, which defines this condition (232, 610). By far the most common species is *F. pedrosoi*, followed by *Phialophora verrucosa* and, less commonly, *Cladophialophora carrioni* and *Rhinocladiella aquaspersa* (610). They can also cause other clinical syndromes, often leading to confusion in the literature as some authors refer to any disease caused by these fungi as "_____ chromoblastomycosis" (66). Other fungi have been implicated, though some reports do not clearly describe the pathognomonic features and so are questionable (594). It is not understood how and under what conditions sclerotic bodies are formed in tissue. Melanin is thought to play an important role, though other compounds such as peptidases, glycosphingolipids, and sialidase may be involved in pathogenesis as well (666).

Therapy is difficult and various modalities have been used, usually over a period of several months and even years. Besides antifungal therapy, surgery, cryotherapy, thermotherapy, and even laser therapy have been tried (90). In a large series, cryotherapy, itraconazole, or the combination resulted in the largest number of cures (88). In developing countries, where systemic antifungals are not easily available or are too expensive, the use of cryotherapy alone in a systematic manner over several months has led to good cure rates as well (126). Such physical therapies are most effective on small, localized lesions. The exact mechanism of this effect is unclear.

Antifungal therapy is essential for moderate to severe or widespread disease. As a single agent, itraconazole appears to be the most effective, and it is the agent with which there is the most clinical experience (88, 426, 610, 611, 620). A variety of other treatments have also been successful, including ketoconazole, flucytosine, local heat therapy, and amphotericin B (44, 377, 515). However, the overall cure rate was only 57% in one large series of 100 cases from Brazil, despite use of multiple modalities (515). Recently, terbinafine has been found to have *in vitro* and clinical activity (91, 684). In refractory cases, the combination of itraconazole and terbinafine has been found to be useful, and some experts recommend this as first-line therapy for moderate to severe disease (90, 317, 610).

Phaeohyphomycosis

The remainder of clinical syndromes can be grouped under the term phaeohyphomycosis. For the purposes of this review, they will be arbitrarily divided into allergic disease, superficial infection, deep local infection, pulmonary infection, central nervous system infection, and disseminated infection.

Allergic disease. Allergic responses to dematiaceous fungi may actually represent the most common clinical manifestation of these fungi. Though asthma has many associated environmental factors, several studies have linked it with exposure to molds and to dematiaceous fungi, *Alternaria* spp. and *Cladosporium* spp. in particular (108, 278, 456, 555). The effect has also correlated with seasonal fluctuations in outdoor mold counts (555). In addition, *Alternaria* has been associated with severe asthma exacerbation in some individuals (541). A frequent finding is the presence of elevated *Alternaria*-specific IgE (456). However, most melanized fungi do not elicit such a response, and it remains unclear why only a few genera are associated with allergic disease.

(i) Allergic fungal sinusitis. Allergic fungal sinusitis is a relatively common condition, with estimates of 6 to 9% of all cases of chronic sinusitis requiring surgery (673). Patients with this condition usually present with chronic sinus symptoms that are not responsive to antibiotics. Previously, *Aspergillus* was thought to be the most common fungus responsible for allergic sinusitis, but it is now appreciated that disease due to dematiaceous fungi actually comprises the majority of cases (239, 674). Geographic variation has also been reported, with an increased incidence in the southern United States (240).

The most common species isolated are *Alternaria*, *Bipolaris*, and *Curvularia*, though other rare fungi (*Epicoccum* and *Nodulisporium*) have also been reported (155, 544, 673). However, fungi are frequently isolated from normal individuals as well (668). Criteria have been suggested for this disease, and these include (i) nasal polyps; (ii) the presence of allergic mucin, containing Charcot-Leyden crystals and eosinophils; (iii) hyphal elements in the mucosa without evidence of tissue invasion, (iv) positive skin test to fungal allergens; and (v) on computed tomography (CT) scans, characteristic areas of central hyperattenuation within the sinus cavity. Not all are considered by experts to be necessary for diagnosis (357, 675). Diagnosis generally depends on demonstration of allergic mucin, with or without actual culture of the organism. Therapy consists of surgery to remove the mucin, which is often tenacious, and systemic steroids, though patients have been cured by surgical therapy alone (498, 631, 732). Antifungal therapy, usually in the form of itraconazole, may play a role in reducing the requirement for steroids, but this is not routinely recommended and small, randomized studies showed no benefit when it is used as primary therapy in addition to surgery (425, 654). However, in refractory cases, itraconazole may improve outcomes (135, 680). Other azoles (voriconazole) have only rarely been used for this disease (223).

In rare cases, patients may present with often chronic symptoms of mass effect due to the inflammation extending from sinuses into adjacent structures, including the orbits (102, 125, 150, 379). These are almost always immunocompetent patients. In addition to surgery and steroids, systemic antifungal therapy is often given.

(ii) ABPM. Allergic bronchopulmonary mycosis (ABPM) is similar in presentation to allergic bronchopulmonary aspergillosis (ABPA), which is typically seen in patients with asthma or cystic fibrosis (5, 658). There is a suggestion that allergic fungal sinusitis and allergic bronchopulmonary mycosis may actually be a continuum of disease and should be referred to as sinobronchial allergic mycosis (SAM) (771). Criteria for the diagnosis of ABPA in patients with asthma include (i) asthma, (ii) positive skin test for fungal allergens, (iii) elevated IgE levels, (iv) *Aspergillus*-specific IgE, and (v) proximal bronchiectasis (5). Similar criteria for ABPM are not established but may include elevated IgE levels, positive skin tests, and response to systemic steroids.

In reviewing cases of ABPM due to dematiaceous fungi, essentially all cases are found to be due to *Bipolaris* or *Curvularia* (323, 432, 526, 622, 631, 658, 753). Asthma was common in these cases, but bronchiectasis was often not

present, perhaps reflecting somewhat different pathogenic mechanisms. All cases had either eosinophilia or elevated IgE levels. Therapy was primarily systemic steroids, with a slow taper over 2 to 3 months or longer, if necessary. Itraconazole has been used as a steroid-sparing agent in ABPA, but its efficacy is not clear and routine use of itraconazole is not generally recommended (5).

Superficial infections. These cases of superficial infections involve only keratinized tissues, such as the fingernails and toenails and the stratum corneum. Consequences of these infections are generally cosmetic. Relatively few fungi are responsible for the majority of infections.

(i) Onychomycosis. Dematiaceous fungi are rare causes of onychomycosis. Clinical features may include a history of trauma, involvement of only one or two toenails, and lack of response to standard systemic therapy (316). *Alternaria*, *Scopulariopsis*, and *Neoscytalidium* have been reported, with the last genus being highly resistant to therapy (68, 316, 643, 752). In one study, *Neoscytalidium* infection was associated with plucking of green tea leaves (68). Itraconazole and terbinafine are the most commonly used systemic agents and may be combined with topical therapy for refractory cases (316, 752). No published data are available for the newer azole agents.

(ii) Tinea nigra. Tinea nigra is an uncommon infection confined to the stratum corneum. The characteristic appearance is that of a pigmented macule, usually on the palms or soles, and may be bilateral (440, 682). It is usually asymptomatic. The most common reported cause is *Hortaea werneckii* (previously *Phaeoannellomyces werneckii*), with some cases due to *Stenella araguata* (87, 588, 682). Most cases are associated with exposure to sandy beaches in tropical regions, where *H. werneckii* is found in areas of high salinity (588). However, individual cases due to *Scopulariopsis brevicaulis*, *Phoma eupyrena*, and *Chaetomium globosum* with findings consistent with tinea nigra have also been reported (57, 154, 287). Diagnosis is made by skin scraping, and biopsy is not needed. Although systemic antifungals have been given with success (318), topical therapy with azoles or keratolytics is very effective (87, 588).

Deep local infections. Deep local infections are a heterogenous group of infectious syndromes that are typically caused by local trauma. Virtually any of the melanized fungi discussed in this review may cause these infections. While they are rarely life-threatening, even in immunocompromised patients, considerable morbidity can result due to difficulties in treatment and complications.

(i) Subcutaneous lesions. Subcutaneous lesions are the most common case reports of infection due to melanized fungi in the literature. *Alternaria* spp. are by far the most common etiologic agent, with a recent review cataloguing over 156 cases up to 2007 (195, 191, 275, 373, 542, 577, 710, 751). *Exophiala* spp. and *Phialophora* spp. are the next most common fungi, followed by *Cladosporium* spp., *Exserohilum* spp., *Veronaea botryosa*, and many others with scattered case reports (7, 12, 19, 23, 32, 36, 56, 61, 65, 81, 140, 143, 194, 209, 230, 241, 251, 258, 306, 313, 342, 362, 365, 369, 387, 413, 418, 421, 457, 469, 482, 486, 487, 495, 539, 559, 556, 568, 571, 576, 590, 609, 613, 614, 646, 659, 694, 699, 720, 728, 749, 764, 776, 807, 818). Minor trauma is the usual inciting factor, though it is frequently unrecognized by the patient. Occasionally wood splinters or other vegetable matter is found upon skin biopsy or excision of the lesion (499, 524, 559, 660).

Many patients are immunocompetent, and they often are from a rural background, i.e., farmers with frequent, minor trauma from plant material or gardeners (133, 192, 206, 233, 277, 359, 576, 751, 815). Organ transplantation is also a common risk factor (28, 38, 112, 142, 235, 236, 262, 271, 286, 296, 465, 484, 514, 556, 587, 645, 679, 704, 725). Apparently nosocomial cases have also been reported, with skin irritations from dressings or i.v. sites as possible risk factors (237). Lesions typically occur on exposed areas of the body and often appear as isolated cystic or papular lesions. Presentation is usually indolent, with weeks to months of gradual enlarging mass, though pain is often absent. Severely immunocompromised patients are at increased risk of subsequent dissemination, though this may rarely occur in apparently immunocompetent patients as well. Occasionally, infection may extend to involve joints or bone, requiring more extensive surgery or prolonged antifungal therapy (198).

Multiple therapeutic options are available, usually depending on the immune status of the patient and the extent of lesions. Oral systemic therapy with an azole antifungal agent in conjunction with surgery is frequently employed and has been used successfully, particularly in immunocompromised patients. This is to prevent possible disseminated infection, though this is actually very rare in all but the most immunosuppressed patients. Terbinafine has also been used successfully, particularly in patients failing azole therapy (7). Surgical excision alone has been successful in a number of cases, even in organ transplant patients (12, 194, 235, 387, 418, 558, 587, 646, 686, 720, 764). The Mohs surgical technique, which was developed for removing melanoma, may be a useful surgical approach, as it spares tissue and completely removes the pathological lesion in staged surgeries (86). Patients for whom prolonged antifungal therapy is problematic may also benefit from this technique, such as transplant patients, who often are on immunosuppressive medications that interact with oral triazole antifungals. For multiple lesions where resection may be difficult, antifungal therapy alone has also been successful, even in immunocompromised patients (251, 514). A variety of alternative therapies have been successfully employed as well, including cryotherapy, thermotherapy (local heat application), and supersaturated potassium iodide (SSKI) (286, 313, 751). These are particularly relevant in developing countries where systemic antifungal therapy is difficult to obtain or too expensive for patients. Recurrences may occur several months to over a year after therapy is complete, so careful clinical follow-up is important (38, 142).

(ii) Keratitis. Fungal keratitis is an important ophthalmologic problem, particularly in tropical areas of the world (298). In one large series, 40% of all infectious keratitis was caused by fungi, almost exclusively molds (298). The most common fungi are *Fusarium* and *Aspergillus*, followed by dematiaceous fungi (up to 8 to 17% of cases) (298, 715). Many species can cause disease, with *Bipolaris* and *Curvularia* most common, though *Lasiodiplodia theobromae* may cause more severe disease (55, 75, 213, 298, 743, 744). Approximately half the cases are associated with trauma; prior eye surgery, diabetes, and contact lens use have also been noted as important risk factors (298,

743). Diagnosis rests on potassium hydroxide (KOH) smear and culture, with many dematiaceous fungi associated with pigmented plaques (270).

Many cases of keratitis due to dematiaceous fungi have come from India (77, 136, 210, 269, 582). In a large experience of keratitis due to dematiaceous fungi, 88 cases were examined (269). The most common dematiaceous genus causing keratitis was *Curvularia*, followed by *Bipolaris*, *Exserohilum*, and *Lasiodiplodia.* Almost half the cases were associated with trauma. Most patients received topical agents only (5% natamycin with or without an azole), though more severe cases also received oral ketoconazole. Overall response was 72% in those available for follow-up. Surgery was needed in 13 patients, with an additional 6 requiring enucleation due to poor response. Itraconazole topically has also been used with success (582).

In a study from the United States of 43 cases of *Curvularia* keratitis, almost all were associated with trauma (800). Plants were the most common source, though several cases of metal injury were seen as well. Topical natamycin was used almost exclusively, with only a few severe cases requiring adjunctive therapy, usually with an azole. Of the oral agents, itraconazole had the best *in vitro* activity, though the majority of isolates were resistant to flucytosine. Surgery, including penetrating keratoplasty, was required in 19% of patients. At the end of therapy, only 78% had a visual acuity of 20/40 or better. Other case series from the United States have noted a rise in contact lens use as a risk factor in recent years (374, 388). In the southern United States, cases are more frequently seen during warm, humid months (799).

Topical polyenes, such as amphotericin B and natamycin, are commonly used, but oral and topical itraconazole have been found to be useful as well (298, 744). Use of voriconazole has become more common, with topical preparations well described (211), but published cases involving dematiaceous fungi are infrequent (564). A series of *Alternaria* keratitis cases that were refractory to natamycin responded to topical azoles (758). A recent analysis of clinical trials involving fungal keratitis suggested that none of the available agents was highly effective (247). Many patients are left with residual visual deficits at the end of therapy. Clearly, further advances in therapy are needed for this debilitating disease.

(iii) Bone and joint infections. There are relatively few case reports of isolated osteoarticular infections due to dematiaceous fungi, perhaps reflecting the significant trauma often required for implantation into these deeper tissues, though some cases did not have noticeable trauma. *S. prolificans* is the most common cause, with all except two cases occurring in young children (166, 299, 325, 406, 453, 474, 716, 718). In addition to surgery, various antifungal therapies have been employed, with three cases using the combination of voriconazole and terbinafine with success (166, 299, 406). Unusual therapies have also been tried, including irrigation with polyhexamethylbiguanide and oral therapy with miltefosine (406, 716). Whether these actually improved the likelihood of a clinical response is unknown.

Alternaria alternata has been reported to cause palatal ulcers with associated osteomyelitis in patients with chronic sinusitis (198, 265, 297). Although immune tolerance has been suggested in these cases, no convincing evidence is available. Recurrences were common despite prolonged antifungal therapy.

Other organisms associated with single case reports include *P. obovatum*, *E. oligosperma*, *C. arxii*, *M. mycetomatis*, *P. richardsiae*, *F. pedrosoi*, and *P. parasiticum* (94, 390, 398, 472, 512, 689, 812). Itraconazole was the most common single agent used with success (398, 512, 689). Antifungal therapy for all these cases is usually prolonged, i.e., >6 months and up to 2 years.

(iv) Peritonitis. Peritonitis occurs essentially only in patients receiving peritoneal dialysis (6, 8, 69, 97, 106, 115, 117, 144, 197, 261, 302, 305, 367, 405, 416, 461, 466, 563, 598, 605, 618, 619, 656, 690, 762, 765, 783, 784). The presentation is usually subacute, with many patients being without significant symptoms. The genera isolated included *Curvularia* (eight cases); *Exophiala* (five); *Alternaria* (four); *Bipolaris* (four); *Aureobasidium* (three); and *Lecythophora*, *Hormonema*, and *Phialemonium* (one each). Eosinophils in peritoneal fluid were not uncommon and were associated with a variety of species. Catheter removal was considered critical, though one case with amphotericin B lock therapy in the catheter with systemic fluconazole resulted in cure with catheter retention (106). Outcomes were generally good, with only three deaths, two associated with persistent infection and the other with a retained catheter (405, 618, 690).

(v) Miscellaneous infections. Various anecdotal cases of unusual infectious syndromes have been reported. A case of epididymitis due to *E. jeanselmei* was reported in a 54-year-old male who had received multiple needle aspirations for a symptomatic hydrocele (248). Surgical excision alone resulted in cure. In another case, a 5-year-old asymptomatic girl was noted to have "black grains" in her urine 3 weeks after treatment for a urinary tract infection. Hyphae and conidia identified as a *Curvularia* sp. were observed in a wet mount but did not grow in culture (635). She received no therapy, and the condition spontaneously resolved. *E. dermatitidis* was isolated from a case of otitis externa in a 19-year-old immunocompetent female, along with *Pseudomonas* (404). She responded to antibiotics and topical antimycotics. *E. jeanselmei* was isolated from esophageal brushings of a patient with Barrett's esophagus, and biopsy revealed hyphal elements as well (669). The patient was treated with ketoconazole, though little clinical improvement was noted after 5 months. A case of acute, invasive sinusitis due to *E. rostratum* was reported in an 18-year-old female with aplastic anemia and persistent neutropenia (442). She underwent surgery and prolonged antifungal therapy with liposomal amphotericin B and voriconazole-itraconazole, although she died of her underlying disease with persistent evidence of infection at autopsy. In contrast to the case for allergic sinusitis, such presentations are rare in immunocompromised patients.

Pulmonary infection. Pulmonary infection is usually seen in immunocompromised patients or those with underlying lung disease, and it may be due to a wide variety of species, including *S. prolificans*, *C. bantiana*, *Chaetomium* spp., *Ochroconis gallopava*, *Exophiala* spp., *Alternaria*, *Cladophialophora boppii*, *F. pedrosoi*, *L. theobromae*, *Aureobasidium pullulans*, *Curvularia* spp., *Sarcinosporin inkin*, and *P. verrucosa* (1, 17, 63, 92, 101, 107, 199, 219, 267, 303, 348, 351, 352, 402, 427, 429, 443, 464, 477, 520, 528, 554, 583, 701, 734, 736, 805, 814). Clinical manifestations include pneumonia, asymptomatic solitary pul-

monary nodules, and endobronchial lesions which may cause hemoptysis. Therapy has consisted of systemic antifungal agents, usually amphotericin B or itraconazole initially, followed by itraconazole for a more prolonged period. Mortality rates are high in immunocompromised patients (>40%). Experience with voriconazole is accumulating and appears promising (17, 199, 219, 348). Posaconazole was effective in a case of *Alternaria* pneumonia in a patient with leukemia that was refractory to amphotericin B and voriconazole (528). Occasional cases of solitary pulmonary nodules in immunocompetent patients may be cured with surgical resection alone (92, 303).

Central nervous system infection. Central nervous system infection is a rare but frequently fatal manifestation of phaeohyphomycosis, often in immunocompetent individuals. In a review of 101 cases of central nervous system infection due to dematiaceous fungi (628), the most common presentation was found to be brain abscess (11, 24, 21, 34, 42, 53, 60, 79, 82, 100, 110, 114, 137, 138, 156, 168, 169, 193, 212, 222, 254, 255, 290, 314, 319, 329, 337, 343, 371, 394, 396, 408, 410, 412, 415, 422, 458, 500, 505, 513, 523, 527, 529–531, 562, 570, 578, 602, 629, 649, 661, 662, 665, 667, 678, 681, 692, 702, 711, 726, 738, 746, 763, 786, 787, 790, 791, 803, 816). What is truly unique about this disease is that over half the cases were in patients with no risk factor or immunodeficiency. In addition, no specific exposures were associated with onset of infection, though many cases seem to occur in rural areas. Typical symptoms included headache, neurologic deficits, and seizures, though rarely all three. The most common species was *C. bantiana*, accounting for half the cases. Other species included *Rhinocladiella mackenziei*, *Ochroconis gallopava*, *Bipolaris spicifera*, *Exophiala dermatitidis*, and *Chaetomium strumarium*. Mortality was >70%. Since that review in 2004, over 50 cases have been reported, with *C. bantiana* remaining the most frequently seen isolate (131, 4, 17, 16, 22, 31, 40, 70, 78, 93, 121, 139, 170, 189, 243, 244, 268, 272, 276, 328, 332, 341, 363, 380, 399, 420, 433, 448, 450, 467, 476, 545, 575, 636, 657, 696, 700, 721, 731, 733, 754, 759). A new species, *Fonsecaea monophora*, has been reported since that time and appears to have a predilection for causing CNS disease, in contrast to its related species, *F. pedrosoi* (420, 721, 733). Encephalitis with diffuse brain involvement is a rare presentation, with essentially 100% mortality (1, 80).

The pathogenesis may be hematogenous spread from an initial, presumably subclinical pulmonary focus, though this remains speculation. Animal models of *C. bantiana* reliably replicate CNS infection with intravenous or intranasal inoculation, though these are generally immunosuppressed mice (15, 200). However, it remains unclear why these fungi preferentially cause CNS disease in immunocompetent individuals.

Meningitis has also been described, usually in immunocompromised patients (3, 17, 59, 74, 260, 366, 423, 444, 470, 729). However, cases with iatrogenic complications related to contaminated steroid preparations injected epidurally have been reported (131). These can be difficult to treat, and mortality is high (>60%).

Many therapeutic strategies have been used in the treatment of brain abscess, though it is unclear if any result in significantly improved outcomes. The retrospective analysis of 101 reported cases mentioned above suggested that the combination of amphotericin B, flucytosine, and itraconazole may be associated with improved survival, though it was not frequently used. Subsequent reports have documented various regimens, some using voriconazole or posaconazole with clinical success, though failures have also been reported. Voriconazole was unsuccessful in treating three out of four cases of *C. bantiana* brain abscess, though two of these patients were immunocompromised, and one received concomitant phenytoin, which may have reduced levels of voriconazole (243, 450, 467, 754). Despite these reports, voriconazole may have a role in therapy of phaeohyphomycotic brain abscess, as it has been successfully used in cases of *Aspergillus* and *S. apiospermum* brain abscess (188, 540). Posaconazole has been reported to be effective in a case of *R. mackenziei* brain abscess, which represents the first reported survival of infection due to this species (16). For cases due to *C. bantiana*, addition of flucytosine to azole therapy may be useful given its *in vitro* activity against this species specifically and *in vivo* and clinical data (481, 628). Based on the experience described above and animal studies, a combination of agents is likely to be more effective than monotherapy, though the optimal combination remains unclear and should be based on the individual case.

What does appear to be consistent is that complete excision of brain abscess whenever feasible is associated with better outcomes than aspiration or partial excision. In a series of 10 cases due to *C. bantiana* at one institution, all surviving patients were able to have complete resection of the brain lesion (268). In another case, repeated surgical excisions alone resulted in cure (189). However, outcomes remain poor, with an overall mortality of >70%.

Disseminated infection. Disseminated infection is the most uncommon manifestation of infection caused by melanized fungi. In a review of 72 cases (627), most patients were immunocompromised, though occasional patients without known immunodeficiency or risk factors developed disseminated disease as well (3, 24, 73, 76, 95, 105, 119, 171, 208, 238, 242, 246, 288, 291, 308, 321, 345, 386, 389, 397, 400, 402, 403, 409, 423, 424, 435, 471, 485, 516, 538, 543, 550, 557, 578, 593, 595, 596, 612, 621, 627, 640, 647, 672, 688, 712, 713, 740, 755, 769, 772, 794, 804, 806, 822). In contrast to most invasive mold infections, blood cultures were positive in over half the cases. The most common isolate was *S. prolificans*, accounting for over a third of cases. Since that review, *S. prolificans* remains the most frequent cause of disseminated disease, almost exclusively in immunocompromised patients (33, 62, 96, 151, 304, 358, 364, 368, 434, 697, 709, 747, 750, 796). *E. dermatitidis*, in contrast, is commonly seen in immunocompetent patients, particularly from Asia (13, 349, 565). A variety of other molds were reported in disseminated disease, including *E. oligosperma*, *Chaetomium perlucidum*, *O. gallopava*, *Lecythophora mutabilis*, *P. parasiticum*, *B. spicifera*, *Exserohilum* sp., *E. spinifera*, and *Curvularia lunata* (25, 64, 85, 207, 256, 335, 417, 451, 536, 741, 788). Interestingly, peripheral eosinophilia has been observed in 9% of cases, and these were generally due to *Bipolaris* and *Curvularia*. These same species are often associated with allergic disease.

The mortality rate was >70%, despite aggressive antifungal therapy. There were no antifungal regimens associated with improved survival for disseminated infection. *Scedosporium prolificans* is generally resistant to all available antifungal agents, and infection with *S. prolificans* was associated with nearly 100% mortality in the absence of recovery from neu-

tropenia, indicating the importance of the host response in this infection. However, recent case reports have suggested that the combination of itraconazole or voriconazole with terbinafine may be synergistic against this species and improve outcomes, though clinical experience is limited (358, 750, 796). Some case reports utilized colony-stimulating factors and/or leukocyte infusions to augment antifungal therapy (96, 368, 796).

Other combinations or therapies have not been shown to be consistently effective, though clinical experience is limited, and will likely be confined to anecdotal reports, given the rarity of this infection. Recent successful case reports have used itraconazole, voriconazole, and posaconazole for a variety of different species (207, 368, 417, 536, 565). Amphotericin B alone is not generally effective (25, 64, 368).

CONCLUSIONS

Melanized fungi remain uncommon causes of infection in humans but have become increasingly recognized in a wide variety of clinical syndromes. Many species across a broad range of genera are associated with disease, which leads to daunting challenges in diagnostic testing. However, relatively few are responsible for the majority of clinical cases. *Alternaria* is a frequent cause of subcutaneous lesions, *Bipolaris* and *Curvularia* are often associated with allergic disease, and *C. bantiana* and *S. prolificans* are the most common causes of brain abscess and disseminated disease, respectively. Taxonomy is constantly evolving as molecular methods shed new light on relationships between species. Melanin appears to be an important virulence factor for these fungi, though much additional work is needed to better understand the pathogenic mechanisms underlying these infections, particularly in immunocompetent patients. Life-threatening infections are rare but may be seen even in individuals with no apparent risk factors, especially in cases of brain abscess. As these are typically soil organisms and common laboratory contaminants, sometimes they are disregarded as nonpathogenic. However, the clinical setting in which they are isolated should always be considered when evaluating their potential as etiologic agents and before making decisions regarding therapy. Diagnosis depends on a high degree of clinical suspicion and careful mycological and pathological examination of clinical specimens. Molecular diagnostic techniques are progressing but are not standardized or reliable for the diverse species encountered.

Therapy for many infectious syndromes has evolved with the advent of several new antifungal agents in recent years. The oral triazoles voriconazole, posaconazole, and itraconazole demonstrate the most consistent *in vitro* activity against this group of fungi and are widely used, though voriconazole is usually the drug of choice in most clinical settings. High doses of amphotericin B lipid formulations may have a role in the treatment of refractory cases or for severe infections in unstable patients, though it is usually not effective as a single agent. Once the patient is stable, "consolidation" therapy with a broad-spectrum oral azole is often employed until a complete response is achieved. Terbinafine has broad activity against melanized fungi, and interest in its use beyond dermatophyte infections is increasing. It appears to provide synergistic activity with azole antifungals, and this may be a useful strategy against refractory subcutaneous infections such as chromoblastomycosis and mycetoma that often do not respond to conventional monotherapy. In addition, the use of terbinafine with voriconazole for disseminated *S. prolificans* infection has been successful with what is otherwise an almost universally fatal infection. It should be pointed out that in these disseminated cases, recovery of immune function, especially phagocytic cells, is critically important as well. Flucytosine has limited activity against dematiaceous fungi, though it may have a role in therapy of chromoblastomycosis and of brain abscess due to *C. bantiana*, in particular. Echinocandins do not appear to be useful as single agents but may be considered in combination therapy of difficult cases. Combination therapy is a potentially useful therapeutic strategy for refractory infections, particularly brain abscess and disseminated disease. However, it is not clear which antifungal drug combinations are most effective. Therapy is evolving for many of the clinical syndromes described, and randomized clinical trials to address this issue are impractical given the sporadic nature of cases. Detailed case reporting of both successful and unsuccessful clinical experiences will be important in attempting to define optimal therapy for infections caused by dematiaceous fungi.

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