SUPPLEMENT ARTICLE

Taxonomy of Fungi Causing Mucormycosis and Entomophthoramycosis (Zygomycosis) and Nomenclature of the Disease: Molecular Mycologic Perspectives

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Molecular phylogenetic analysis confirmed the phylum Zygomycota to be polyphyletic, and the taxa conventionally classified in Zygomycota are now distributed among the new phylum Glomeromycota and 4 subphyla *incertae sedis* (uncertain placement). Because the nomenclature of the disease zygomycosis was based on the phylum Zygomycota (Zygomycetes) in which the etiologic agents had been classified, the new classification profoundly affects the name of the disease. Zygomycosis was originally described as a convenient and inclusive name for 2 clinicopathologically different diseases, mucormycosis caused by members of Mucorales and entomophthoramycosis caused by species in the order Entomophthorales of Zygomycota. Without revision of original definition, the name "zygomycosis," however, has more often been used as a synonym only for mucormycosis. This article reviews the progress and changes in taxonomy and nomenclature of Zygomycota and the disease zygomycosis. The article also reiterates the reasons why the classic names "mucormycosis" and "entomophthoramycosis" are more appropriate than "zygomycosis."

Before Whittaker created the kingdom Fungi in 1969 [1], the agents causing mucormycosis, entomophthoramycosis, and other fungi that produce coenocytic (aseptate) vegetative hyphae and sexual spores called "zygospores" or "oospores" were classified in the Phycomycetes of the subdivision Thallophyta in the plant kingdom [2]. The taxonomy of the fungi during that era was based on the morphologic similarities of sexual reproductive structures, and 3 classes were recognized: Phycomycetes, Ascomycetes, and Basidiomycetes. Those species that reproduced only by asexual spores were grouped in the form-class Deuteromycetes, or Fungi Imperfecti [3]. As the knowledge on life cycle, ecology, nutritional modes, ultrastructure, and other aspects of the organisms increased, taxonomists attempted to place organisms in the taxa that more closely reflected their hypothetical evolutionary relationships. As a result, fungi acquired their own kingdom (kingdom Fungi) and underwent significant changes in classification. Because Phycomycetes comprised a miscellaneous assemblage of evolutionarily unrelated organisms, the class Phycomycetes was abolished [1], and the members of Phycomycetes were accommodated in a series of classes: Zygomycetes, Chytridiomycetes, Hypochytridiomycetes, Trichomycetes, and Oomycetes [3]. Further classification of the fungal kingdom on the basis of shared, derived characters delimited the kingdom to include only Chytridiomycota, Zygomycota, Ascomycota, and Basidiomycota, and this classification scheme has been universally accepted until a decade ago (Figure 1*A*). The phylum Zygomycota contained Mucorales, Entomophthorales, and 8 other orders [4].

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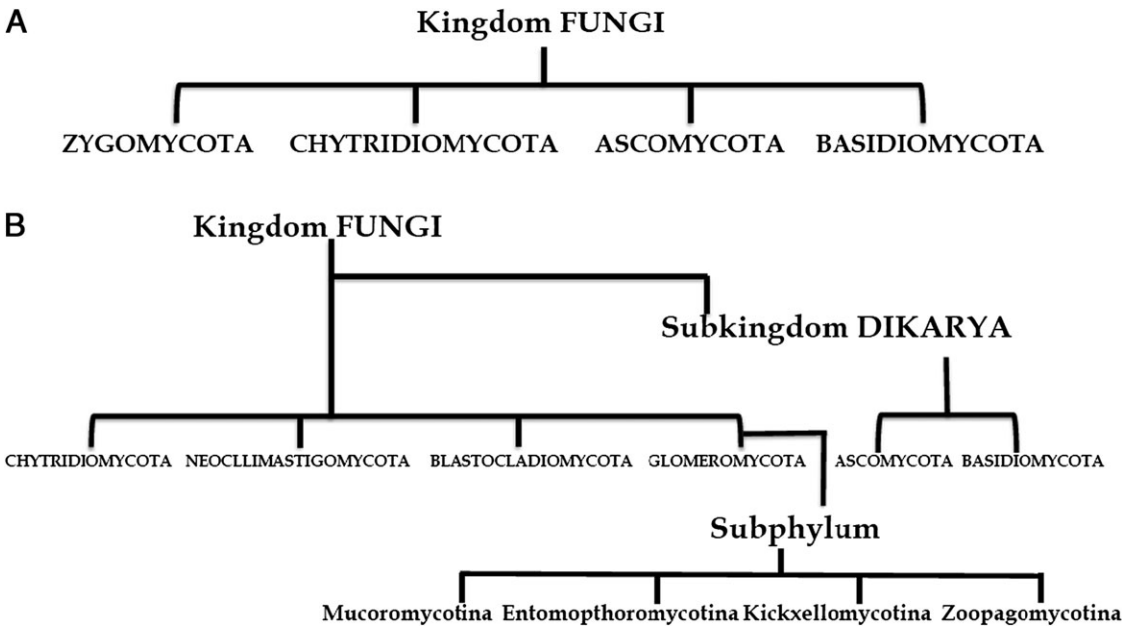

Figure 1. Old (*A*) and a proposed new (*B*) classification schemes of the kingdom Fungi.

TAXONOMY OF ZYGOMYCOTA

Because the goal of modern taxonomy is to understand the evolutionary relationships of the organisms reflected in their genomes, taxonomists in 1990s started applying molecular techniques to resolve fungal lineages among eukaryotic organisms. As a result, the molecular phylogenetic classification of each fungal phylum has been proliferating during the past 15 years. For the molecular phylogenetic studies to resolve the lineages of Zygomycota, sequence analysis of ≥9 gene regions have been used: 3 nuclear ribosomal RNA subunits (large subunit, small subunit, and 5.8S) [5], 2 RNA polymerase subunits (*RPB1* and *RPB2*) [6], elongation factor (*EF1α*) [5], α- and β-tubulins [7], and mitochondrial small subunit ribosomal DNA [8]. These studies commonly indicated that Zygomycota contained at least several different monophyletic taxa and that the group as a whole was polyphyletic or paraphyletic. One exception was found in the analysis of *RPB1* and *RPB2,* which indicated Zygomycota to be monophyletic [6]. However, analysis using combinations of multiple genes, including the RNA polymerase subunits, indicated that the phylum is clearly polyphyletic [5].

The first major taxonomic change in the phylum Zygomycota that was based on the molecular phylogeny was made in 2001. Schüssler et al constructed a phylogenetic tree on the basis of an analysis of small subunit ribosomal RNA [9] and removed arbuscular mycorrhizal (AM) fungi from Zygomycota and placed them into the new monophyletic phylum, the Glomeromycota. All AM fungi are not only obligate symbionts of vascular plants, but they did not form a clade with any other group of Zygomycota (Figure 2). Zygomycota underwent further taxonomic changes in 2007. Hibbett, along with 66 international fungal taxonomists, published a comprehensive phylogenetic classification of the kingdom Fungi that was based on well-supported monophyletic groups consistent across multiple phylogenetic studies. They used the available data generated by recent molecular phylogenetic studies, as well as the data contributed by diverse members of the fungal taxonomy community [10]. They proposed to eliminate Zygomycota because the phylum was found to be polyphyletic and the taxa conventionally placed in Zygomycota were distributed among the phylum Glomeromycota and 4 subphyla of uncertain placement (*incertae sedis*) (Figure 1*B*). The Mucorales and Entomophthorales, which contain zoopathogenic fungi, and 2 other orders including Kickxellales and Zoopagales were raised to the rank of subphyla: Mucoromycotina, Entomophthoromycotina, Kickxellomycotina, and Zoopagomycotina. Furthermore, they determined that the phylum Zygomycota had not been validly described because it was published without a Latin diagnosis [11]. Hibbett et al indicated that the relationships among these groups are not yet clearly resolved and that most studies used incomplete taxon sampling of the major Zygomycete lineages [10]. They also suggested that Zygomycota could be resurrected and validated to include Mucoromycotina and perhaps other clades when future studies result in better resolution of the lineages in this basal group of fungi. Subsequently, when a 6-gene phylogeny was used to reconstruct the early evolution of fungi, the results were consistent with those of previous studies: Zygomycota is polyphyletic, and the

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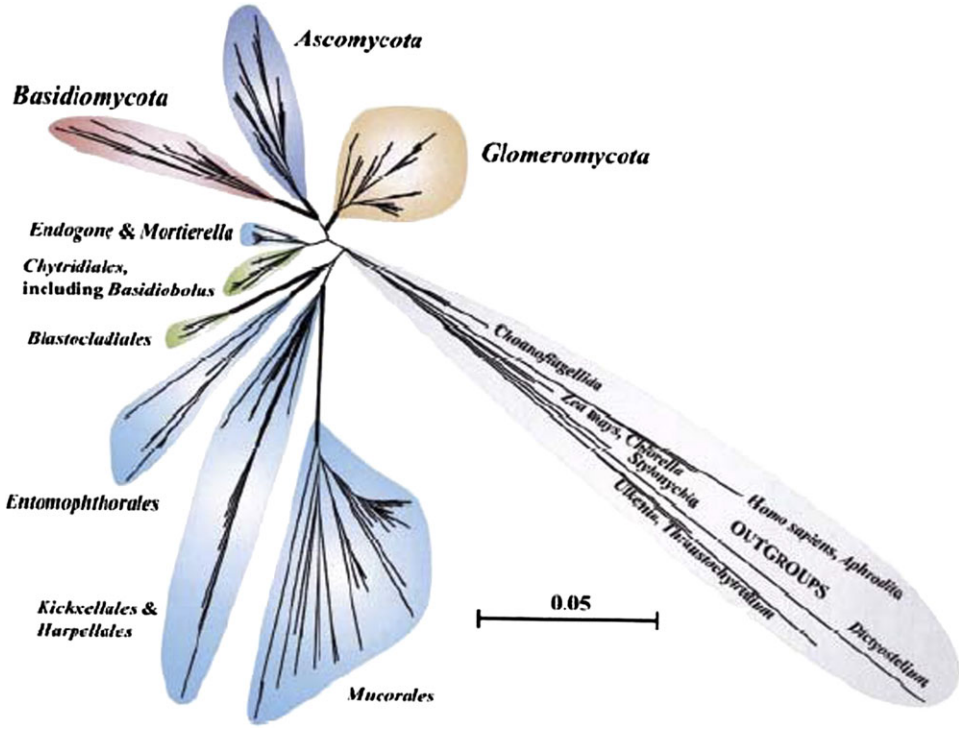

Figure 2. Phylogeny of fungi determined on the basis of small subunit ribosomal RNA sequences. Thick lines delineate clades supported by bootstrap values >90%. "Zygomycota" do not form monophyletic clades [9]. The metric bar indicates number of substitutions per site.

Mucoromycotina and Entomopthoromycotina were clearly separated into 2 different clades (Figure 3).

One of the challenges that remains for the resolution of evolutionary relationship among fungi is the high variable evolutionary rates among fungi, combined with the lack of a known close phylogenetic outgroup. Recently, however, Nucleariids organisms (amoeboids of enigmatic status) were proposed to be the closest known relatives of fungi [12]. Analysis of the 118 nuclear proteins and 13 mitochondrial proteins made by Liu et al indicated that the Nucleariids and Fungi are indeed closely related sister groups [13]. As they analyzed phylogenetic relationship of fungi by using Nucleariids as an outgroup, the elevation of Glomeromycota as a separate phylum, a sister group of Dikarya, or the introduction of certain other higher-level taxa seemed questionable from a molecular phylogenetic standpoint [13]. Analysis of 14 mitochondrially encoded proteins of *Glomus intraradices*, a widespread species of AM fungi, also indicated that the Glemeromycota are not the sister group of the Dikarya [14]. To resolve the phylogenetic position of newly elevated taxa of Zygomycota relative to other phyla, a broad sampling of additional genome sequences from these taxa was deemed necessary [13]. These results suggest that the newly proposed taxonomic classification of Zygomycota into "Glomeromycota plus 4 subphyla" may have to undergo further revision. However, the phylogenetic diversity between the etiologic agents of mucormycosis and entomophthoramycosis has been confirmed by many studies [5, 7–10], and further sequence analysis will not alter the fact that they are unrelated.

NOMENCLATURE OF ZYGOMYCOSIS (MUCORMYCOSIS AND ENTOMOPHTHORAMYCOSIS)

The first well-documented case of disease caused by members of Mucorales was published in 1885 by the German pathologist Paltauf. It was a systemic infection with gastric and rhinocerebral involvement, which Paltauf described as "Mycosis Mucorina" [15] (Table 1). Though not conclusive, his drawings of the etiologic agent appeared more like a species of *Rhizopus* than a species of *Mucor,* owing to the presence of unbranched sporangiophores and rhizoid-like structures. The disease name "mucormycosis" was subsequently used by the American pathologist R. D. Baker to denote a mycosis caused by certain members of Mucorales [16, 17].

Before establishment of the kingdom Fungi, the species producing coenocytic hyphae were classified in the class Phycomycetes, which included not only those that produce zygospores

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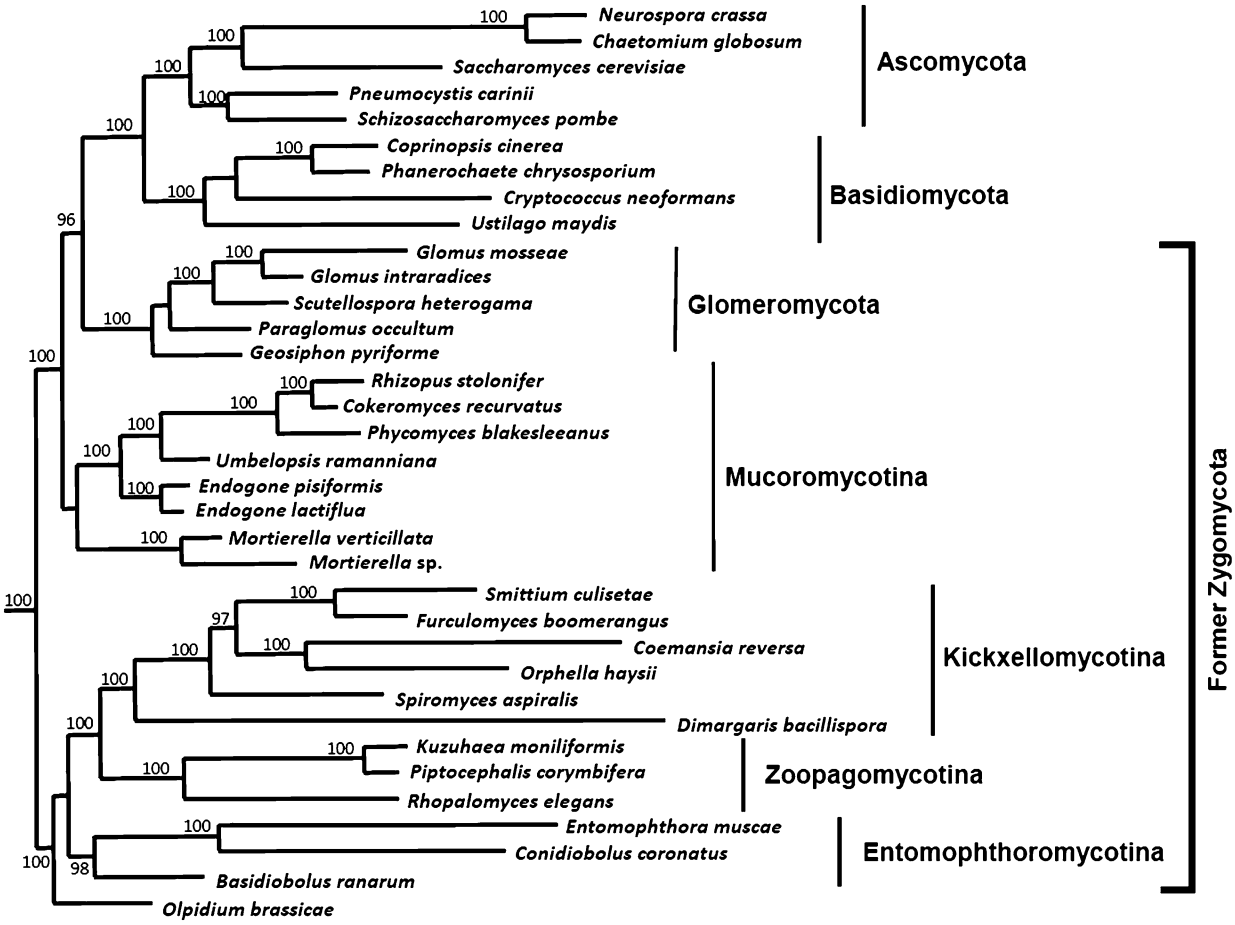

Figure 3. Phylogenetic tree provided by T. Y. James at the University of Michigan, Ann Arbor, which was based on unpublished results from the AFTOL (Assembling the Fungal Tree of Life) project [10]. Results are similar to those reported by James et al [5], but additional basal taxa are included.

but also water molds that produce oospores as sexual spores [18]. When more members of Phycomycetes were reported as pathogenic to humans, Emmons proposed the name "phycomycoses" to provide a convenient and an inclusive term for mycoses caused by any one of the several species of Phycomycetes [2, 19, 20]. The term was useful for mycoses in which the etiologic agent was not cultured and only identified as an unknown species of Phycomycetes in histopathologic sections. "Phycomycosis" became widely accepted as a convenient disease name, irrespective of its diversity in clinical course and etiology [21]. Clark, in 1968, however, supported use of the term "mucormycosis" for the diseases caused by species of Mucorales, to distinguish them from "subcutaneous phycomycosis" caused by fungi belonging to Entomophthorales. She also proposed the name "Entomophthoromycosis" for subcutaneous phycomycosis [22].

As the kingdom Fungi was established and Phycomycetes were reclassified into Zygomycetes and other series of new classes, the disease name "phycomycosis" became obsolete. To concur with the taxonomic changes, Ajello et al, in 1976, proposed to replace the name with "zygomycosis" [23]. The disease was defined to include any mycosis caused by the species of 2 orders: Mucorales, with the 4 genera *Rhizopus, Mucor, Absidia,* and *Saksenaea,* and Entomophthorales, with the 2 genera *Basidiobolus* and *Conidiobolus* [23]. Species of 3 more genera, *Rhizomucor, Apophysomyces,* and *Cunninghamella,* have since been documented as pathogenic Mucorales organisms that produce invasive disease in humans. [24, 25]. *Absidia corymbifera*, the major pathogenic species of the genus *Absidia*, was recently transferred to the genus *Mycocladus* as *Mycocladus corymbiferus* [26] and subsequently reclassified as *Lichtheimia corymbifera* [27]. Species of *Cokeromyces, Syncephalastrum, Actinomucor,* and *Mortierella* have been reported from human clinical specimens but without any evidence of tissue invasion [25, 28]. The Entomophthorales organisms that cause human infection to date are confined to 2 genera, *Conidiobolus* and *Basidiobolus* [24]. For many years, however, the name "zygomycosis" has been increasingly used as a synonym of only mucormycosis while disregarding the original definition [29–32].

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Table 1. Historical Summary of the Nomenclature of Mucormycosis and Entomophthoramycosis

Disease Name	Author(s)	Date of Publication	Reference
Mycosis mucorina	Paltauf	1885	[15]
Mucormycosis	Baker	1957	[17]
Phycomycoses	Kian Joe et al	1959	[20]
Mucormycosis and entomophthoramycosis	Clark	1968	[22]
Zygomycosis	Ajello et al	1976	[23]
Mucormycosis and entomophthoramycosis	Kwon-Chung and Bennett	1992	[24]

DIFFERENCES BETWEEN INFECTIONS CAUSED BY MUCORALES AND ENTOMOPHTHORALES

The pathogenic species classified in the order Mucorales and those classified in Entomophthorales are profoundly different in ecologic, epidemiologic, morphologic, and clinicopathologic characteristics [33, 34]. While species of Mucorales are distributed worldwide, those of Entomophthorales are tropical and subtropical fungi. The morphology and manner of asexual and sexual sporulation between the 2 orders are distinct (Figure 4*A–G*). Contrary to pathogenic Mucorales organisms, which produce numerous deciduous asexual spores within the sporangium (sporangiospores) (Figure 4*E* and 4*F*), except for the species of *Cunninghamella,* which produce numerous spores on the surface of sporangium, pathogenic Entomophthorales organisms produce a single conidium (with no sporangium) on each conidiophore and are forcibly ejected upon maturation and then may replicate to produce secondary conidia (Figure 4*A–C*). The manner of zygospore formation is also different. Zygospores of Mucorales are produced between 2 opposed suspensors originating from different hyphae, whereas zygospores of Entomophthorales are produced by the union of 2 contiguous cells of a hypha (Figure 4*D* and 4*G*) [33].

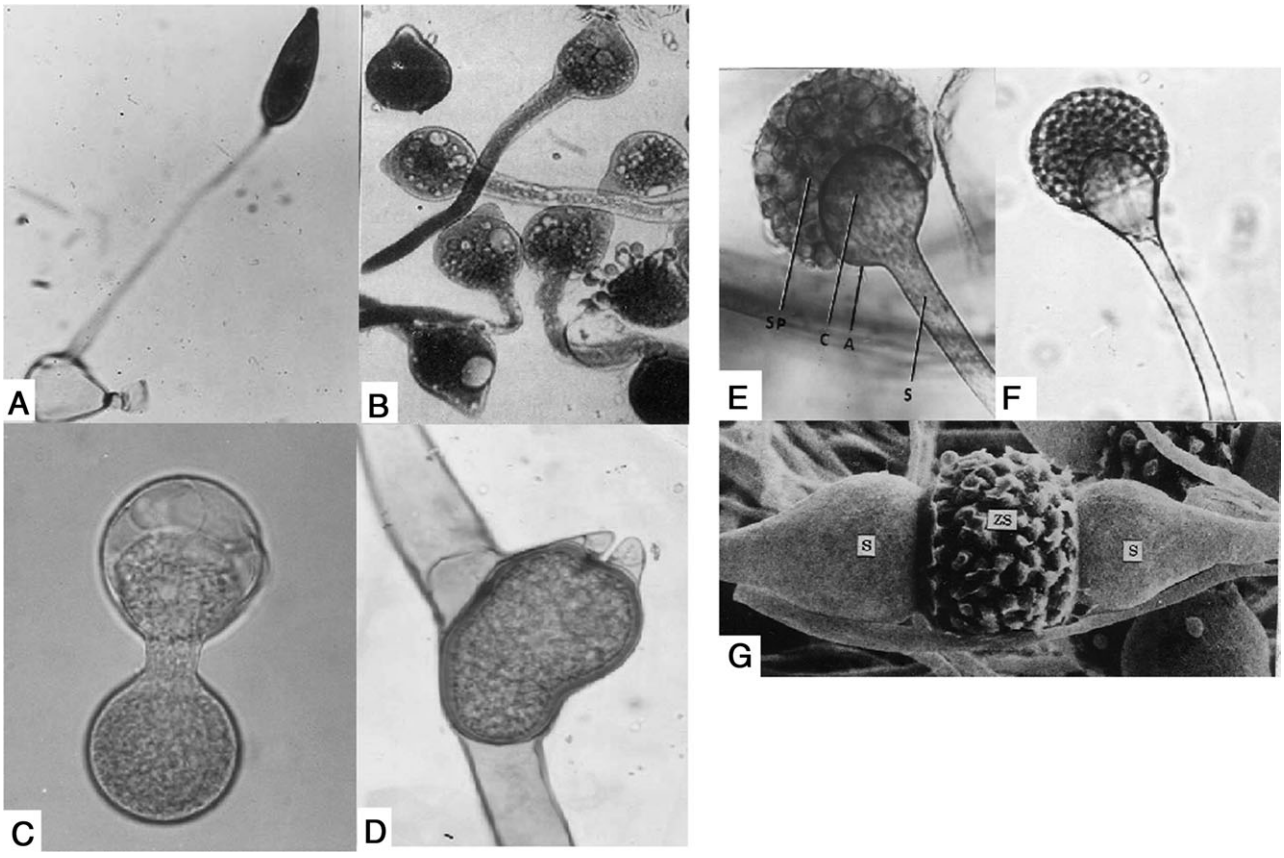

Figure 4. Morphology of conidia and zygospores (scale bar, 20 μm). *A,* Reproduction of a conidium in *Basidiobolus ranarum*. A conidium discharged onto a Petri dish cover germinated and produced a conidiophore bearing a single conidium. *B,* Primary conidia of *Conidiobolus incongruus* germinated to produce long hyphae bearing subglobose conidia [38]. *C,* Secondary conidium formation by replication in *Conidiobolus coronatus*. *D,* Zygospore of *Basidiobolus ranarum,* with a characteristic beak, is produced by the fusion of 2 adjacent hyphal cells. *E,* Sporangial structure of *Rhizopus* species showing the sporangiophore (*S*), apophysis (*A*), columella (*C*), and sporangiospores (*SP*). *F,* Sporangium of *Lichtheimia* (*Absidia*) *corymbifera*. *G,* Electron microscopy of Zygospore (*ZS*) of *Rhizopus* species produced between 2 suspensors (*S*) originating from hyphae of 2 sexually compatible strains (courtesy of Dr S. L. Flegler). Images in *A* and *C–F* are from Kwon-Chung and Bennett [33].

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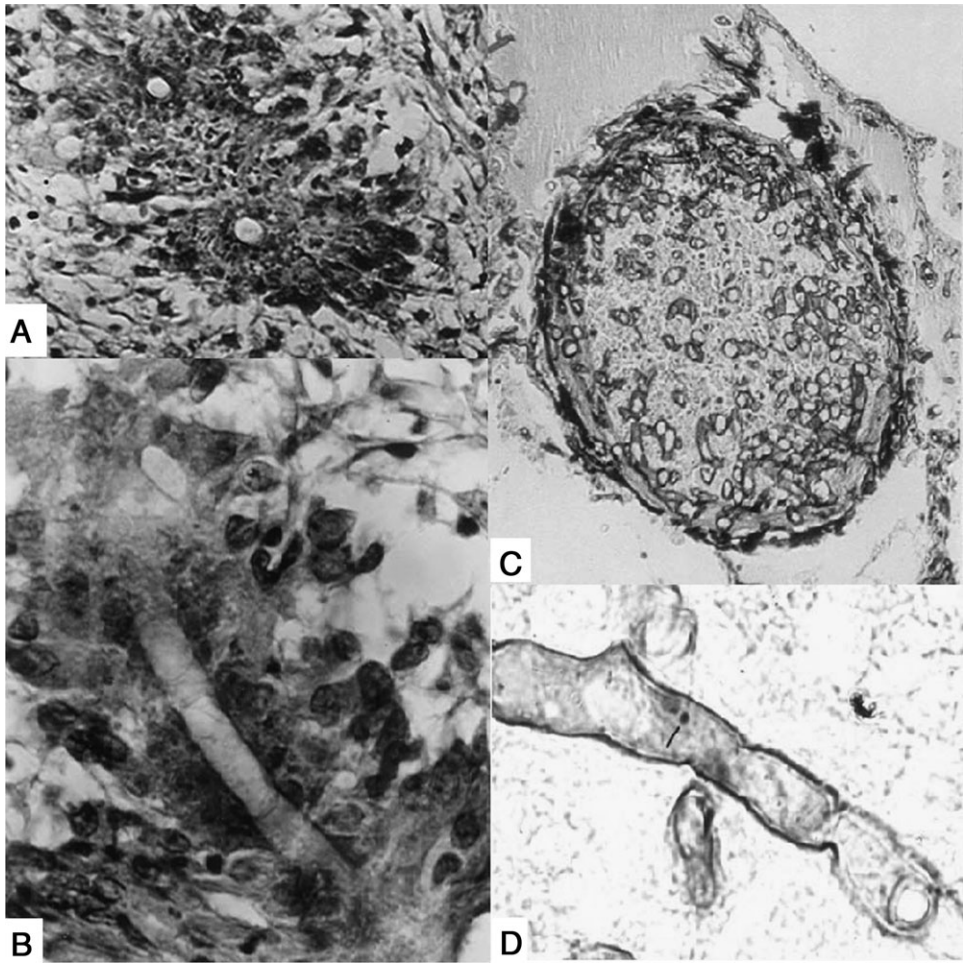

Figure 5. *A, Basidiobolus ranarum* in hematoxylin-eosin–stained tissue section showing a cross-section of hyphae with sleeves of eosinophilic material. *B,* Hyphae in longitudinal section in the same tissue shown in *A. C,* Angioinvasion in mucormycosis. A pulmonary blood vessel occluded by hyphae of *Cunninghamella bertholletiae* stained with hematoxylin-eosin. *D,* Hyphae of *Rhizopus* species in tissue stained by hematoxylin-eosin. Note the lack of eosinophilic material around the hyphae. Images are reproduced from Kwon-Chung and Bennett [33] (scale bar, 10 μm).

The pathogenic species of Mucorales cause an acute angioinvasive infection primarily in immunocompromised individuals, whereas those of Entomophthorales produce chronic and subcutaneous infection mostly in immunocompetent individuals [33]. Although the size and morphology of hyphae of the 2 orders grown in host tissues are indistinguishable, thick eosinophilic sleeves surrounding the fungal hyphae of Entomophthorales organisms allow them to be differentiated from hyphae of Mucorales organisms (Figure 5). Just as in any other biologic systems, there have been a dozen cases of entomophthoramycosis in which the clinicopathology deviated from typical disease and overlapped with that of mucormycosis. The invasive diseases caused by *Basidiobolus ranarum* [35, 36], *Conidiobolus incongruous* [37–39], or *Conidiobolus coronatus* [40] could have been mistaken as mucormycosis if cultures were not available. However, in all of these cases in which the histopathologic sections were stained with hematoxylin-eosin, hyphal elements were seen with surrounding eosinophilic sleeves, a characteristic of entomophthoramycosis but not of mucormycosis (Figure 5*A–D*) [35, 36, 38, 39]. The inclusive name "zygomycosis" was only useful for those cases in which cultures were unavailable and the clinicopathology of the 2 diseases overlapped. However, the availability of polymerase chain reaction primers that can be used to amplify fungal ribosomal DNA sequences from host tissue is rapidly increasing in the databases, and identification of etiologic agent is possible without cultures.

NOMENCLATURAL STABILITY OFFERED BY "MUCORMYCOSIS" AND "ENTOMOPHTHORAMYCOSIS"

The name "zygomycosis" has been increasingly used instead of mucormycosis for 2 reasons: (1) mucormycosis sounds as

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though the disease is caused by *Mucor* spp., not the most common causes of the disease, and (2) some infections caused by the species of Entomophthorales, although rare, are clinically not distinguishable from classic mucormycosis (available at: http://www.doctorfungus.org/thefungi/zygomycetes.php). Contrary to such nomenclatural debate, "mucormycosis" was defined to include disease caused by any member of Mucorales and not by organisms from the genus *Mucor* [16]. Some investigators have privately suggested that mucormycosis be termed "mucoralomycosis," to denote that the name represents the order Mucorales and not the genus *Mucor*. Though it sounds reasonable, the order has already been elevated to the subphylum Mucoromycotina [10], and there is a distinct possibility that the taxa may be elevated to the phylum Mucoromycota as the sampling of the taxa increases (T. James, personal communication). In such a case, should the suggested name "mucoralomycosis" be changed again to "mucoromycosis"? Regardless of the future fate of "Mucorales" or "Zygomycota" as classifications, the first 5 letters of the disease name "mucormycosis" will withstand the future taxonomic revisions. Although entomophthoramycosis can mimic mucormycosis in rare cases, the number of systemic entomophthoramycosis cases thus far recognized is only a minute fraction of all "zygomycosis" cases reported. The appropriate name of a disease should represent typical rather than exceptional cases and should offer nomenclatural stability that would be unaffected by the taxonomic changes. The names "mucormycosis" and "entomophthoramycosis" have been embedded in the medical literature for >50 years, and the time has come to replace "zygomycosis" with these 2 names.

Notes

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