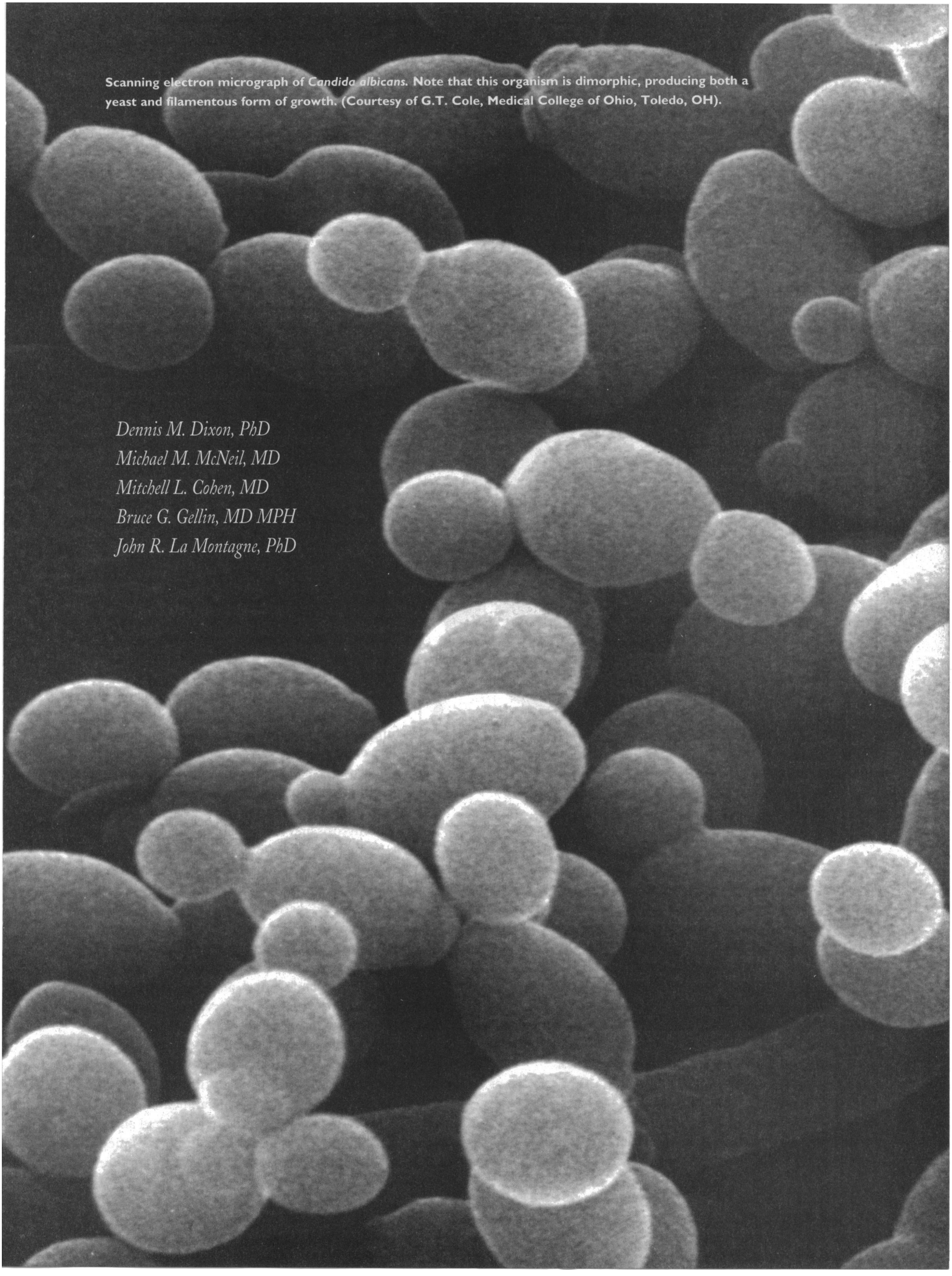
FUNGAL INFECTIONS

A Growing Threat

SYNOPSIS

THE EMERGENCE OF newly identified fungal pathogens and the reemergence of previously uncommon fungal diseases is primarily related to increases in the numbers of susceptible persons: people with HIV infection, bone marrow and organ transplant recipients, cancer patients being treated with chemotherapy, critically ill persons, and very low birth weight (≤ 1500 g) infants. These immunocompromised populations are at risk for infection not only with opportunistic pathogens (for example, *Pneumocystis, Candida, Cryptococcus, Trichosporon, Malassezia, Aspergillus, Penicillium marneffei,* and numerous other moulds or yeasts) but also with fungal pathogens that usually infect otherwise healthy persons not previously exposed to endemic fungi (for example, *Coccidioides immitis, Histoplasma capsulatum,* and *Blastomyces dermatitidis*) and *Sporothrix schenckii.* Morbidity, mortality, and health care costs associated with fungal infections are high. Addressing the emergence of fungal diseases will require increased surveillance coupled with the availability of rapid, noninvasive diagnostic tests; monitoring the development of resistance to antifungal agents; and research focused on the understanding, prevention, and control of fungal infections.

The emergence of newly identified fungal pathogens and the reemergence of diseases that had previously been uncommon is a serious and growing public health problem.[1] In 1992, an Institute of Medicine (IOM) report defined emerging infectious diseases as diseases of infectious origin whose incidence in humans has increased within the past two decades or whose incidence threatens to increase in the near future.[2] The IOM report listed six broad categories in which recent developments have fostered the emergence of infections constituting a growing public health threat. These include: human demographics and behavior; technology and industry; economic development and land use; international travel and commerce; microbial adaptation and change; and the breakdown of public health measures (box 1).



Scanning electron micrograph of *Candida albicans*. Note that this organism is dimorphic, producing both a yeast and filamentous form of growth. (Courtesy of G.T. Cole, Medical College of Ohio, Toledo, OH).

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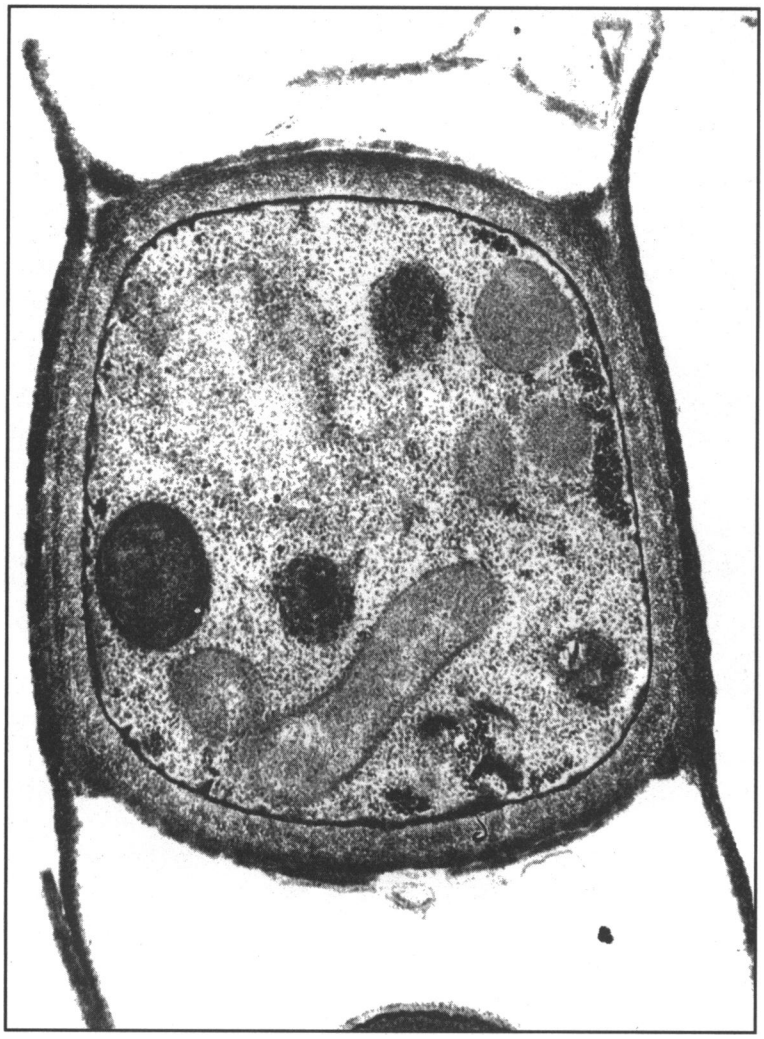
Medically important fungi can be characterized as either primary or opportunistic pathogens. Primary pathogens are those that are capable of routinely causing disease in otherwise healthy hosts, whereas opportunistic pathogens are those that generally require overt immunosuppression in order to cause disease. Primary fungal pathogens such as *Coccidioides immitis* and *Histoplasma capsulatum* may also infect immunocompromised hosts.[3,4] *Cryptococcus neoformans* is usually classified as an opportunistic pathogen because of its rarity in the apparently normal host (see table).



Transmission electron micrograph of the mould phase of *Coccidioides immitis*. A single, infective arthroconidium (spore) has ruptured free from adjacent cells of the parental filament, with remnants of the cell walls visible at either end. Its aerodynamic stability enhances its ability to infect by inhalation. (Courtesy of G.T. Cole, Medical College of Ohio, Toledo, OH).

Three fungi were identified in the IOM report as important emerging pathogens: *Candida albicans, Cryptococcus neoformans*, and *Pneumocystis carinii* (then listed as "a protozoan parasite with genetic similarities to a fungus"). Subsequently, the primary fungal pathogen *Coccidioides immitis* was identified in a feature article in the American Society for Microbiology's journal, *ASM News*, as an example of an emerging infectious disease agent following its resurgence in the central valley of California and the more recent outbreak in Ventura County, California, following the Northridge earthquake in January 1994.[5] *Coccidioides immitis* and numerous other fungi can now be added to the list of emerging pathogens (table).

Contributing Factors

The emergence of fungal diseases is stemming from: *(a)* changing demographics and technology—increases in the number of susceptible hosts, *(b)* microbial adaptation—the evolution of drug-resistant fungi, *(c)* land use and travel—fungal infections in immunocompetent persons not previously exposed, and *(d)* the breakdown of public health measures—the failing laboratory infrastructure.

Changing demographics and technology: increases in the number of susceptible hosts. The heightened recognition of fungi as important medical pathogens has resulted from both increased awareness and increased incidence. Key to both increases has been the expanding population that is at risk for fungal infections; immunosuppressed populations in hospitals and the community are at increased risk for the development of several emerging fungal infections (box 2).

Concomitant with the AIDS epidemic there has been a dramatic increase in the occurrence of fungal infections due to the increased prevalence of a variety of associated fungal diseases such as mucocutaneous candidiasis, *Pneumocystis carinii* pneumonia (PCP), and cryptococcal meningitis. In highly endemic areas, the prevalence of coccidioidomycosis and histoplasmosis in AIDS patients is as high as 20 to 30%. Casadevall and Currie have recently reported an estimated annual prevalence of 6.1 to 8.5% for cryptococcosis among HIV-infected patients in New York City.[6] In a statewide survey in New York, three of the top five AIDS-specific diseases were fungal diseases: PCP, esophageal candidiasis, and cryptococcosis.[7]

The impressive technological advances in the care of critically ill patients, including very low birth weight infants, has become the standard of care in modern, well-equipped clinical facilities and has led to increased survival in these patient populations. New developments have included the use of prophylactic antibiotics, indwelling catheters and prosthetic devices, hyperalimentation, intensive cancer chemotherapeutic regimens, and organ and bone marrow transplants. Yet these same lifesaving medical advances predispose these patients to a variety of fungal

Box 1. Factors influencing the emergence of infectious diseases

Human demographics and behavior
Technology and industry
Economic development and land use
International travel and commerce
Microbial adaptation and change
Breakdown of public health measures

infections (box 2). For example, the incidence of *Candida* infection in neonates and outbreaks in neonatal intensive care units are increasing, threatening the lives of these vulnerable, very low birth weight infants.[8,9]

Survivors of organ transplants represent a growing group of susceptible individuals.[10] In 1988, 12,756 organ transplants (excluding bone marrow) were performed in the United States, and in 1995, this number increased to 19,024 (United Network for Organ Sharing, 1996, unpublished data) However, the same medications that protect transplanted tissues and organs from immune rejection predispose these patients to a variety of opportunistic infections. In one study of liver transplant recipients, invasive fungal infections occurred in over 20% within 100 days of transplantation and *Candida* accounted for 82% of all infections.[11] Another study demonstrated the occurrence of systemic mycoses in 6% of 310 renal transplant recipients; these included cryptococcosis, candidiasis, zygomycosis, and aspergillosis.[12] A review of 341 patients with hematologic malignancies noted that systemic mycoses were detected in 17.6%. [13] Among these patients, fatal aspergillosis occurred in 8 of 10 patients (80%) who had bone marrow transplantation complicated by graft-versus-host disease and its therapy, in contrast to 2 of 36 (5.5%) bone marrow transplant recipients without graft-versus-host disease.[13] In one multicenter study of cardiac transplant-associated opportunistic infections, bacterial and viral infections each accounted for nearly 40% of infections while fungal and protozoan infections accounted for only 12% of infections. However, the case fatality rate resulting from invasive fungal infections (36%) was nearly three times higher than that for bacterial or viral infections (13%).[14] In another study, coccidioidomycosis was reported in 4.5% of 199 heart transplant recipients in an area highly endemic for the disease.[15]

Microbial adaptation: the evolution of drug resistant fungi. The high incidence and mortality of fungal infections in transplant recipients has led to clinical trials of various antifungal prophylactic regimens. In addition, the development of effective oral antifungal agents has resulted in their widespread use in hospital settings and in the community at large, including over-the-counter use. As in the development of resistance in response to increased use of antibacterial and antiviral agents, it seems all too likely that the increased use of antifungal therapy will be complicated by the emergence of fungi that innately possess or acquire resistance to these agents. The increased use of azoles in general, and fluconazole in particular, has been associated with clinical and microbiological unresponsiveness of *Candida* species to fluconazole.[16-20] This has fueled a debate on the magnitude of the problem, the role of clinical and microbiological resistance factors, and the capability of person-to-person transmission of microbiologically resistant strains to spread through different hosts.

A recent review called attention to the fact that all four major classes of antifungals; polyenes (for example, amphotericin B), the azoles (for example, fluconazole), the allylamines/thiocarbamates (for example, naftifine or terbinafine), and the morpholines (for example, amorolfine) all involve ergosterol in their mechanism of action.[21] This raises the fear that a common resistance mechanism could make all classes of antifungals simultaneously ineffective. The authors called for new approaches, indicated that problems existed both in detection of resistance and in standardization of antifungal susceptibility testing, and noted that the factors that led to the emergence of fungal infections are likely to persist.[21]

Land use and travel: fungal infections in immunocompetent persons not previously exposed. The outbreak of coccidioidomycosis in California highlighted the risk of fungal infections for susceptible individuals who travel or move into increasingly populated endemic areas. The statistics on the outbreak in California did not include data on visitors to the area who are likely to have been exposed during their stay but did not manifest disease until after returning home

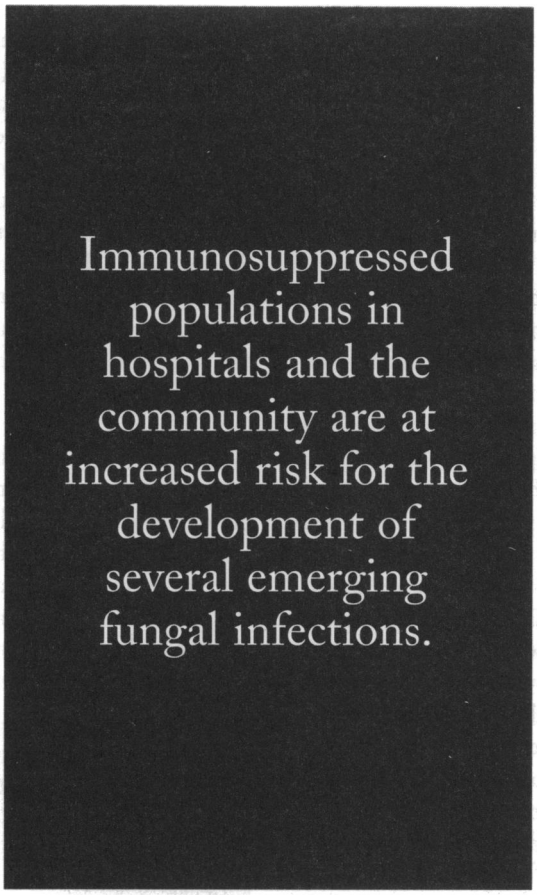
Box 2. Conditions and therapies predisposing to invasive fungal infections

Conditions
Granulocytopenia
Advanced HIV infection
Bone marrow and solid organ transplantation
Very low birth weight (≤1500 g)
Diabetes mellitus
Fibrotic and cavitary lung disease
Severe burns or trauma
Severe malnutrition or debilitation
Intravenous drug abuse

Therapies
Intravenous hyperalimentation
Broad-spectrum antibiotics
Indwelling catheters and devices
Prosthetic devices
Corticosteroid treatment
Hemodialysis and peritoneal dialysis
Intravascular implants (cardiac valves, shunts)

to nonendemic areas. Unfamiliarity with the clinical spectrum of this disease by physicians in nonendemic areas may result in delays in diagnosis and treatment. Further, in nonendemic areas case reporting may not be required.[22] Two cases of coccidioidomyeosis disease have been reported in military personnel who traveled to California to undergo training at camps located in the endemic area for periods as short as three weeks.[22]

Penicillium marneffei, the only dimorphic human pathogen from the large genus *Penicillium*, is an example of a recently recognized fungal pathogen that may be significantly influenced by the movement of susceptible persons into endemic areas.[23] Prior to the AIDS epidemic this opportunistic infection occurred among severely immunosuppressed patients, such as those with lymphoproliferative disorders being treated with chemotherapeutic agents toxic to T cells. Currently, over 70% of reported cases have occurred in HIV-infected hosts, yet no cases have been reported in individuals who have not lived in or traveled to the endemic region in Southeast Asia (including China, Thailand, and Vietnam).[23,24]



Breakdown of public health measures: the failing laboratory infrastructure. Diagnosing fungal diseases by their identification in the Mycology Laboratory is fundamental to their control. There are currently only a few reference laboratories that identify unusual fungal pathogens, and there is serious concern that diagnostic mycology services which have already experienced considerable difficulty in attracting continued support and personnel will be further threatened. The situation is all too similar to the dismantling of reference mycobacterial laboratory services a decade ago when tuberculosis was no longer considered to be a threat. Only the overwhelming resurgence of tuberculosis and the emergence of multidrug-resistant TB in HIV-infected patients turned this situation around, at the cost of rebuilding the system to provide these essential services. We should learn from this experience that the infrastructure for fungal diagnostics should, if anything, be strengthened.

The Public Health Challenge

Given the growing numbers of immunocompromised and other susceptible individuals in the population, fungal infections accrue tremendous costs in terms of human life and health care dollars. In 1993, for example, a cost assessment study of fatal fungal infections in liver transplant recipients estimated the total health care-related cost to be between $121.8 million and $242.7 million. This demonstrates that the substantial investments in health care for many such life-saving procedures are threatened by these diseases (Bullock, W., personal communication). Therefore, a concerted and coordinated effort is required to assure that fungal diseases do not become an overwhelming threat to health.

Enhanced surveillance and reporting. Surveillance is the single most important tool for monitoring emerging fungal infections. The morbidity, mortality, and cost of cases of mycotic infections can all be measured through surveillance. To improve the capacity to monitor emerging fungal diseases, new disease threats must be detected and responded to quickly wherever they emerge, domestically or internationally. In addition to surveillance efforts that assess the general population, focusing on populations that are especially vulnerable to emerging fungal infections will provide the opportunity to improve health care delivery to these populations and may facilitate early recognition of new fungal disease threats in this sentinel population.

Fungal infections are underdiagnosed and underreported. The recognition of the emergence of serious fungal infections demands an appreciation of both the background rates of infection and the typical presentations and natural history of infection. Assessing the true incidence of systemic mycoses is difficult. First, fungal diseases are not nationally notifiable. Second, even where state health departments report the incidence of mycoses, gross underreporting is common. Further, given the various ecologic niches for the different endemic mycoses (blastomycosis, coccidioidomycosis, and histoplasmosis) and sporotrichosis and of the opportunistic infection penicilliosis marneffei, the leading fungal infection in one patient population, hospital, or region may not be the same in another.[25-29,30-32]

Candidiasis can be used to illustrate the last point. Mucocutaneous candidiasis is the most frequent AIDS-defining condition and differs significantly from the invasive, disseminated, life-threatening form of disease seen in severely granulocytopenic cancer patients. Thus, the patho-

Emerging fungi and at-risk populations

Fungus	Disease	Risk Groups	Selected References
Primary pathogens			
Coccidioides immitis	Coccidioidomycosis: Primary pulmonary and disseminated	Normal hosts: Ongoing epidemic in endemic area	22,46–50
		Compromised hosts: AIDS patients Organ transplant recipients	3,4,15,46
Histoplasma capsulatum	Histoplasmosis: Primary pulmonary and disseminated	Normal hosts: Sporadic epidemics in endemic areas	25–28
		Compromised hosts: AIDS patients Organ transplant recipients	29,51
Sporothrix schenckii	Sporotrichosis: Cutaneous Primary pulmonary and disseminated	Normal hosts: Sporadic epidemics Compromised hosts: AIDS patients	30 31,32,51
Opportunistic pathogens			
Candida albicans	Candidiasis: Mucocutaneous	Compromised hosts: AIDS patients Organ transplant recipients Cancer patients Patients receiving antibacterial treatment Diabetes patients	51–56
	Candidemia	Organ transplant recipients Neutropenic cancer patients Non-neutropenic surgical and trauma patients	10,13,36,37,51,57
	Deep/Disseminated	Same as candidemia, with neutropenics at greater risk	36,37,51,57,58
Other *Candida* species *C. glabrata* *C. tropicalis* *C. parapsilosis* *C. krusei* *C. lusitaniae*	Similar to *C. albicans* disease presentation and risk groups, except: other than *C. glabrata*, this group doesn't typically cause mucocutaneous disease		36,51,59,60
Pneumocystis carinii	*Pneumocystis carinii pneumonia* (PCP): Primary pulmonary and disseminated	Compromised hosts: AIDS patients Malnourished individuals	61
Cryptococcus neoformans	Cryptococcosis: Meningitis, primary pulmonary, and disseminated	AIDS patients Renal transplant recipients Cancer patients Subset of normal hosts	51,55,56
Aspergillus spp. (*A. fumigatus; A. flavus*)	Aspergillosis: Primary pulmonary and disseminated	Compromised hosts: Neutropenic cancer patients Organ transplant recipients AIDS patients	13,51,62–65
Penicillium marneffei	Penicilliosis marneffei: Primary pulmonary and disseminated	AIDS patients Cancer patients Patients receiving cytotoxic treatment	23,24,51
Trichosporon beigelii	Trichosporonosis: Fungemia	Organ transplant recipients Neutropenic cancer patients Non-neutropenic surgical and trauma patients	33,34,51,66
	Deep/Disseminated	Same as candidemia, with neutropenics at greater risk	51
Malassezia furfur	Fungemia	Patients receiving hyperalimentation	35,51
Hyaline moulds (*Fusarium* spp., *Pseudallescheria* spp; *Paecilomyces* spp., etc.)	Hyalohyphomycosis	Spectrum ranges from no known immunological defect (rare) to a variety of factors including trauma and immunosuppression, especially granulocytopenia	51,66–69
Dematiaceous Moulds (*Bipolaris* spp., *Drechslera* spp., *Exophiala* spp., *Exserohilum* spp., *Phialophora* spp., *Wangiella* sp., *Xylohypha* spp., etc.)	Phaeohyphomycosis Spectrum of cutaneous, primary pulmonary, and disseminated	Same as for Hyalohypomycosis	66–69

Dust clouds in the Santa Susana and San Gabriel mountains following an aftershock of the January 17, 1994, Northridge earthquake. Environmental exposure to dust from these clouds was linked to an outbreak of coccidioidomycosis. (Courtesy of Tom Freeman, Woodward-Clyde Consultants, Santa Ana, CA)

genic potential of the fungus and the form of disease that results differ according to risk group. Although not normally life-threatening in the HIV-infected host, mucocutaneous candidiasis can have a substantial impact on the patient's qualify of life; *Candida* esophagitis in AIDS patients may be especially problematic, and chronic or recurrent infections may develop despite prolonged systemic antifungal therapy, which may reflect acquisition of drug-resistant strains of the fungus. Whether drug-resistant populations of *C. albicans* will increase in significance through person-to-person transmission is not currently known.

Fungi occur as both community-acquired and nosocomial pathogens, posing different problems for surveillance. The current epidemic of coccidioidomycosis best illustrates that there is considerable underreporting of community-acquired, primary fungal infections. From 1990 to 1991, the number of coccidioidomycosis cases reported to the California Department of Health increased 281%, and a single laboratory accounted for the majority of cases reported in California.

Understanding exposure and transmission. Fungal diseases are different from many other infectious diseases in that the life-threatening mycoses are generally not communicable from person to person. The endemic mycoses are generally acquired via inhalation of infectious spores from an environmental reservoir, usually soil. This has important public health implications ranging from the need for specific containment measures in highly endemic areas to the consideration of vaccines as a means of prevention. Cryptococcosis, aspergillosis, coccidioidomycosis, histoplasmosis, blastomycosis, penicilliosis marneffei, and PCP are all either known or thought to be transmitted by inhalation of infectious spores, not via person-to-person spread. In contrast, the yeasts *Candida, Trichosporon*, and *Malassezia* are normally resident on human skin or in the gastrointestinal tract and pose the potential for person-to-person transmission, particularly in health care settings.[33-35]

Better detection measures. The most recent National Nosocomial Infections Surveillance System report estimates that fungi, predominantly *C. albicans*, are responsible for approximately 10% of nosocomial bloodstream infections.[36] However, the limitations of available diagnostic techniques make the true incidence of invasive mycoses difficult to assess. For example, routine blood culture techniques have limited sensitivity for fungemia—approximately 50% for

invasive candidiasis and less than 20% for invasive aspergillosis—yet the attributable mortality for candidiasis may be as high as 38%.[37] All too often fungal infections are first diagnosed at autopsy.

The availability of rapid, noninvasive, reliable, and economical diagnostic tests, including molecular epidemiologic techniques, is critically important in defining the full extent of fungal infection. The emergence of this fungal threat calls for increased support for the development and use of proper tools to identify these infectious agents and prevent their spread.

Strengthening public health laboratories. Drug resistance represents one general means by which microbes that were previously well controlled can evolve and become emerging pathogens. The 1992 IOM report identified the antimicrobial resistance of several bacterial, viral, and protozoan pathogens.[2] Recent data document examples of fungal resistance to antifungal agents, including 5-fluorocytosine (5-FC), amphotericin B, and azoles.[38,39] Documenting and tracking microbiological resistance and proper determination of primary (innate) and secondary (acquired) resistance will be needed to monitor this trend. In immunocompromised patients, both primary and secondary resistance to 5-FC occurs with *Candida* and other species. Because of this recognition, 5-FC is rarely used as a single agent and is most often used in combination with other classes of antifungals. To date, primary and secondary resistance to amphotericin B is rare, but both primary and secondary resistance to the azole antifungals have been documented, with most attention currently directed toward the resistance of *Candida* species to fluconazole.[38] Monitoring the development of antifungal drug resistance and enhanced virulence should help direct early and effective therapeutic intervention, and thereby reduce morbidity, mortality, and costs. For example, as antifungal resistance emerges in *C. albicans*, reliable information about the extent and distribution of this problem will be crucial to the recognition of potential difficulties in treating such common infections as vulvovaginal candidiasis as well as life-threatening, invasive candidiasis and other fungal infections.

The role of research: from the bench to the field. Innovative approaches to combining basic and applied laboratory research and epidemiologic research and surveillance are essential for controlling all infectious diseases. NIH's National Institute of Allergy and Infectious Diseases (NIAID) has launched a comprehensive workshop series in medical mycology addressing molecular methods for the diagnosis and treatment of systemic mycoses, immunology (including vaccines), and epidemiology.[40,41]

Laboratory research. For mycotic diseases, important areas of basic and applied research include: (*a*) studies of fungal pathogenesis and host defenses, (*b*) drug development, (*c*) laboratory identification of new or previously unrecognized fungal agents, (*d*) development of rapid tests for the diagnosis of infectious fungal agents and the identification of resistance to antifungal drugs, and (*e*) vaccine development.[42]

Advances in biotechnology offer valuable tools to prevent, detect, and control fungal pathogens. For example, recent work addressing immune-based therapies and vaccine prevention strategies for cryptococcosis could have important correlates in PCP as alternatives to the management of this important and related opportunistic infection.[43,44] For example, the reclassification of *Pneumocystis carinii* as a fungus rather than a protozoan may have important implications for basic research, for the development of improved diagnostic tests, as well as for a complete understanding of the natural history of the disease.[45]

Epidemiologic and ecologic research. Epidemiologic research is also critical to the development of effective preventive and control strategies. In addition to improved community and nosocomial surveillance and reporting of fungal diseases, outbreak investigations and prospective studies are critical to the rapid identification of risk factors for new mycotic diseases. When coupled with molecular techniques, these studies are often a critical first step toward identifying the cause or source of the outbreak and usually provide important prevention information early in the evolution of a potential epidemic. Additional epidemiologic studies that can impact on emerging fungal diseases include social and economic analyses of the burden of disease, cost-effectiveness analyses of proposed interventions, and studies of behaviors that affect risk.

Studies of fungal ecology, reservoirs, and modes of transmission will aid in formulating specific prevention measures. Coccidioidomycosis is an excellent example of an emerging infection for which climatologic, ecologic, and demographic factors have combined to contribute to an increased public health burden in terms of morbidity and mortality as well as financial costs.[46] *Coccidioides immitis* is maintained primarily in the soil; the emergence of this disease may be particularly subject to ecologic factors. There is evidence that the increase in reported cases of coccidioidomycosis in California may be linked to cyclical weather conditions (long periods of drought followed by periods of heavy rain, periods of drying, and heavy winds). Supporting this hypothesis, the CDC investigation of the outbreak of coccidioidomycosis following the Northridge earthquake correlated the outbreak with widespread environmental exposure to dust carried aloft by the earthquake and its larger aftershocks.[47] Such conditions may facilitate airborne dispersal of fungal arthroconidia, the infectious stage of the organism. In addition, the recent immigration of previously unexposed and therefore nonimmune people from nonendemic regions is also contributing to increased rates of infections. The critical assessment of ecologic factors responsible for this outbreak should provide the information needed to develop strategies to prevent future outbreaks. It is also likely that increased opportunities for the emergence of new fungal diseases in humans will result from expanded

human settlement into areas endemic for such diseases. Climatic changes may also increase the incidence of these diseases and the likelihood that they may spread to new places.

Further environmental control measures such as the treatment of soil to prevent histoplasmosis may sometimes be warranted, but expanded research is required to ensure that these measures are both safe and cost-effective. As part of instituting the CDC plan *Addressing Emerging Infectious Diseases Threats: A Prevention Strategy for the United States*,[48] CDC has worked together with officials of the California Department of Health Services to continue to monitor the ongoing outbreak in California, in particular in Kern County. In 1995, coccidioidomycosis was added to the list of notifiable diseases reported to CDC.

Conclusion

Fungal diseases were once primarily inconveniences or, rarely, life-threatening illnesses. Because of increasing numbers of immunocompromised hosts, the fungi have become important problems in both the hospital and the community, with ever-increasing morbidity, mortality, and economic costs. Addressing these emerging pathogens will require greater awareness and a concerted effort by clinicians, researchers, the pharmaceutical industry, and public health officials.

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