CHAPTER 1

Introduction

The last several decades have seen unprecedented changes in the pattern of fungal infections in humans. These diseases have assumed a much greater importance because of their increasing incidence in persons with the acquired immunodeficiency syndrome (AIDS), in recipients of solid organ or haematopoietic stem cell transplants (HSCT), in persons with haematological malignancies and in other debilitated or immunocompromised individuals. Although gains have been made in the treatment and prevention of fungal disease, major changes in health care practices have resulted in the emergence of new at-risk populations.

1.1 The nature of fungi

The fungi form a large, diverse group of organisms, most of which are found as saprophytes in the soil and on decomposing organic matter. They are eukaryotic, but differ from other groups, such as plants and animals, in several major respects. First, fungal cells are encased within a rigid cell wall, mostly composed of polysaccharides (glucan, mannan), chitin and glycoproteins in various combinations. This feature contrasts with animals, which have no cell walls, and plants, which have cellulose as the major cell wall component. Second, fungi are heterotrophic. This means that they are lacking in chlorophyll and therefore require preformed organic carbon compounds for their nutrition. Fungi obtain their nourishment by secreting enzymes for external digestion and by absorbing the released nutrients through their cell wall. Third, fungi are simpler in structure than plants or animals. There is no division of cells into organs or tissues. The basic structural unit of fungi is either a chain of tubular, filament-like cells

_Fungal Infection: Diagnosis and Management_, Fourth Edition. Malcolm D. Richardson and David W. Warnock
© 2012 Malcolm D. Richardson and David W. Warnock. Published 2012 by Blackwell Publishing Ltd.
Chapter 1

(termed hypha) or an independent single cell (termed yeast). Fungal cell differentiation is no less sophisticated than is found in plants or animals, but it is different. Many fungal pathogens of humans and animals change their growth form during the process of tissue invasion. These dimorphic pathogens usually change from a multicellular hyphal form in the natural environment to a budding, single-celled yeast form in tissue.

In most multicellular fungi, the vegetative stage consists of a mass of branching hyphae, termed mycelium. Each individual hypha has a rigid cell wall and increases in length as a result of apical extension with mitotic cell division. In most fungi, the hyphae are septate, with more or less frequent cross walls. In the more primitive fungi, the hyphae usually remain aseptate (without cross walls). Fungi that exist in the form of microscopic multicellular mycelium are commonly called moulds.

Many fungi exist in the form of independent single cells. Most yeasts propagate by an asexual process called budding, in which the cell develops a protuberance from its surface. The bud enlarges and may become detached from the parent cell, or it may remain attached and itself produce another bud. In this way, a chain of cells may be produced. Under certain conditions, continued elongation of the parent cell before it buds results in a chain of elongated cells, termed pseudohypha. Some yeasts reproduce by fission of the cells. Yeasts are neither a natural nor a formal taxonomic group, but are a growth form shown in a wide range of unrelated fungi.

Moulds reproduce by means of microscopic propagules called either conidia or spores. Many fungi produce conidia that result from an asexual process (involving mitosis only). Except for the occasional mutation, these spores are identical to the parent. Asexual conidia are generally short-lived propagules that are produced in enormous numbers to ensure dispersion to new habitats. Many fungi are also capable of sexual reproduction (involving meiosis). Some species are self-fertile (homothallic) and able to form sexual structures within individual colonies. Most, however, are heterothallic and do not form their sexual structures unless two different mating strains come into contact. Meiosis then leads to the production of sexual spores. In some species, the sexual spores are borne singly on specialized generative cells and the whole structure is microscopic in size. In other cases, however, the spores are produced in millions in ‘fruiting bodies’ such as mushrooms. Many fungi can produce more than one type of spore, depending on the growth conditions, the precise method of spore production and type(s) of spore produced being
unique to each species. Sexual reproduction and its accompanying structures form the main basis for classification of the fungi.

1.2 Classification and nomenclature of fungi and fungal diseases

The fungal kingdom is one of the six kingdoms of life. It is organized in a hierarchical manner and is currently divided into seven phyla, which include the Ascomycota and Basidiomycota. The phylum name Zygomyccota is no longer accepted because of its polyphyletic nature. In its place, the phylum Glomeromycota and four subphyla, including the Mucoromycotina and Entomophthoromycotina, have been created pending further resolution of taxonomic questions. Historically, fungal classification has largely been based on morphological features, in particular the method of sexual spore production. In some fungi, however, the asexual stage (termed the anamorph) has proved so successful as a means of rapid dispersal to new habitats, that the sexual stage (termed the teleomorph) has diminished or even disappeared. In these fungi, the shape of the asexual spores and the arrangement of the spore-bearing structures have been of major importance in classification and identification. With the advent of DNA sequence analysis, fungal species are now defined as groups of organisms with concordant sequences at multiple different genetic loci, rather than organisms that share common morphological characteristics or organisms that can mate with one another. Even in the absence of the sexual stage, it is now often possible to assign asexual, anamorphic or mitosporic fungi to genera within the phyla Ascomycota or Basidiomycota on the basis of DNA sequence analysis.

The scientific names of fungi are subject to the International Botanical Code of Nomenclature, a convention that dates from the time when biologists regarded these organisms as ‘lower plants’. In general, the correct name for any species is the earliest name published in line with the requirements of the Code. Any later names are termed synonyms. To avoid confusion, however, the Code allows for certain exceptions. The most significant of these is when an earlier generic name has been overlooked, a later name is in general use, and a reversion to the earlier name would cause problems. Another reason for renaming a fungus is when new research necessitates the transfer of a species from one genus to another, or establishes it as the type of a new genus. Such changes are quite in order, but with the provision that the specific epithet should remain unchanged.
Many fungi bear two names, one designating their sexual stage and the other their asexual stage. Often this is because the anamorphic and teleomorphic stages were described and named at different times without the connection between them being recognized. The Code of Nomenclature permits this practice, and while the name of the teleomorph takes precedence and covers both stages, the name given to an anamorph may be used as appropriate. Thus, it is permissible to refer to a fungus by its asexual designation if this is the stage that is usually obtained in culture.

Unlike the names of fungi, the names of fungal diseases are not subject to strict international control. Their usage tends to reflect local practice. One popular method has been to derive disease names from the generic names of the causal organisms: for example, aspergillosis, cryptococcosis, histoplasmosis, etc. However, if the fungus changes its name, then the disease name has to be changed as well. For example, the term zygomycosis has been used for decades to describe infections caused by members of the class Zygomycetes. With the recent abolition of this class, the more precise terms mucormycosis and entomophthoromycosis have begun to supplant zygomycosis to describe diseases caused by species belonging to the orders Mucorales and Entomophthorales, respectively (see Chapters 13 and 20).

In 1992, a sub-committee of the International Society for Human and Animal Mycology recommended that the practice of forming disease names from the names of their causes should be avoided and that, whenever possible, individual diseases should be named in the form ‘pathology A due to (or caused by) fungus B’. This recommendation was not intended to apply to long-established disease names, such as aspergillosis, rather it was intended to offer a more flexible approach to nomenclature.

There is also much to be said for the practice of grouping together mycotic diseases of similar origins under single headings. One of the broadest and most useful of these collective names is the term ‘phaeohyphomycosis’, which is used to refer to a range of superficial, subcutaneous and systemic infections caused by any brown-pigmented mould that adopts a septate hyphal form in host tissue (see Chapter 25). The number of organisms implicated as aetiological agents of phaeohyphomycosis has increased from 16 in 1975 to more than 250 at the present time. Often these fungi have been given different names at different times, and the use of the collective disease name has helped to reduce the confusion in the literature. The term ‘hyalohyphomycosis’ is another collective name that is increasing in usage. This term is used to describe infections caused by colourless (hyaline) moulds that adopt a septate hyphal form in tissue (see Chapter 23). To date, more than 70 different organisms have been
implicated, including a number of important emerging fungal pathogens, such as *Fusarium* species, that are not the cause of otherwise-named diseases, such as aspergillosis.

### 1.3 Fungi as human pathogens

There are at least 100,000 named species of fungi. However, fewer than 500 have been associated with human disease, and no more than 100 are capable of causing infection in otherwise normal individuals. The remainder is only able to produce disease in hosts that are debilitated or immuno-compromised in some way. Most human infections are caused by fungi that grow as saprophytes in the environment and are acquired through inhalation, ingestion or traumatic implantation. Some yeasts are human commensals and cause endogenous infections when there is some imbalance in the host. Many fungal diseases have a worldwide distribution, but some are endemic to specific geographical regions, usually because the aetiological agents are saprophytes restricted in their distribution by environmental conditions.

Fungal infections can be classified into a number of broad groups according to the initial site of infection. Grouping the diseases in this manner brings out clearly the degree of parasitic adaptation of the different groups of fungi and the way in which the site affected is related to the route by which the fungus enters the host.

#### 1.3.1 The superficial mycoses

These are infections limited to the outermost layers of the skin, the nails and hair, and the mucous membranes. The principal infections in this group are the dermatophytoses and superficial forms of candidosis. These diseases affect millions of individuals worldwide, but there are regional variations. They are readily diagnosed, and usually respond well to treatment.

The dermatophytes are limited to the keratinized tissues of the epidermis, hair and nail. Most are unable to survive as free-living saprophytes in competition with other keratinophilic organisms in the environment and thus are dependent on passage from host to host for their survival. These obligate pathogens seem to have evolved from unspecialized saprophytic forms. In the process, most are now no longer capable of sexual reproduction and some are even incapable of asexual reproduction. In general, these organisms have become well adapted to humans, evoking little or no inflammatory reaction from the host. Only dermatophyte infections are truly contagious.
The aetiological agents of candidosis, like the dermatophytes, are largely dependent on the living host for their survival, but differ from them in the manner by which this is achieved. These organisms, of which *Candida albicans* is the most important, are normal commensal inhabitants of the human digestive tract or skin. Acquisition of these organisms from another host seldom results in overt disease, but rather results in the setting-up of a commensal relationship with the new host. These organisms do not produce disease unless some change in the circumstances of the host lowers its natural defences. In this situation, endogenous infection from the host’s own reservoir of the organism may result in mucosal, cutaneous or systemic infection.

Other common superficial infections include pityriasis versicolor, a mild and often recurrent infection of the stratum corneum, caused by lipophilic yeasts of the genus *Malassezia*. These organisms are skin commensals. Disease is probably related to host and environmental factors. Pityriasis versicolor is most common in hot, humid tropical climates.

1.3.2 The subcutaneous mycoses

These are infections of the dermis, subcutaneous tissues and adjacent bones that generally show slow localized spread. They usually result from the traumatic implantation of saprophytic fungi from soil or vegetation. More widespread dissemination of the infection, through the blood or lymphatics, is uncommon, and usually only occurs if the host is in some way debilitated or immunocompromised. The principal subcutaneous mycoses are mycetoma, sporotrichosis, phaeohyphomycosis and chromoblastomycosis. These infections are most frequently encountered among the rural populations of the tropical and sub-tropical regions of the world, where individuals go barefoot and wear the minimum of clothing.

1.3.3 The systemic mycoses

Deep-seated fungal infections usually originate in the lungs, but may spread to many other organs. These infections are most commonly acquired as a result of inhaling spores of organisms that grow as saprophytes in the environment, or as pathogens on plants.

The organisms that cause systemic fungal infection can be divided into two distinct groups: the true pathogens and the opportunists. The first of these groups is comprised of a handful of organisms, mostly dimorphic fungi that are able to invade and develop in the tissues of a normal host with no recognizable predisposition. The principal diseases are blastomycosis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis. The second group, the opportunists, consists of less virulent and less
well-adapted organisms that are only able to invade the tissues of an immunocompromised host. Although new species of fungi are regularly being identified as causes of disease in immunocompromised patients, five diseases still account for most reported infections: aspergillosis, candidiasis, cryptococcosis, mucormycosis and pneumocystosis.

In many instances, infections with true pathogenic fungi are asymptomatic or mild and of short duration. Most cases occur in geographical regions where the aetiological agents are found in nature and follow inhalation of spores that have been released into the environment. Individuals who recover from these infections may enjoy marked and lasting resistance to reinfection, while the few patients with chronic or residual disease often have a serious underlying illness.

In addition to their well-recognized manifestations in otherwise normal persons, infections with true pathogenic fungi have emerged as important diseases in immunocompromised individuals. Histoplasmosis and coccidioidomycosis, for instance, have been recognized as AIDS-defining illnesses. Both diseases have been seen in significant numbers of human immunodeficiency virus (HIV)-infected persons throughout North and South America. In immunocompromised individuals, infections with true pathogenic fungi are often life-threatening and unresponsive to antifungal drugs, or relapse following discontinuation of treatment.

Opportunistic fungal infections occur in individuals who are immunosuppressed as a result of an underlying illness or their treatment. In most cases, infection results in significant disease. Resolution of the infection does not confer protection, and reinfection or reactivation may occur if host resistance is again lowered. In contrast to the restricted geographical distribution of most of the true pathogenic fungi, many opportunistic fungi are ubiquitous in the environment worldwide, being found in the soil, on decomposing organic matter and in the air. These infections are associated with high case fatality rates, but estimates of their incidence are thought to be quite conservative in comparison with their true magnitude, because many cases go undiagnosed or unreported.

1.4 The changing pattern of fungal infection

Over the past few decades, major advances in health care have led to an unwelcome increase in the number of life-threatening infections due to true pathogenic and opportunistic fungi. These infections are being seen in ever increasing numbers, largely because of the increasing size of the population at risk. This population includes persons with HIV infection, transplant recipients, cancer patients and other individuals receiving
immunosuppressive treatment. Among patients undergoing transplants or treatment for malignancies, novel and more intensive regimens have resulted in more profound levels of immunosuppression that are sustained for longer periods. Likewise, the increasing use of invasive monitoring and aggressive therapeutic technologies in intensive care units has resulted in improved survival of individuals with life-threatening illnesses, but has also contributed to an increase in the number of persons at risk for fungal infections. Other developments in medical practice that have led to significant changes in the incidence of invasive fungal diseases among the different groups of at-risk patients include the increasing use of triazole antifungal agents for treatment and chemoprophylaxis, and the widespread use of amphotericin B for empirical treatment of suspected fungal infection.

In addition to the rise in prevalence of opportunistic fungal infections due to such well-recognized organisms as *Aspergillus fumigatus*, *C. albicans* and *Pneumocystis jirovecii*, an ever increasing number of fungi, hitherto regarded as harmless saprophytes, are being reported as the cause of serious or lethal infection in immunocompromised individuals. For instance, *Fusarium* species, long recognized as a cause of nail and corneal disease, are now well documented as the aetiological agents of lethal invasive infections in neutropenic cancer patients and HSCT recipients. The emergence of these organisms as significant pathogens has important implications for diagnosis and management, not only because the clinical presentation can mimic a more common disease, aspergillosis, but also because the organisms are usually resistant to amphotericin B, the drug of choice for empirical treatment of suspected fungal infections in febrile neutropenic patients.

There has also been a marked increase in the incidence of several of the fungal diseases that are endemic in North America, in particular histoplasmosis and coccidioidomycosis. Urban development and changing land use in the endemic regions have contributed to this trend, as has the seasonal migration of previously unexposed populations from non-endemic regions to the desert South West. Many of these migrants are older, have underlying chronic illness and debilitation, and consequently are at greater risk of developing the more serious forms of coccidioidomycosis. In addition, there is evidence that the increase in reported cases of this disease may be linked to changing climatic conditions.

Increased international travel has also led to a rise in the number of reported outbreaks and sporadic cases of histoplasmosis and coccidioidomycosis among individuals who normally reside in places far distant from the regions where these diseases are endemic. The largest number
of travel-related mycoses has been reported from US residents, many of whom have acquired an infection while visiting an endemic region within North or Central America or, less commonly, in South America, Africa or Asia. Travel-related fungal infections have also been reported among international visitors to North America, or to countries in Latin America, Africa and Asia. Most of these infections have occurred among persons returning to European countries, Australia or Japan. However, with increasing numbers of visitors and immigrants to the United States from Asia, travel- and migration-related infections are now being reported from regions such as the Indian sub-continent.

In many respects, the current pattern of invasive fungal disease in developing countries is quite different from that seen in developed countries. In the industrialized world, opportunistic fungal infections predominantly occur in the context of aggressive immunosuppressive therapies. Throughout the developed world, the widespread use of combination antiretroviral treatment regimens has led to a marked reduction in the rates of AIDS-associated opportunistic infections. In contrast, in many resource-poor countries in sub-Saharan Africa and parts of Asia, the burden of fungal diseases among those with HIV infection is large and increasing. According to recent estimates, around 958,000 cases of cryptococcal meningitis occur worldwide in persons with HIV infection each year. The region with the greatest number of cases is sub-Saharan Africa, with 720,000 cases, followed by South and South East Asia with 120,000 cases. The disease is one of the leading causes of infection-related mortality in sub-Saharan Africa, with around 500,000 deaths each year. Moreover, cryptococcosis is estimated to cause more deaths in this region than diseases such as tuberculosis, which are more common in the population.

1.5 New directions in diagnosis

Among the many challenges in dealing with opportunistic invasive fungal diseases, none is more critical than early diagnosis of these infections. This is essential to reduce the high case fatality rates of these diseases in immunocompromised individuals. There has been some progress in the field of diagnosis in recent years, but this has largely been due to the increased use of computed tomographic scanning and other imaging procedures. Laboratory methods for the diagnosis of fungal infections continue to be updated, but still depend, for the most part, on isolation of the fungus in culture, on its microscopic detection in clinical material and on the detection of a serological response to the pathogen (see Chapter 2).
Nevertheless, the search for more rapid, sensitive and specific non-culture-based tests is continuing.

New approaches to the diagnosis of invasive fungal infections include the detection of fungal cell wall components or metabolites and the detection of fungal DNA in clinical specimens. However, despite much recent progress, the goal of developing simple, rapid and cost-effective clinical tests for the diagnosis of invasive fungal infections remains elusive. New diagnostic procedures based on the detection of fungal DNA are presently being developed, but have not yet had a significant impact in most clinical laboratories, largely because they have not been standardized and validated. Only a few of these methods are commercially available.

1.6 New directions in treatment and prevention

The rising prevalence of invasive fungal infections has brought about an increased use of existing antifungal agents and has stimulated research for new ones. The last two decades have seen the introduction of an important new class of antifungal agents (the echinocandins), the expansion of an established class of agents (the azoles) and the development of novel methods for delivering established agents (lipid-based formulations of amphotericin B). The new drugs that have been introduced have changed the standards of care for the treatment of many invasive fungal infections, particularly aspergillosis and candidosis, but some problems remain (see Chapter 3). There are now few life-threatening infections for which there is no effective treatment, and there are many for which there are several reliable therapeutic options. On the other hand, triazole and echinocandin resistance, an uncommon clinical problem at present, is of concern and requires more rapid approaches to detection and continued surveillance.

Although opportunistic fungal infections in persons with AIDS are no longer a major problem in developed countries, the burden of these diseases is continuing to increase in many developing countries with large HIV epidemics. Throughout the developed world, the use of combination antiretroviral treatment has proved to be the most effective method of preventing all opportunistic infections in persons with AIDS. Because these drugs are seldom available in resource-limited countries, other measures are needed to prevent diseases such as cryptococcosis and penicilliosis. In this respect, antifungal chemoprophylaxis is currently the most promising of the potential prevention strategies.
Further reading


