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and Thira Sirisanthana 8.7.7 Microsporidiosis 1378 Louis M. Weiss 8.7.1 Fungal infections Roderick J. Hay ESSENTIALS The mycoses are disorders caused by fungi, which are saprophytic or parasitic organisms found in every continent and environment. Many are common commensals in nature, but others cause agricul- tural disease. The mycoses that are human infections include diseases ranging from those that are worldwide and common, such as derm- atophytosis and candida infections, to those that are rare and often potentially life-threatening (e.g. histoplasmosis). In humans, fungi usually adopt one of two morphologies: (1) the yeast form—where individual cells produce daughter cells by a process of budding and subsequently separate; or (2) the hyphal form—where cells do not separate but multiply to produce chains of cells joined end to end. Diagnosis Mycological diagnosis is often complex because many fungi are also commensals or transiently carried in humans, hence it is necessary to show both that the organisms are present and that they are causing disease, which is particularly difficult in the context of opportunistic fungal infection. The main laboratory diagnostic tests involve (1) visu- alization of fungi in tissue—by direct microscopy or histopathology; (2) culture—often using a glucose peptone agar (Sabouraud's agar); (3) detection of antibody, fungal antigens, or DNA—assimilation of genetic tests such as polymerase chain reaction-based methods into routine diagnosis has been slow, and they are offered by few laboratories. Superficial infections Superficial fungal infections may reach prevalence rates of 15–25% in some communities, with the common infections being dermato- phytosis or ringworm, pityriasis versicolor, and superficial candidiasis. Dermatophytoses—otherwise known as tinea infections— commonly affect the feet (tinea pedis), the body (tinea corporis), the scalp (tinea capitis) and the finger and toe nails (onychomycosis). They occur in all climates and usually present in primary care as scaly rashes. Diagnosis is made by direct microscopy of skin scales mounted in potassium hydroxide (20%) to demonstrate hyphae, and by culture. Pityriasis versicolor—caused by a skin surface commensal, Malassezia globosa, and often triggered by sun exposure. Presentation is with hypo– or hyperpigmented scaling on the trunk. Laboratory diagnosis (if required) is by demonstration of the yeasts and hyphae in skin scales removed by scraping. Superficial candidiasis—these infections affect the mouth, vagina, and body folds, often in the context of some form of predisposition (e.g. recent antibiotic therapy or, in the case of severe oral infec- tion, immunosuppression including that associated with HIV/AIDS).

Infections are diagnosed by microscopy and culture, the latter being particularly important where non-albicans Candida species may be involved. Treatment—the main treatments for superficial mycoses are top- ical agents that include imidazole preparations (e.g. ketoconazole, clotrimazole), but for widespread infections or those involving hair or nails, oral imidazoles (e.g. itraconazole, fluconazole) or the allylamine, terbinafine, are employed. Subcutaneous mycoses Subcutaneous fungal infections, for example, mycetoma (Madura foot), chromoblastomycosis and sporotrichosis, are not common and usually restricted to the tropics and subtropics. They might present in immigrants from tropical areas, sometimes years after the person has left the tropics, and hence cause diagnostic confusion. Diagnosis is

8.7.1 Fungal infections 1339 by histological examination of affected tissues or culture. Treatment is often difficult, with only partial responses being achieved, but oral imidazole drugs or terbinafine are helpful in some cases. Systemic mycoses Systemic mycoses are deep and often disseminated infections that involve many different sites, including the blood and bone marrow. They can be caused by organisms which invade normal hosts (en- demic mycoses) and those which only cause disease in comprom- ised patients (opportunistic mycoses). Endemic mycoses—these include histoplasmosis, coccidioido- mycosis (see Chapter 8.7.3) and infections due to Talaromyces (Penicillium marneffei) (see Chapter 8.7.6), all of which can occur in healthy people, although many are also common complications of HIV/AIDS. Initial manifestations are as respiratory infections, but they can spread haematogenously to other sites (e.g. skin, liver, and brain). Diagnosis is made on culture or biopsy of affected areas. Opportunistic mycoses—these occur in those who are immuno- compromised (e.g. patients with neutropenia secondary to cancer). The routes of fungal entry into the body are very variable (e.g. skin, gastrointestinal tract, lung). Infections include systemic candidiasis, aspergillosis, and mucormycosis, but in severely compromised pa- tients (e.g. those with profound neutropenia, many organisms not usually associated with human disease can cause invasive infections, e.g. Fusarium species). Cryptococcus neoformans, a yeast that can in- vade the lungs, often presents with meningitis or other signs of intra- cranial infection. Prognosis and treatment—the endemic mycoses are often fatal if untreated, and even with treatment the mortality of opportunistic fungal infection can be high (e.g. over 40% for the severely neutro- penic patient with aspergillosis). Aside from supportive care, oral or parenteral agents such as amphotericin B, fluconazole, itraconazole, voriconazole, posaconazole, and caspofungin are the treatments of choice, but detecting the organisms and successfully treating the in- fections remains a challenge. Introduction Fungi are saprophytic or parasitic organisms that are normally as- signed to a distinct kingdom. As eukaryotes, they have the complex subcellular organization and highly organized genetic material seen in both animal and plant cells. The cell wall is a distinctive feature of fungi and has a complex cytoskeleton based on mannan, glucan, or chitin subunits. The arrangement and reproduction of indi- vidual cells is also characteristic. Most fungi form new cells termin- ally, which remain connected to form long, branching filaments or hyphae (the mould fungi). Some reproduce in a similar manner but each new cell separates from the parent by a process of budding (the yeast fungi). It is a feature of certain fungi to be yeast-like during one phase of their life history but hyphal at another, a phenom- enon known as dimorphism. In culture, mould fungi usually form a cottony growth on laboratory media while yeasts normally have a smooth, shiny appearance. Fungi adversely affect humans in several ways. They cause disease indirectly by spoilage and destruction of food crops, with subsequent malnutrition and starvation. Many of the common moulds produce and release spores, which can act as airborne allergens to produce asthma or hypersensitivity pneumonitis. Fungi elaborate complex metabolic

byproducts, some of which are useful to humans, such as the penicillins. However, others are toxic. Disease caused by the ingestion of fungal toxins includes both poisoning by eating certain mushrooms (mycetism) and damage caused by the ingestion of mi- nute quantities of toxin (mycotoxicosis), for example, in contam- inated grain. The contribution of the latter mechanism to human disease remains largely unexplored, as does the question of whether inhalation of toxic fungal spores may cause pathology. Finally, fungi might invade human tissue. Medical mycology is largely concerned with this last group. Invasive fungal diseases are normally divided into three groups: the superficial, subcutaneous, and deep mycoses. In superficial infections, such as ringworm or thrush, fungi are con- fined to the skin and mucous membranes. Extension deeper than the surface epithelium is rare. Subcutaneous infections are usually tropical: the main site of involvement is within subcutaneous tissue, although secondary invasion of adjacent structures such as bone or skin can occur. In deep or systemic infections, deep organs such as the lung, spleen, or brain are invaded. This classification of mycoses is based on the main 'sphere of involvement' by the causal organ- isms, but there are exceptions. For instance, brain involvement has been recorded in patients with chromoblastomycosis, which is nor- mally a subcutaneous infection. The fungi causing systemic mycoses are often classified in two groups: the opportunists (which cause disease in immunocomprom- ised individuals) and the endemic pathogens. These contrast with the true pathogens, which cause infection in all subjects inhaling airborne spores. Superficial fungal infections The main superficial mycoses are the dermatophyte infections, superficial candidiasis, and tinea versicolor (see Section 23). These are both common and widespread. Rare superficial infections in- clude tinea nigra, and black or white piedra. Dermatophyte infections (dermatophytoses) Aetiology The dermatophyte or ringworm infections are caused by a group of organisms capable of existing in keratinized tissue such as stratum corneum, nails, or hair. The mechanism of invasion is thought to be linked to production of extracellular enzymes; at least three distinct metalloproteinase genes are found in Microsporum canis. Epidemiology Some dermatophyte fungi have a worldwide distribution; others are more restricted. The most common and most widely distributed is Trichophyton rubrum, which causes different types of infection in different parts of the world. It is commonly associated with athlete's foot (tinea pedis) in temperate areas as well as tinea corporis or tinea cruris in the tropics. This distinction is not based solely on climatic factors, as immigrants from tropical countries, particularly eastern Asia, might still have tinea corporis caused by T. rubrum when living in northern Europe. Certain dermatophytes are limited to defined

 areas. For instance, tinea imbricata caused by T. concentricum, is found in hot, humid areas of the eastern Asia, Polynesia, and South America. Scalp ringworm tends to occur in well-defined endemic areas in Africa and elsewhere. In different regions, different spe- cies of dermatophytes might predominate. Thus, in North Africa, the most common cause of tinea capitis is T. violaceum; in southern parts of the continent, the major agents might be Microsporum aud ouinii, M. ferrugineum, and T. soudanense. Not all dermatophyte infections are endemic and dominant species can disappear to be replaced by others. M. audouinii, once endemic and common in the United Kingdom, is now infrequent. By contrast, T tonsurans is now established as a major cause of tinea capitis in urban areas in the United Kingdom, parts of Europe, and the United States of America. Dermatophytes can be passed from person-to-person (anthropophilic infections), from animal to person (zoophilic), or from soil to person (geophilic). Sources of zoophilic organisms in Europe include cats and dogs, cattle, hedgehogs, and small rodents. Rarer sources include horses, monkeys, and chickens. Lesions pro- duced by zoophilic species can be highly

inflammatory. Factors governing the invasion of stratum corneum are largely un- known, but heat, humidity, and occlusion have all been implicated. Susceptibility to certain infection, such as tinea imbricata, might be genetically determined. Clinical features The clinical features of dermatophyte infections are best considered in relation to the site involved. Often the term tinea, followed by the Latin name of the appropriate part (such as corporis, meaning ‘body’) is used to describe the clinical site of infection. Tinea pedis Scaling or maceration between the toes, particularly in the fourth interspace, is the most common form of dermatophytosis seen in temperate countries. Itching is variable, but can be severe. Sometimes blisters might form both between the toes and on the soles of the feet. The causative organisms are commonly T. rubrum and T. inter digitale, the latter being responsible for the vesicular forms. Similar appearances can be caused by Candida albicans and in the bacterial infection, erythrasma. Gram-negative bacterial infection causes erosive interdigital disease associated with discomfort. ‘Dry type’ infections of the soles and palms These are normally caused by T. rubrum. Palms (Fig. 8.7.1.1) or soles have a dry, scaly appearance, which in the soles may encroach on to the lateral or dorsal surfaces of the foot. The palmar involve- ment is often unilateral, an important diagnostic feature. Nail inva- sion is often seen (see next). Itching is not prominent, and infections are usually chronic. Tinea cruris Infections of the groin, most often caused by T. rubrum or Epidermophyton floccosum, are relatively common. They occur in both tropical and temperate climates, although in the former the infection can spread to involve the whole waist area in both males and females. Tinea cruris in females is uncommon in Europe. An erythematous and scaly rash with a distinct margin extends from the groin to the upper thighs or scrotum. Itching can be severe. Coincident tinea pedis is common, and patients should be examined for this. The rash of crural erythrasma shows uniform scaling without a margin, whereas in candidiasis, satellite pustules occur distal to the rim. Onychomycosis (caused by dermatophytes) Invasion of the nail plate is most often seen with T. rubrum infec- tions. The plate is invaded distally and becomes thickened and fri- able with terminal loss of the nail plate. Onycholysis might be seen. More rarely, and most often with T. interdigitale, the dorsal surface of the plate is invaded, causing superficial white onychomycosis. Tinea corporis (body ringworm) Dermatophyte or ringworm infection on the trunk or limbs might produce the characteristic annular plaque with a raised edge and central clearing (Fig. 8.7.1.2). Scaling and itching is variable. Lesions caused by zoophilic organisms can be highly inflammatory and in certain cases, particularly those caused by T. verrucosum, intense itching, oedema, and pustule formation (kerion) can de- velop. This reaction is seldom secondarily infected by bacteria but is a response to the fungus on hairy skin. Infections of the beard, tinea barbae, are often highly refractory to treatment. Facial derm- atophyte infections can mimic a variety of nonfungal skin dis- eases, including acne, rosacea, and discoid lupus erythematosus. However, the underlying annular configuration can usually be distinguished. The term tinea incognito is used to describe such atypical lesions. Fig. 8.7.1.1 Palmar scaling due to Trichophyton rubrum. Fig. 8.7.1.2 Tinea corporis due to Microsporum gypseum.

8.7.1 Fungal infections 1341 Tinea capitis (scalp ringworm) In the United Kingdom as in the United States of America, the most common cause of scalp ringworm is T. tonsurans, an anthropophilic fungus which mainly occurs in inner cities, particularly in black Caribbean or African children. This has now replaced Microsporum canis, originating from an infected cat or dog, although this derm- atophyte is dominant elsewhere in the United Kingdom and Europe. Scalp ringworm is mainly a disease of childhood, but infections can occur in adult women. Spontaneous clearance at puberty is the rule. M. canis causes an ‘ectothrix’ infection where spores form on the out- side of the hair shaft and the scalp hair breaks above the skin surface. Scaling, itching, and loss of hair occur.

Other causes of ectothrix in- fection include M. audouinii, which is still seen in West Africa. This infection can be spread from child to child and causes serious social handicap. The infection can occur in epidemic form, particularly in schools. By contrast, infections with M. canis are acquired from a pri- mary animal source rather than by spread from human lesions. In endothrix infections where sporulation is within the hair shaft, scaling is less pronounced, and hairs break at scalp level (black dot ringworm). Examples include T. tonsurans and T. violaceum, the latter being most prevalent in the Middle East, parts of Africa, and India, although it also is being recognized with increasing frequency in Europe. Favus, now most often seen in isolated foci in the tropics, is a par- ticularly chronic form of ringworm caused by T. schoenleinii where hair shafts become surrounded by a necrotic crust or scutulum (Fig. 8.7.1.3). Individual crusts coalesce to form a pale, unpleasant-smelling mat over parts of the scalp. Such infections can cause exten- sive and permanent hair loss. Tinea imbricata (tokelau) This infection is endemic in parts of eastern Asia, West Pacific, and Central and South America, and is caused by T. concentricum. In many cases the trunk is covered with scales laid down in concen- tric rings producing a ripple effect (Fig. 8.7.1.4). Alternatively, large, loose scales can form (hence the name; imbricata is the Latin word for ‘tiled’). The infection is often chronic, and can constitute a ser- ious social handicap. There is some evidence that susceptibility of this disease in Papua New Guinea might be inherited as an auto-somal recessive trait. Infection in HIV and immunocompromised patients While dermatophyte infections are no more common in the im- munocompromised patient, they might differ clinically. In patients with untreated HIV infection there can be (1) more tinea facei, (2) more widespread and atypical skin lesions, and (3) a distinct pat- tern of nail infection characterized by white discoloration spreading rapidly through the nail plate from the proximal nail fold. Laboratory diagnosis The mainstays of diagnosis are direct microscopy of skin scales mounted in potassium hydroxide (20%) to demonstrate hyphae, and culture. Scalp hairs can also be examined in a similar way, and the site of arthrospore formation, inside or outside the shaft, deter- mined. Fluorescent whitening agents (Calcofluor) or chlorazol black stain have been used to highlight fungi in scales. Further tests, such as the ability to penetrate hair, can be used to separate similar cul- tures. Identification of organisms is important, as it will indicate the source of infection in scalp ringworm, for example. When large numbers of children are involved, screening of scalp infections with a filtered ultraviolet lamp (Wood’s light) is useful. Certain species, including M. canis and M. audouinii, cause infected hair to fluoresce with a vivid greenish light. Scalps can also be screened for infection by passing a sterile brush or scalp massager through the hair and plating this directly on to an agar plate. Fig. 8.7.1.3 Advanced favus of scalp in a Nigerian child caused by Trichophyton schoenleinii. Copyright D. A. Warrell. Fig. 8.7.1.4 Tinea imbricata, Papua New Guinea. Courtesy of Dr B. Hudson, Sydney.

 Treatment The treatment of dermatophyte infections depends, to an extent, on the nature and severity of infection. Topical therapy is reserved for circumscribed infections such as athlete’s foot and tinea corporis, not involving hair or nail keratin. Scalp and nail infections, severe or widespread ringworm, and failures of topical therapy are usually treated orally with griseofulvin, itraconazole, or terbinafine. Specific antifungal drugs in topical form are effective and well tolerated. The important compounds in this group are miconazole, clotrimazole, ketoconazole, and econazole, which are imidazole derivatives, undecenoic acid, and tolnaftate and the allylamine, terbinafine. Generally treatment is given for 7–30 days. They are all very similar in their clinical efficacy, but topical terbinafine is particularly rapid in foot infection (≤7 days). Adverse reactions are rare. For oral therapy the main alternatives are terbinafine, itraconazole, or

fluconazole. Terbinafine (250 mg/day) is rapidly effective in most forms of dermatophytosis that require oral therapy and also produces rapid responses in toenail (12 weeks) and sole infections (2 to 4 weeks), without a high rate of relapse. Side effects include headache and nausea, but loss of taste might also occur. Itraconazole is somewhat similar in its profile, but is given intermittently (200 mg twice daily for 7 days). This course is given once for sole infections but repeated three times at monthly intervals for toenail infections, as pulsed therapy. Side effects include nausea and abdominal dis- comfort. Fluconazole is also active and is given in a dose of 150 mg weekly; 300 mg might be necessary for toenail infections. This side effect profile is similar to itraconazole. All three drugs are ex- tremely rare causes of hepatic toxicity. Griseofulvin is still used for tinea capitis in a dose of 10 to 20 mg/kg daily. Treatment should be continued for at least 6 weeks in tinea capitis. Side effects are not common, but include headache, nausea, and urticaria. The drug can also precipitate acute intermittent porphyria and systemic lupus erythematosus in predisposed subjects. Neoscytalidium infections The organisms Neoscytalidium dimidiatum (Hendersonula toru loidea) and N hyalinum, can cause a superficial scaly condition that resembles the ‘dry type’ of dermatophyte infection on the palms or soles. Nail plate destruction can also occur, the lateral border of the nail being the initial site of invasion. The disease has been seen in Europe, almost invariably in immigrants from the tropics, particu- larly the Caribbean, West Africa, India, or Pakistan. Its prevalence in the tropics is unknown, although in some surveys it has been shown to be relatively common. In skin scrapings the tortuous hyphae might resemble those of a dermatophyte, but the organisms do not grow on media containing cycloheximide, which is often incorpor- ated into agar for routine dermatophyte isolation. Treatment is difficult, but some improvement might follow the use of keratolytic compounds such as salicylic acid. Nail infections seldom respond to terbinafine, griseofulvin, or azoles. Miscellaneous nail infections Occasionally, fungi other than dermatophytes or Neoscytalidium spe- cies are isolated from dystrophic nails. These include Scopulariopsis brevicaulis, Onychocola canadensis, acremonium, and fusarium species, and certain types of aspergillus. These infections are usu- ally seen in elderly or immunosuppressed individuals. It is often difficult, particularly with aspergillus, to establish that the organism is playing a pathogenic role. Pityriasis versicolor (tinea versicolor) Aetiology Pityriasis versicolor is a superficial infection caused by Malassezia species, usually M. globosa. Although most common in tropical countries, it has a worldwide distribution. Dermal penetration does not occur. There are six species of malassezia that can be found on normal skin, the commonest of which are M. sympodialis and M. globosa. In pityriasis versicolor there is transformation of yeast cells to pro- duce hyphae. It is likely that the state of host immunity plays some part in pathogenesis and depression; for instance, endogenous or exogenous corticosteroids potentiate the disease in some individ- uals. However, it is also commonly seen in normal individuals, and climatic factors or sun exposure are believed to trigger the infection in many cases. There is no effective animal model for studies of this disease. Epidemiology Pityriasis versicolor is very common in the tropics, where it might be widespread on the body. Its incidence in temperate climates has increased over the last 20–30 years. It is not more common in HIV- infected individuals. Clinical features The rash of pityriasis versicolor is asymptomatic or mildly pruritic. Its presents with scaling, confluent macules on the trunk, upper arms, or neck. These can be hypopigmented or hyperpigmented. In some people and in the tropics, other areas including face, forearms, and thighs might be involved. The diagnosis is rarely confused with other complaints, although eczema or ringworm infections are sometimes considered. Patients are often anxious to exclude leprosy, but the two are unlikely to be mistaken. In vitiligo, depigmentation is complete and there is no scaling. Laboratory diagnosis The diagnosis is made by demonstration of the yeasts

and hyphae of malassezia in skin scales removed by scraping. Culture is difficult and unnecessary. Treatment Topical ketoconazole, miconazole, clotrimazole, or econazole is ef- fective. Oral itraconazole can be used in recalcitrant cases. Whatever the treatment, relapse is common. Other malassezia-associated conditions Malassezia yeasts have been implicated in the pathogenesis of several other skin diseases such as seborrhoeic dermatitis and a form of itchy folliculitis, malassezia folliculitis. The evidence con- necting seborrhoeic dermatitis, one of the most common of skin diseases, and Malassezia is largely concerned with the response of antifungal drugs and the observation that improvements in the rash mirror disappearance of organisms from the skin as well as the production of fungal specific inflammatory mediators such as indolocarbazoles.

8.7.1 Fungal infections 1343 Superficial candidiasis Aetiology Superficial candidiasis is a term used to describe a group of in- fections of skin or mucous membranes caused by species of the genus Candida. They range in severity from oral thrush to chronic mucocutaneous candidiasis, a chronic infection refractory to con- ventional antifungal treatment. Candida albicans is the species most frequently involved. It is a saprophytic yeast often found as a commensal in the mouth and gastrointestinal tract, and is commonly present in the vagina. Several factors influence the incidence of carriage. For instance, oral colonization is more common in hospital staff than in equiva- lent nonhospital employees. Vaginal carriage is more common in pregnancy. Other factors (Box 8.7.1.1) are known that predispose to conversion from a commensal to a parasitic role with the causation of disease—candidosis. The list includes factors that influence host immunological response, such as carcinoma, AIDS, or cytotoxic therapy; those that disturb the population of other microorganisms, such as antibiotics; and those that affect the character of the epithe- lium, such as dentures. Other species of candida can also cause superficial infections, but are less common. They include C. glabrata, C. dubliniensis, and C. parapsilosis. There is evidence that the first two species are more common in oral infection in patients with HIV and C. glabrata in vaginal candidiasis. Epidemiology Superficial candida infections are seen in all countries. Clinical features There are several clinically distinct types of superficial infection caused by candida species, as follows. Oral candidiasis (thrush) Oral infection by candida is fairly common, particularly in infancy and old age, or in association with antibiotic or cytotoxic therapy, or in diseases where the neutrophil or T-lymphocyte responses may be impaired. In older people, the wearing of dentures is a predisposing factor. The lesions present with discomfort both in the mouth and at the corners of the lips. The mouth and buccal mucosa show patchy or confluent, white adherent plaques; less commonly the mucosa and tongue are sore and glazed—erythematous candidosis. Angular cheilitis usually accompanies the oral lesions. In long-standing cases, the plaque might become hypertrophic, with oedema of the mucosal surfaces, or the mucosa can appear glazed and raw. There is a significant correlation between leucoplakia and oral candidiasis, and it has been suggested that the infection might lead to epithelial dysplasia. The diagnosis is made by the demonstration of yeasts and hyphae of candida in smears, and by culture. Vaginal candidiasis (thrush) See Chapter 9.4 for further detail. Paronychia Infection around the nail fold is seen in people whose occupations involve frequent wetting of the hands (such as cooks) or in those with eczema or psoriasis. The aetiology is complicated and there might be a mixture of bacterial infection and irritant or allergic con- tact dermatitis as well as candida infection. The condition presents with painful, red swelling of the nail fold. Pus might be discharged. Secondary invasion of the lateral border of the nail plate by candida can occur from this site. Candida intertrigo Infection of the moist folds of the skin in the groin or under the breasts causes itching and discomfort. The area becomes macerated and erythematous. Candida might contribute to this condition, but is certainly not the only factor. It might also

superinfect the napkin area in infants. The presence of satellite pustules (see earlier) is a useful indicator of involvement by candida in the disease process. Direct invasion of toe-web folds by candida closely resembles ‘ath- lete’s foot’ caused by dermatophytes. A similar erosive infection can occur in the finger webs—interdigital candidiasis—and is seen most commonly in the tropics. Chronic superficial candidiasis Chronic candida infections of the mouth, vagina, and nail pre- sent problems in management. Chronic oral candidiasis, for in- stance, is associated with leucoplakia. Predisposing causes should be searched for. The most serious of this group of infections is chronic mucocutaneous candidiasis, a rare condition in which chronic skin, nail, and mucosal infection coexist (Fig. 8.7.1.5). A series of underlying genetic, endocrine (hypoparathyroidism, hypoadrenalism, or hypothyroidism), and immunological abnor- malities has been found; in some cases, it has been associated with mutations in the autoimmune regulator (AIRE) or STAT1 genes. Extensive human papillomavirus (wart) or dermatophyte infections might also be present in these patients, whose condition is normally diagnosed in childhood. Oral candidiasis is one of the earliest signs of untreated AIDS, occurring in a high proportion of patients. The appearances are similar to those seen with other groups, although plaque forma- tion might be very extensive. Oesophageal infection is common in this group. Box 8.7.1.1 Predisposing factors in superficial candidiasis • Local epithelial defects, occlusion, constant immersion in water (e.g. damaged nail folds, beneath dentures) • Defects of immunity (primarily T cell or phagocytosis) — Primary immunological disease (e.g. chronic granulomatous disease) — Immunodefects secondary to intercurrent illness (e.g. leukaemia) — Immunodefects secondary to therapy (e.g. cytotoxic therapy in organ transplantation) • Drug therapy (e.g. antibiotics) • Carcinoma or leukaemia • Endocrine disease — Diabetes mellitus — Hypothyroidism, hypoparathyroidism, hypoadrenalism (all in chronic mucocutaneous candidiasis) • Physiological changes (e.g. infancy, pregnancy, old age) • Miscellaneous disorders, for example: — Iron deficiency — Zinc deficiency — Malabsorption

 Laboratory diagnosis All these infections are diagnosed by microscopy and culture. When associated with the condition, candida cells are always evident on microscopy. Culture establishes the specific identity and is important particularly where species other than C. albicans might be involved. Treatment Two groups of drugs are effective in superficial candidiasis. The polyenes such as nystatin and amphotericin B are topically active in many forms of candidiasis. They are often less effective in oral can- didiasis in immunodeficient patients, including those with AIDS. Likewise, topical azole drugs such as miconazole and clotrimazole are usually effective in superficial candidiasis. For unresponsive cases, oral therapy with fluconazole and itraconazole might be ne- cessary. Fluconazole resistance can occur and C. glabrata is seldom responsive to this drug. For vaginal infections, topical creams or vaginal preparations should be used—many requiring only a single treatment. Single- dose oral fluconazole is an alternative. In recalcitrant cases it might be necessary to use longer courses of fluconazole or itraconazole. Miscellaneous superficial mycoses There are several relatively rare, superficial fungal infections such as tinea nigra, and black or white piedra. They never cause invasive disease, and are mainly confined to the tropics. Tinea nigra Tinea nigra is a superficial infection confined to the epidermis of the palms or soles, and more rarely elsewhere. The initial lesion is a dark macule without scaling, which resembles a brown stain on the skin and spreads slowly over the palmar or plantar surface. The disease is normally asymptomatic. On scraping the skin, brown pigmented hyphae can be seen by direct microscopy, and the causative organism, Phaeoanellomyces werneckii, isolated. The lesion responds to Whitfield’s ointment. Black piedra Black piedra is a disease of the tropics in which small, dark nodules form on hair shafts in the scalp or, less commonly, elsewhere. There are

no symptoms. Each nodule consists of a dense mat of hyphae containing the sexual spores (ascospores) of the fungus. The diagnosis is made by direct microscopy of infected hair, and the isolation of Piedraia hortae. Treatment using a 1% azole solution or amphotericin B lotion is usually effective. White piedra White piedra occurs in both temperate and tropical climates, and is rare. It produces pale nodules on the hair of the beard, groin, or scalp. The hair shaft may fracture. The nodule consists of hyphae, arthrospores (spores formed by fragmentation of hyphae), and blastospores (budding yeast cells). The organism Trichosporon spe- cies can be readily cultured. The treatment is similar to that for black piedra. Subcutaneous mycoses Subcutaneous infections caused by fungi are rare, and are mainly seen in the tropics. The organisms gain entry via the skin; in my- cetoma, organisms may be implanted subcutaneously via a thorn. Most of the causative organisms in this group of infections can be isolated from vegetation or soil. Involvement of deep viscera is rare. Attempts to establish experimental infections that resemble the human diseases have been largely unsuccessful. A clearer under- standing of the pathogenesis therefore awaits such a model system. These infections tend to be chronic, chemotherapy might be lengthy, and in the case of mycetoma, often unsuccessful. Mycetoma (Madura foot) Aetiology Mycetoma is a chronic infection involving subcutaneous tissue, bone, and skin, in which colonies of infecting fungi or actinomy- cetes (grains) are found within a network of burrowing abscesses and sinuses (Fig. 8.7.1.6). The more common organisms that cause mycetoma are listed in Box 8.7.1.2. The organisms are divided into two groups, the actinomycetomas and the eumycetomas, caused by actinomycetes and fungi, respectively. The size and colour of the grains (red, pale, Fig. 8.7.1.5 Oral candidiasis in a patient with chronic mucocutaneous candidiasis. Fig. 8.7.1.6 Grains in abscess in actinomycetoma (Nocardia brasilensis) (haematoxylin and eosin stain).

 or dark) are important clues to their identification. The organisms can be found in the natural environment such as soil, and some have even been identified in association with acacia thorns in an endemic area. The infection is initiated when an infected thorn is implanted in deep tissue. However, many years might elapse before the forma- tion of a clinically apparent mycetoma. Epidemiology The disease is seen primarily in the tropics, although rare cases, apart from imported ones, can occur in temperate areas. Countries with the most reported cases include India, Mexico, Senegal, Sudan, and Venezuela. However, the disease is widely distributed in the tropics, particularly in Africa to the south and east of the Sahara Desert. The pattern of prevalence of infections caused by certain or- ganisms differs strikingly in different parts of the world. For in- stance, Streptomyces somaliensis is most common in the Sudan and Middle East, but Madurella grisea is mainly found in the New World. Altogether about 60% of reported infections are caused by actinomycetes, of which Nocardia brasiliensis is the most common (Chapter 8.6.31). Clinical features Early mycetomas might present with a circumscribed area of hard painless subcutaneous swelling (Fig. 8.7.1.7). Later, sinus tracts open on to the skin surface and visible grains might be discharged, along with serosanguinous fluid (Fig. 8.7.1.8). Bone erosion and de- struction, leading to deformity, can occur. However, severe pain is rarely a problem. Local lymph node invasion can occur, but more widespread involvement is very rare. Feet and lower legs are the areas most commonly involved, but the arms, buttocks, chest, and head can all be sites of infection. Mycetoma caused by N. brasiliensis can occur in any site, but one favoured area is the chest wall. The radiological features of mycetoma are cortical erosion, fol- lowed by the development of lytic deposits in bone. Periosteal pro- liferation and destruction, leading to deformity, may follow. MRI provides a clearer picture of bone involvement and might be positive earlier than radiography. Laboratory diagnosis The diagnosis is made by the demonstration and

identification of grains obtained from the sinus openings by gentle pressure or curettage. If these measures are not successful, tissue should be obtained by deep surgical biopsy. Grains can be mounted in potas- sium hydroxide and examined microscopically. Those containing filaments 3–4 μm or more in diameter are caused by true fungi (eumycetomas), and those with filaments of less than 1 μm by ac- tinomycetes (actinomycetomas). These features can usually be dis- tinguished by direct microscopy. The morphology of grains fixed, sectioned, and stained with haematoxylin and eosin is typical. Special stains are less helpful. Grains can be used for culture, although several attempts at isolation may have to be made. Serology (such as immunodiffusion) can also be helpful, although the tests are not widely available. Treatment Actinomycetomas might respond to sulphones such as dapsone (50– 100 mg daily) or sulphonamides such as sulphadiazine. The treatment of choice for many is long-term co-trimoxazole (2–3 tablets twice daily) with an initial 2 to 3 months of streptomycin or rifampicin. Treatment might have to be continued for many months or years. Dapsone is an effective and cheaper alternative to co-trimoxazole. Extensive actinomycetomas might respond poorly and additional treatment with amikacin, moxifloxacin, or linezolid might be ne- cessary. The eumycetomas seldom respond to antifungal therapy. But in some infections griseofulvin, amphotericin B, voriconazole, ketoconazole, and itraconazole have rarely produced remission or Box 8.7.1.2 Causes of mycetoma • Fungi, for example: — Madurella mycetomatis, M fahalii, M. pseudomycetomatis — Madurella grisea — Scedosporium apiospermum — Exophiala jeanselmei — Plenodomus senegalensis — Species of Acremonium, Aspergillus, Fusarium • Actinomycetes, for example: — Nocardia brasiliensis — Actinomadura madurae — Actinomadura pelletieri — Streptomyces somaliensis Fig. 8.7.1.7 A mycetoma caused by Madurella grisea. Fig. 8.7.1.8 Nocardia brasiliensis actinomycetoma draining sinus.

 cure. A trial of therapy can be attempted, where the patient can be monitored closely in outpatient departments. Otherwise, radical surgery or amputation is usually necessary. Small, local excisions are rarely successful. Mycetoma is slowly progressive and increasingly disabling. However, wider dissemination is very rare, and therefore cases are seldom fatal, except where the skull is involved. However, the de- formity caused by the disease can be severely disabling. Chromoblastomycosis (chromomycosis) Aetiology Chromoblastomycosis, one of the intermediate subcutaneous my- coses, is a chronic granulomatous fungal infection characterized histologically by the presence of brown, spherical fungal cells known as sclerotic cells or fumagoid bodies. In most cases, the lesions are confined to the skin and subcutaneous tissues. In the past there has been great confusion over nomenclature of the aetiological agents of chromoblastomycosis. At present, five agents assigned to four genera are recognized as causing chromoblastomycosis—most are due to the first two. They are: • Fonsecaea pedrosoi, which occurs in high-rainfall areas and is found worldwide • Cladophialophora carrionii, the sole cause of chromoblastomycosis in arid areas • Phialophora verrucosa, the first agent to be described • Fonsecaea compactum, an uncommon cause and isolated only a few times • Rhinocladiella aquaspersa, a rare cause Sporadic cases caused by other dematiaceous fungi such as Cladosporium trichoides and Taeniolella boppii have been reported from Uganda and Brazil. Epidemiology The principal endemic areas for chromoblastomycosis are tropical and subtropical countries including Central and South America, Costa Rica, Africa, Japan, Australia, Madagascar, and Indonesia. Curiously, sporadic cases have been reported from Finland and Russia. Although soil itself does not seem to be a particularly good sub- strate, the various agents of chromoblastomycosis occur as saprobic fungi in the environment and have been isolated from soil, decaying vegetation, and rotting wood. Strains of F. pedrosoi and P. verrucosa have been isolated

from the atmosphere but proved less virulent than those isolated from human lesions or organic material. Infection occurs as a result of trauma, however minor, the fungi gaining entrance through a cut, abrasion, or thorn prick. Farmers and labourers in agricultural areas are most likely to be exposed to contaminated material. Although lesions on exposed areas might be accounted for in this way, it was suggested by Wilson in 1958 that lesions on nonexposed areas might result from a previously unrec- ognized pulmonary focus. Bacquero later demonstrated the pres- ence of F. pedrosoi in bronchial washings and subsequently proved their pathogenicity by inoculating those strains into normal skin of human volunteers and recovering the fungus from the ensuing skin lesions. Other methods of transmission have included metal particles from automobiles, and acupuncture. Person-to-person and animal-to-human transmission have not so far been reported. Chromoblastomycosis has rarely been reported in children, and it might be that factors other than trauma and exposure to contamin- ated material are necessary for its development. Pathogenesis Host resistance and virulence of the organism are the two main factors associated with the pathogenesis of this disease. Chromoblastomycosis occurs mainly in healthy individuals. However, it has been found in immunosuppressed patients. Although the mechanism of granuloma formation is not well under- stood, it appears that lipids extracted from these fungi and cell-wall constituents might be responsible for this reaction. Clinical features The initial lesion of chromoblastomycosis is a small papule at the site of trauma, which gradually enlarges (Fig. 8.7.1.9). Nodules and tumours develop, producing a malodorous discharge; eventu- ally, over a period of years, a wide variety of morphological patterns may emerge including dry, hyperkeratotic plaques, verrucose le- sions, and large, cauliflower-like masses (Fig. 8.7.1.10). Extensive cicatricial plaques, surrounded by peripherally spreading vegetative lesions, can also be present. Evolution is slow, and lesions usually in- volve the lower limb. However, any part of the body can be involved and the sites can be multiple. Dissemination occurs by (1) surface spread; (2) the lymphatics, the most common method; (iii) autoinoculation from scratching; and (iv) haematogenously, resulting in subcutaneous lesions at sites distant from the primary. Visceral metastases are known to occur and involvement of the central nervous system, respiratory system, larynx, and vocal folds has been recorded. Therapeutically, there- fore, early diagnosis is important. Fig. 8.7.1.9 Chromoblastomycosis. Early lesion in a Brazilian patient. Copyright D. A. Warrell.

 Complications of long-standing chromoblastomycosis include lymphoedema, flexion deformity of joints, and development of squamous carcinoma. Diagnosis Although the history and clinical presentation might suggest the diagnosis, the varied clinical presentation of chromoblastomycosis necessitates consideration of other granulomatous diseases such as sporotrichosis, cutaneous tuberculosis, Hansen’s disease, blasto- mycosis, candidiasis, leishmaniasis, paracoccidioidomycosis, rhinosporidiosis, tertiary syphilis, squamous carcinoma, and even psoriasis, sarcoidosis, and discoid lupus erythematosus. Therefore, to establish a definitive diagnosis, histological and myco- logical investigations are essential. Diagnosis is confirmed by the presence of the characteristic brown, sclerotic bodies in histological sections. From both epidemiological and therapeutic points of view, culture is necessary as F. pedrosoi is the most difficult of the causative fungi to eradicate whereas C. carrionii responds rapidly to treatment. Treatment Small, single, localized lesions are satisfactorily eradicated by cryo- surgery, but long-term follow-up is needed to assess accurately the success of this treatment. Thermotherapy has been found effective by some, again principally in the management of small, single le- sions, but here the possibility of a burn must be borne in mind. Rapid spread of the disease has been associated with inadequate sur- gery, curettage, and electrodesiccation. Itraconazole and

terbinafine have both been reported as effective agents. A combination of 5-flucytosine with either thiabendazole or itraconazole can also be efficacious, particularly in long-standing disease. Whatever method of treatment is used, chromomycosis although clinically healed, should be followed-up for at least 2 years before its total eradication can be assumed. Sporotrichosis Aetiology The most common clinical form of sporotrichosis is a subcutaneous infection, which can spread proximally from its initial site in a series of nodules along the course of a lymphatic (Fig. 8.7.1.11a, b). More rarely, systemic involvement is seen, for example, in the lung (see ‘Systemic mycoses’, next). The causative organism, Sporothrix schenckii, which is a complex of closely related species such as S. braziliensis, S. mexicana can be found in soil, in vegetation, or in association with plants or bark. People who develop the subcutaneous infection might have had contact with material that harbours the organism, such as moss or flowers (e.g. florists). It is assumed that the pathogen gains entry via an abrasion and in some endemic areas there is often a preceding history of a cat scratch or insect bite. Epidemiology Although sporotrichosis was once prevalent in Europe, particularly France, nonimported cases are now very rare in this area. However, the disease is seen in the United States of America, Mexico, Central and South America, and Africa. In the late 1930s, there was a remark- able epidemic of sporotrichosis in workers in the Witwatersrand gold mines (South Africa). The source of infection was a large number of wooden pit props contaminated with the organism. Other, smaller Fig. 8.7.1.10 Chromoblastomycosis: late lesion. Courtesy of João LC Cardoso, São Paulo, Brazil. (a) (b) Fig. 8.7.1.11 (a) Sporotrichosis. (b) Histopathological appearances. (a) Courtesy of João LC Cardoso, São Paulo, Brazil; (b) copyright Professor R. Hay.

 ‘epidemics’ have been described in certain groups, such as Mexican pottery workers packing ceramics in straw. Normally, however, cases are sporadic in incidence. There are also ‘hyperendemic’ areas where there is an unexpectedly high incidence of this infection (e.g. Rio de Janeiro State, Brazil). Systemic sporotrichosis is much rarer, and cases have mainly been described from the United States. Clinical features There are two main clinical types of subcutaneous sporotrichosis. The first, the fixed type, presents with a solitary cutaneous ulcer or nodule. In this form of the disease, infection does not spread along lymphatics. It has been suggested that it is most common in children, and it has been described most frequently in Central and South America. In the lymphangitic form, an initial nodule forms on a limb or extremity, such as a finger. This may break down and ulcerate. Subsequently, one or more secondary nodules develop along the draining lymphatic channel, which may ulcerate through the skin (Fig. 8.7.1.11a). Other variants include the psoriasiform or verru- cous types or a superficial granuloma that resembles lupus vulgaris. These usually represent chronic infection. Rarer forms include secondary spread via scratching, which might present with multiple widespread ulcers or multiple cutaneous le- sions secondary to systemic disease. In HIV-positive individuals, widespread cutaneous lesions can develop. Fixed-type sporotrichosis can resemble many other forms of cuta- neous ulceration. However, in endemic areas a major source of con- fusion is cutaneous leishmaniasis. The lymphangitic variety can also resemble other infections, notably atypical mycobacterial infections, particularly fish-tank granuloma, or ‘sporotrichoid’ leishmaniasis. Treatment Some cases of sporotrichosis heal spontaneously. However, treat- ment is usually advised to prevent scar formation. The cheapest treatment is potassium iodide, which is administered in a satur- ated aqueous solution. The starting dose is 0.5–1 ml, given three times daily, and this is increased drop by drop per dose to 3–6 ml, three times daily. The mixture is more palatable if given with milk. Treatment should be given for a month after clinical resolution.

However, both itraconazole and terbinafine are also effective; min- imal durations of treatment for these agents have not been defined. Subcutaneous mucoromycosis due to Basidiobolus Subcutaneous mucoromycosis is an infection primarily seen in chil- dren in Africa or eastern Asia (Indonesia). It is characterized by the development of localized woody swellings on the limbs or trunk. The swelling is rarely inflammatory, but has a well-defined leading edge, and is hard. Progression is slow. The causative organism, Basidiobolus haptosporus, can be cultured or demonstrated histologically in biopsy material. Although resolution has been recorded without treatment, therapy is normally given. Potassium iodide solution is the treatment of choice, and is given in as high a dose as possible (see ‘Sporotrichosis’, earlier). Itraconazole might also be effective. Subcutaneous mucoromycosis due to Conidiobolus (conidiobolomycosis or rhinoentomophthoromycosis) Conidiobolomycosis is a similar infection confined to subcutaneous tissue and presenting with painless swelling. The infection is mainly seen in West Africa, but a case has been seen in the Caribbean. There are important differences from the subcutaneous mucoromycosis caused by basidiobolus. The disease is most common in young adults, and is confined to facial tissues around the nose, the forehead, and the upper lip (Fig. 8.7.1.12). The initial site of infection is in the region of the inferior turbinate in the nose. The diagnosis is estab- lished by biopsy or culture. The causative organism is Conidiobolus coronatus. Treatment with itraconazole or ketoconazole is effective, but an alternative is high-dose potassium iodide. Relapse after treat- ment is common, and residual fibrosis can be severely disfiguring. Lobo’s disease (lobomycosis) Lobo’s disease is a subcutaneous infection. The organism, Lacazia loboi, in tissue, appears to be a yeast. It has a tendency to form chains of four to six yeast cells with prominent nucleoli, joined by a narrow intercellular bridge. However, the organism has never been cultured from human cases and can only be identified by biopsy and hist- ology. The disease is seen in countries of South America around and to the north of the Amazon basin, and cases are also seen in Central America. Apart from humans, the only other species affected are freshwater dolphins. Often, exposed sites (such as earlobes) are in- vaded and small nodules containing the organisms develop. These may resemble keloids (Fig. 8.7.1.13). More diffuse plaques may also be seen. Deep invasion has not been documented. The treatment is excision, and there is no effective chemotherapy, although there have been recent reports that posaconazole might be effective. Systemic mycoses The systemic or deep visceral mycoses include some of the rare and more serious fungal infections. There are two main types of infection Fig. 8.7.1.12 Subcutaneous mucoromycosis (Conidiobolus coronatus). Copyright Professor R. Hay.

 in this group: (1) the endemic mycoses, caused by organisms that in- vade normal hosts, and (2) the opportunistic mycoses, which cause disease only in compromised patients. The fungi associated with these two types of infection differ in their innate levels of pathogen- icity, but an element of opportunism, depending on host suscepti- bility, is usually recognizable in all cases of systemic mycoses. The endemic pathogens cause infections such as histoplasmosis or coccidioidomycosis. These diseases have well-defined endemic zones and most of those exposed remain symptomless but usually develop positive skin tests. However, in certain patients, chronic local or disseminated disease can occur. In the systemic infections caused by opportunistic fungi, there is usually a serious underlying abnormality in the patient affecting T lymphocytes (such as HIV) or neutrophils (such as cancer chemotherapy). Such infections are worldwide in occurrence: where tissue invasion occurs, the mor- tality is high. Cryptococcosis, a systemic yeast infection, has features of both types of systemic disease and occurs in both normal and immunosuppressed subjects (Chapter 8.7.2). The systemic endemic infections are

histoplasmosis, coccidioido- mycosis (Chapter 8.7.3), blastomycosis, paracoccidioidomycosis (Chapter 8.7.4), and infections due to Talaromyces marneffei (Chapter 8.7.6). The significance of various laboratory tests in these infections is shown in Table 8.7.1.1. Histoplasmosis There are two forms of histoplasmosis. In both types, the organism is present in tissue in its yeast phase. In small-form or classic histo- plasmosis, the diameter of the yeast cells is between 3 and 4 µm. Infections are most common in the United States of America, but sporadic cases are reported widely from the New World, Africa, and eastern Asia. By contrast, large-form or African histoplasmosis is most common in Central Africa, south of the Sahara, and north of the Zambezi River. Yeast forms in infected tissue are much larger, 10–15 µm in diameter. Both infections are clinically distinct (see next), but cultural isolates are indistinguishable. Histoplasmosis (classic or small-form histoplasmosis) Aetiology Histoplasmosis is a systemic infection caused by Histoplasma capsu latum. The main route of infection is pulmonary. Most of those ex- posed are sensitized without overt signs of infection, but more rarely chronic pulmonary or disseminated forms of the disease are seen. Table 8.7.1.1 Laboratory tests in systemic mycosesa Direct microscopy Significance of positive cultures Serology Histopathology Histoplasmosis Classic (small form) Sometimes positive Significant ID, CIE, CFT Urine antigen detection Yeasts (3–4 µm) African histoplasmosis Positive in pus (valuable) Significant ID, CFT Yeasts (10–15 µm) Coccidioidomycosis Positive in pus, sputum, etc. (valuable) Significant, NB Handle with caution ID, CFT, TP, CIE Spherules (50–150 µm) Blastomycosis Positive in pus, sputum, etc. (valuable) Significant ID, CFT, CIE (unreliable) Yeasts (4–10 µm) Broad- based buds Paracoccidioidomycosis Positive in pus, sputum etc. (valuable) Significant ID, CFT, TP Antigen detection Yeasts (5–15 µm) Multiple buds Cryptococcosis Often positive in CSF (rare in urine, pus), NB Indian ink Significant Latex agglutination or ELISA for antigen (ID, CFT, WCA, IF) Encapsulated yeasts (5–10 µm) Mucicarmine positive Systemic candidiasis Positive in oral smzears, sputum, etc. (interpret with caution) Significance depends on site
and presence of positive microscopy ID, CFT, WCA, CIE Antigen detection Yeasts (5–10 µm) and hyphae Invasive aspergillosis Rarely positive, depends on site Positive sputum cultures not always significant ID, CIE, rarely positive Antigen detection, e.g. Pasteurex Hyphae—dichotomous branching Mucormycosis Rarely positive Depends on site Rarely positive Hyphae—broad and aseptate CFT, complement fixation test; CIE, counterimmunoelectrophoresis; CSF, cerebrospinal fluid; ID, immunodiffusion; IF, immunofluorescence; RIA, radioimmunoassay; TP, tube precipitation; WCA, whole-cell agglutination. a Molecular diagnostic techniques are increasingly used but are not standardized. Fig. 8.7.1.13 Lobo’s disease in a Brazilian man. Copyright D. A. Warrell.

 The organism, H. capsulatum, can be found in soil in endemic areas. Its growth is facilitated by the presence of bird excreta (e.g. in old chicken houses, bird roosts, and barns). In tropical and some temperate areas, bat guano plays a similar role. Exposure to a suitable source, such as a cave containing bats, is often recorded in acute epidemic histoplasmosis (see next). It is rarely identified in more slowly evolving cases. The condition of the host is important in determining the clin- ical course and manifestations of histoplasmosis. Slowly evolving (chronic), disseminated disease can occur in normal individuals. However, infants, elderly people, or those with untreated AIDS ap- pear to be more likely to develop the more rapidly progressive forms of disseminated infection. Epidemiology The major endemic area, as shown by skin testing, is in the central region of the United States around the Ohio and Mississippi valley basins. Prevalence is highest in the states of Tennessee, Kentucky, and Ohio. Up to 95% of those skin-tested in certain parts of these areas have positive delayed reactions to intradermal

histoplasmin. Scattered cases of active disease, healed calcified foci in chest radiographs, and foci found at autopsy representing inactive histoplasmosis also pro- vide evidence of spread within this area. However, the disease also oc- curs in other parts of the United States, Mexico, Central and South America, Africa, eastern Asia, and Australia. Outside the major en- demic areas in the United States, human cases are less frequent, and much of the evidence of the endemicity comes from positive skin tests or the presence of the organism in selected sites, such as caves. Although there has been considerable discussion on the nature of soil factors responsible for the growth of H. capsulatum, the conditions limiting its occurrence to certain areas are largely unknown. Clinical features The clinical forms of histoplasmosis can be placed in several groups: • asymptomatic • acute symptomatic pulmonary: ■ acute epidemic ■ acute reinfection • chronic pulmonary • disseminated (acute, subacute, and chronic) • primary cutaneous (by inoculation) Asymptomatic infection Over 99% of patients becoming infected in endemic areas record no overt symptoms but develop a positive skin test. The incidence of positive skin tests declines in individuals above the age of 60 years. Acute (symptomatic) pulmonary histoplasmosis Acute epidemic histoplasmosis Groups of people exposed to a source of infection (e.g. during cave exploration, or those who might have inhaled a large infecting dose, often develop a symptomatic illness 12–21 days after exposure). The main features are pyrexia, cough, chest pain, and malaise. Flitting arthralgia and, less commonly, erythema nodosum or multiforme may occur. The radiological appearances might be much more se- vere than would be supposed from the symptoms, and enlargement of hilar lymph nodes and diffuse or patchy consolidation suggesting pneumonitis can occur (Fig. 8.7.1.14). These patients develop precipitating or complement-fixing anti- body, but this often follows the peak of illness. About 50% of those with symptoms do not develop positive antibody responses. Likewise, skin-test conversion is often too late to be of diagnostic value, and its use is normally contraindicated, as a single histoplasmin test might cause the development of false-positive serological results. Cultures are often negative. The symptoms and history of exposure to a suit- able source, combined with a rising antibody titre, are often the best evidence of infection. Most cases require no specific therapy apart from rest. Those with severe or prolonged symptoms or impaired gas exchange require intravenous amphotericin B or itraconazole. The lung lesions often heal to leave multiple scattered pulmonary calcifications. Acute reinfection histoplasmosis Massive acute exposure to H. capsulatum in sensitized individ- uals is believed by some physicians to cause a less severe infection associated with bilateral pulmonary infiltrates. The incubation period is shorter than with acute epidemic histoplasmosis, namely 5–10 days. Chronic pulmonary histoplasmosis Chronic pulmonary disease caused by H. capsulatum is mainly seen in the United States. It is more common in men and smokers, and there is often underlying pulmonary disease such as emphysema. Early cases might present with pyrexia and cough, but malaise and weight loss occur later. Lesions might heal initially, but relapse is common, leading to established consolidation and cavitation. The most common radiological appearance of early lesions is of uni- lateral, wedge-shaped, segmental shadows in the apical zones. Subsequently, the disease can become bilateral, with fibrosis and cavitation. In some cases, extensive and progressive destruction of lung tissue may occur. Fig. 8.7.1.14 Acute pulmonary histoplasmosis. Copyright Professor R. Hay.

 Culture and serology are both helpful methods of diagnosis in this form of histoplasmosis, but repeated attempts might be required be- fore positive results are obtained. In early cases, resolution might occur with rest alone. However, relapse occurs in at least 25% of cases, and these patients might re- quire amphotericin B therapy or itraconazole. Although chemo- therapy might virtually sterilize lesions, fibrosis persists, and relapse can occur. Surgical

excision or lobectomy is sometimes effective. Solid lung tumours might persist after the primary infection. These can be single (coin lesions) or multiple, and have to be distin- guished from carcinomas. The diagnosis is normally made at sur- gery, although the presence of calcification might give a clue to the nature of the lesion (histoplasmoma). The organisms can be demon- strated by histopathology, but they are seldom viable. Disseminated histoplasmosis There is considerable variation in the rate of progression of histo- plasmosis that has spread beyond the initial focus in the lung. In rapid or acutely disseminated cases, widespread infiltration of re- ticuloendothelial cells of bone marrow, spleen, and liver might occur. Gastrointestinal lesions, endocarditis, and meningitis are less common, and meningitis is more usually associated with a slower course of disseminated disease. Infants, elderly people, or immuno- suppressed patients are more susceptible to acute dissemination. The most prominent symptoms are fever and weight loss, with ac- companying hepatosplenomegaly. Extensive purpura and bruising secondary to thrombocytopenia can occur. The blood picture can reflect marrow infiltration with organisms, leading to pancytopenia. Disseminated histoplasmosis is also seen in patients with AIDS. The clinical manifestations are not significantly different, although skin papules and ulcers have been reported in many (Fig. 8.7.1.15); isolation of histoplasma from blood has also been reported more frequently in these patients. Cultures, including sputum or bone marrow, should be taken. Serology is often positive, with high titres of complement-fixing antibodies occurring in some patients. However, new antigen detection systems in serum or urine provide a better means of confirming the diagnosis and monitoring treatment. A much more slowly progressive form of disseminated histoplas- mosis can present with fewer localized lesions, such as persistent oral ulcers, chronic laryngitis, or adrenal insufficiency. Granulomas, few of which contain organisms, can be found in the liver in some patients. Such cases present up to 30 years after the patient has left an endemic area. Outside endemic areas this form is the most widely recognized presentation of histoplasmosis, occurring in Europeans, for instance, who have worked in Africa or eastern Asia. The diagnosis of disseminated histoplasmosis is made on culture or biopsy of affected areas. Antibodies might only be positive in low titres and in all cases adrenal involvement should be looked for. Treatment is required in all forms of disseminated histoplasmosis. Itraconazole is preferred by most physicians, although amphotericin B might be necessary in some patients. Posaconazole is an alterna- tive. In patients with AIDS who are acutely ill, the disease is often controlled by a short (2-week) course of amphotericin B and there- after patients receive continuous itraconazole indefinitely or until their immune system improves with antiretrovirals. Primary cutaneous histoplasmosis Primary infection sometimes follows accidental inoculation of vi- able organisms in a laboratory or autopsy room. This type of infec- tion is normally associated with a chancre at the site of inoculation and regional lymphadenopathy. The condition is self-limiting. African histoplasmosis Overt pulmonary involvement is rare in this form of histoplasmosis, and the normal portal of entry of the pathogen is not known. The most common presenting features are skin lesions (papules, nodules, abscesses, or ulcers) (Fig. 8.7.1.16) or lytic bone deposits. Solitary or Fig. 8.7.1.16 Nodular subcutaneous lesions of African histoplasmosis in a Nigerian man. Copyright D. A. Warrell. Fig. 8.7.1.15 Histoplasmosis. Molluscum-like skin lesions in an HIV- positive Peruvian patient. Copyright D. A. Warrell.

section 8 Infectious diseases 1352 multiple foci may be present, and in the latter instances rapid pro- gression and death may occur. In such cases, gastrointestinal and lung lesions may develop. The diagnosis is normally made by culture, smear, or biopsy. The organism H. capsulatum var. duboisii is identical to that causing classic histoplasmosis in culture, but in lesions the yeast forms

are considerably larger (10–15 μm). Although local excision of skin nodules has been reported to be curative, treatment with itraconazole, ketoconazole, or amphotericin B is usual. Some patients will respond to co-trimoxazole. A skeletal scan should be made to detect occult foci of infection. Blastomycosis (See also Section 23.) Blastomycosis (North American blastomycosis) caused by Blastomyces dermatitidis is a systemic fungal infection in which skin and lung involvement are common features. The infective organism, B. dermatitidis, has only been isolated from the environment on rare occasions. Positive sites have included soil and rotten timbers. The organism infects humans and domestic animals, particularly dogs. Epidemiology Blastomycosis was originally thought to be confined to North America, where it occurs sporadically throughout the south and east-central area, and in areas of central Canada. 'Epidemics' of acute disease are rare, and where these occur a source of infection is rarely demonstrated. There is evidence that sources might include areas exposed to flooding. More recently, cases have been found in Africa. Again, these are widely scattered from the north coast to the southern parts of the continent, and are rare in all areas. Patients with the disease have also been reported from the Middle East and central Europe. Clinical features The clinical forms of blastomycosis differ from histoplasmosis in sev- eral important aspects. The existence of an asymptomatic form has not been proved conclusively, because there is no reliable skin test. Acute infections or infections in groups are rare, and the features are often similar to histoplasmosis (acute pulmonary). However, specific serological tests might be negative in 30–50% of cases. The demon- stration of the organisms in sputum and positive cultures are more reliable diagnostic criteria. Although some cases undoubtedly re- solve without sequelae, some physicians advise chemotherapy, with a short course of amphotericin B in acute cases of blastomycosis. Chronic pulmonary blastomycosis Chronic consolidation or cavitation of the upper or mid zones occur with chronic pulmonary infections. Fever, malaise, and cough with sputum are seen. Weight loss might be prominent. Culture is again the most reliable method of diagnosis. The mainstays of treatment are itraconazole or amphotericin B. Disseminated blastomycosis Although generalized infiltration in skin, lungs, and liver can occur over a short period, leading to rapid death, signs of chronic extrapulmonary dissemination are more usual. The skin is an area that is frequently involved (chronic cutaneous blastomycosis). The face or forearms and hands are common sites for skin lesions. These are slow, spreading, verrucose plaques with central scarring. The initial lesion is often a dermal nodule. Many such cases have underlying pulmonary consolidation, or cavities. The diagnosis is established by biopsy and culture. Bone deposits in the form of lytic lesions, and involvement of the genitourinary tract, particularly the epididymis, are also seen in chronic disseminated blastomycosis. Unlike tuberculosis, the kidneys are usually spared. In slowly progressive forms of blastomycosis, itraconazole (200–400 mg daily) has proved to be very effective. Alternatively, amphotericin B can be given intravenously and is indicated where there is rapidly progressive disease. Coccidioidomycosis See Chapter 8.7.3. Paracoccidioidomycosis See Chapter 8.7.4. Systemic sporotrichosis In addition to causing cutaneous disease, Sporothrix schenckii may be responsible for a systemic mycosis. The infection is rare and has been mainly reported from the United States of America. Involvement might be confined to a single site such as a lung or a joint, or it might be multifocal. Cavitation in the lung associated with weight loss and pyrexia is probably the most common variety of systemic sporotrichosis. Unlike cutaneous forms of the disease, systemic sporotrichosis responds poorly to potassium iodide, and amphotericin B is the treatment of choice. Rare systemic infections These include pulmonary invasion by Geotrichum candidum (geotrichosis) and adiaspiromycosis, a respiratory infection caused by Emmonsia crescens or E. parva. Isolated examples of human disease caused by fungi are consistently reported and almost always occur in the

immunosuppressed host. In these patients many fungi that are nor- mally saprophytes in the environment invade and cause disease. Systemic mycoses caused by opportunistic fungi The opportunistic mycoses are a worldwide problem, although fortunately rare in most countries. In recent years they have been recognized more frequently with the increase in transplant- ations of organs such as heart or bone marrow and in the more effective but immunocompromising regimes of cancer chemo- therapy. Opportunistic invasion by organisms such as candida or mucoromycetes (rhizopus, absidia) may also occur in cases of mal- nutrition. One of the recent trends in the management of the pa- tients with neutropenia has been the emergence of new pathogens such as non-albicans species of Candida or other organisms such as fusarium, trichosporon, or scedosporium species. The opportunists present particular problems in diagnosis and management. Because many of the organisms are normally sapro- phytic, it has to be positively established that they have assumed an invasive role. Mere isolation might not provide sufficient evidence and in some instances low titres of antibody can be present even in normal hosts. The significance of various laboratory tests in these

8.7.1 Fungal infections 1353 infections is shown in Table 8.7.1.1. Treatment is also difficult and it is important in most cases to attempt to reverse the process that led to the establishment of the infection. Systemic candidiasis Aetiology In addition to their role in superficial infections, candida yeasts can also cause invasive systemic disease. The clinical forms described range from bloodstream isolation or candidaemia to disseminated invasive disease, sometimes with involvement of a single organ, site, or body cavity (deep focal candidiasis) as can occur in peritonitis or meningitis. Urinary tract infections can also be caused by candida species. The factors underlying systemic candida infections are shown in Box 8.7.1.3. All these factors are important in disrupting the balance by which candida is maintained as a saprophyte. Intravenous or central venous pressure lines can serve as a portal of entry or as a nidus for circulating yeasts in a candidaemia. Antibiotic therapy might upset the balance by inhibiting a potentially competitive bacterial flora. Candida albicans is the most common species involved but other species might be isolated, particularly in cases of endocarditis (e.g. C. parapsilosis). C. tropicalis has been implicated in infections of pa- tients with neutropenia. These non-albicans Candida species are now more frequent causes of systemic infection and are important to recognize as their antifungal susceptibility can differ from that of C. albicans. Portals of entry include the gastrointestinal tract (common), skin, and urinary tract (rare). However, superficial candidosis or saprophytic colonization of mouth, skin, or airways can also occur in compromised patients and does not necessarily indicate systemic invasion. Epidemiology Systemic infections caused by candida species are worldwide in distribution. However, they are particularly associated with sev- eral predisposing factors such as neutropenia, antibiotic usage, indwelling lines, and abdominal surgery. Clinical features Candidaemia The isolation of candida in blood culture may be linked to any of the factors listed in Box 8.7.1.3. Common predisposing features are the presence of intravenous lines, previous surgery (mainly gastrointes- tinal), antibiotic therapy, hepatic failure, or neutropenia. Patients develop a swinging fever and feel generally unwell. Clinical shock might occur. Some such cases resolve following removal of predisposing fac- tors, particularly the intravenous lines. Generally, however, all such patients receive treatment and a careful investigation should be made to identify the presence of established invasive disease. Other sites should be searched for evidence of infection (e.g. urine by culture or the presence of white cells). Signs of muscle invasion (tenderness) or metastatic skin nodules should be excluded (Fig. 8.7.1.17). Other signs of invasion include the development of new cardiac murmurs or of soft,

white, retinal plaques caused by candida. Persistently posi- tive blood cultures or serum candida antigen levels or high antibody titres might also indicate possible deep invasion. Disseminated candidiasis Although multiorgan invasive candidiasis can follow candidaemia, at least 50% of disseminated infections develop in patients without initially positive blood cultures. The features of some forms of inva- sive candidiasis are listed earlier (under ‘Candidaemia’). Although candida might be isolated from the sputum in these patients, there is rarely objective evidence of lung invasion. Moreover, there is no radiological appearance that is diagnostic of pulmonary candidiasis and, indeed, chest radiographs might even appear normal. General localizing signs are a late feature of disseminated candidiasis. Laboratory diagnosis of disseminated candidiasis The diagnosis can be made by culture or PCR, and repeated attempts to isolate should be made where cultures are initially negative. Numerous techniques have been used to detect antibody or antigen in disseminated candidiasis. However, in many patients, particularly those with neutropenia, it might not be possible to confirm the diag- nosis using laboratory tests and treatment is often initiated on the basis of clinical suspicion (empirical therapy) as the risk of delaying antifungal therapy is great. By themselves, positive cultures, particularly from sputum, or the presence of antibodies do not necessarily prove the existence of deep-seated candidiasis. A positive isolation might simply indicate the presence of colonization and normal individuals can have low
Fig. 8.7.1.17 Candidiasis disseminated to skin (methenamine silver, × 516). Box 8.7.1.3 Predisposing factors in deep candida infections • Local defects, foreign bodies (e.g. prosthetic heart valves, intravenous lines) • Defects of immunity (primarily T cell or phagocytosis) (e.g. cytotoxic therapy or systemic lupus erythematosus) • Drug therapy (e.g. antibiotics) • Carcinoma or leukaemia • Endocrine disease (e.g. diabetes mellitus in urinary tract candidiasis) • Physiological changes (e.g. infancy, old age, and pregnancy) (urinary tract) • Miscellaneous disorders, for example: — Malnutrition — Surgery such as gastrointestinal resections — Drug addiction

 titres of antibody to candida. If there is a readily accessible lesion from which to take a biopsy, such as a skin nodule or even a pul- monary infiltrate, this might provide the best evidence of invasion, although such procedures carry their own risk (Fig. 8.7.1.16). Treatment of disseminated candidiasis Untreated disseminated candidiasis is normally progressive and fatal. The signs must be separated from, for instance, bacterial septicaemia, which might coexist with the candida infection. The treatment of invasive candidiasis is intravenous amphotericin B or caspofungin or intravenous or oral fluconazole given until there is a clinical and mycological response. This might take between 2 and 20 weeks depending on the site of infection and the underlying state of the patient. Fluconazole is usually used in infections where the pa- tient is not neutropenic. Lipid-associated forms of amphotericin B are also useful and carry a lower risk of renal impairment. An alternative approach is to add flucytosine in doses of 150–200 mg/kg body weight daily to amphotericin B in serious infections or where cure might be hampered by poor penetration of amphotericin B, such as in the eye. A biologic, Mycograb, which is an antibody against candida heat shock protein 70 has been shown to improve treatment responses in candidaemia when used in combination with amphotericin B. Deep focal candidiasis Candida infections in the peritoneum or meninges most often follow direct implantation after dialysis or surgery. Alternatively, secondary invasion from the middle ear or a perforated bowel is also possible. The signs and symptoms are similar to bacterial men- ingitis or peritonitis, but candida is isolated. Sometimes these in- fections clear spontaneously, but normally treatment is instituted with fluconazole, which penetrates areas such as peritoneum, or amphotericin B. Candida endocarditis Invasion of heart valves, mainly the mitral or aortic valves, most commonly follows

homograft replacement, but it can occur also in patients with neutropenia or drug addicts. The symptoms are similar to bacterial endocarditis. However, candida vegetations might reach considerable size. Embolic phenomena may involve obstruction of large vessels including the femoral artery or large cerebral vessels. The detection of large vegetations using an echocardiography, par- ticularly in cases with negative blood cultures, should raise the pos- sibility of fungal endocarditis. Blood cultures are usually positive at some stage in the illness but repeated sampling might be necessary. High antibody titres are usually seen in such cases and serological tests are therefore of considerable value. Untreated candida endocarditis is uniformly fatal. There is also a high mortality associated with cases in which early surgical interven- tion is precipitated by impending heart failure. Normally, treatment consists of amphotericin B given intravenously and, where possible, valve replacement. There is no evidence to suggest that the addition of flucytosine to the regimen increases the effectiveness of treatment. However, the relapse rate is high and combination therapy might, therefore, be a reasonable approach on theoretical grounds. Urinary tract candidiasis Candida species might be isolated from the urine, particularly in conditions associated with urinary stasis such as neurogenic bladder or where there is an indwelling catheter. Type 2 diabetes is another predisposing factor. There is no value in using the presence of pyuria or quantitative yeast-colony counts to assess the significance of in- fection. Treatment is normally given where there are symptoms such as dysuria or frequency or where there is a potential risk of invasion such as in immunosuppressed patients. Fluconazole is very useful in these patients as urinary levels are above inhibitory concentrations. Aspergillosis (See also Chapter 8.2.4 and Section 18.) Aspergillosis is the name given to diseases associated with spe- cies of mould fungi of the genus Aspergillus. As such, it comprises a series of clinically distinct infections: aggressive pulmonary infec- tions with angio-invasion and the potential for widespread systemic haematogenous spread (invasive pulmonary aspergillosis); slow but progressive paranasal sinus infection mainly seen in the tropics (paranasal aspergillus granuloma); and colonization of a pre-existing space or cavity (aspergilloma) which can give rise to medical problems including severe haemorrhage. They are also associated with both superficial and subcutaneous fungal infections. Aspergillus species cause several different allergic disorders including asthma and allergic bronchopulmonary aspergillosis (Chapter 18.14.2). Box 8.7.1.4 indi- cates the range of diseases associated with aspergillus. Aspergillus species are ubiquitous and have established them- selves in every conceivable terrain and environment. As they propagate through the production of large number of airborne spores, exposure is difficult to avoid. Production of spores is also determined by local and environmental conditions. For example, construction or destruction of buildings and turnover of soil have been associated with focal outbreaks of infection in predisposed and immunosuppressed individuals. Susceptibility to aspergillus in- fections is dependent, to a large extent, on defective immunity or structural abnormalities, and therefore the major diseases caused Box 8.7.1.4 Diseases caused by aspergillus species Superficial infections • Onychomycosis • Otitis externa • Keratomycosis Subcutaneous infections • Mycetoma • Systemic infections • Localized invasive aspergillosis: — Aspergilloma, chronic aspergillosis of the paranasal sinuses, chronic pulmonary aspergillosis, paranasal aspergillus granuloma • Invasive aspergillosis with potential for systemic spread: — Invasive (pulmonary) aspergillosis (common sites for dissemination are brain, liver, skin) — Aspergillus endocarditis Allergic disease • Asthma, allergic rhinitis, • Extrinsic hypersensitivity pneumonitis (A. clavatus) • Allergic bronchopulmonary aspergillosis • Allergic aspergillus sinusitis Toxicosis • Mycotoxin-producing aspergilli (e.g. A. flavus—aflatoxins)

8.7.1 Fungal infections 1355 by these organisms are usually seen in immunosuppressed individuals, including, in particular, neutropenic patients or people with anatomocal abnormalities such as lung cavities. The incidence of in- fection can reach high levels in certain populations such as patients following bone marrow transplantation (Chapter 8.2.4). Aspergillus can produce several potent metabolic byproducts or myxotoxins, such as the aflatoxins produced by A. flavus which, if present in contaminated food, can induce liver necrosis. The most common human pathogen among the aspergillus spe- cies is A. fumigatus, followed by A. flavus which causes infections more commonly in warmer climates. A. niger causes aspergilloma rather than invasive disease but A. nidulans rarely causes mycetoma. A. terreus is sometimes found as a cause of onychomycosis. Hence aspergillus infections might present to a wide range of different specialities and, in the severely immunocompromised patient, dis- semination of aspergillus through the blood stream can result in in- fection of almost any organ. Cryptococcosis See Chapter 8.7.2. Invasive mucuromycosis (mucormycosis, zygomycosis, phycomycosis) Aetiology Invasive disease caused by mucor-like (mucoromycete) fungi is rare. In the compromised host it may lead to paranasal destruction, necrotic lung or skin lesions, and disseminated disease. The causative organisms commonly belong to three genera: Absidia, Rhizopus, and Rhizomucor. More rarely other or- ganisms such as Cunninghamella or Saksenaea have been implicated. Most of the agents are associated with decaying vegetable matter and are common airborne moulds. The route of infection is highly variable: they might invade via the lungs, paranasal sinuses, gastrointes- tinal tract, or damaged skin. The predisposing illness might, in some way, determine the site of clinical invasion. Underlying factors in- clude diabetic ketoacidosis (rhinocerebral involvement), leukaemia and immunosuppressive therapy (lung and disseminated infection), malnutrition (gastrointestinal infection), and burns and trauma or wounds (cutaneous invasion). These patterns are not always strictly followed. Epidemiology Mucoromycosis is rare but has a worldwide distribution. Its invasive nature, particularly the tendency to involve blood vessels and its selection of compromised hosts, distinguishes this form of in- fection from subcutaneous mucuromycosis, which is also caused by mucuromycete species. Clinical features The most characteristic features of this type of infection are the ex- tensive necrosis and infarction that follow blood vessel invasion leading to thrombosis. A similar type of invasion can occur with in- vasive aspergillosis, but is usually less prominent. Mucuromycosis follows several different patterns. The infection might initially localize in one of several sites. The most common is in the paranasal sinuses and this is most often seen in diabetic patients with ketoacidosis. The patient presents with fever and unilateral facial pain. Subsequently, there might be facial swelling with nasal obstruction and proptosis. There can be invasion into the orbit leading to blindness, into the brain, and into the palate. Palatal ulceration should be searched for. Widespread dissemin- ation with infarction of major organs or limbs might occur subse- quently. A similar pattern of invasion of surgical wounds or burns might occur and has on occasions been associated with contam- ination of dressing packs. Infections are initially localized causing extensive necrosis around the original wound. Gastrointestinal in- vasion might be heralded by perforation of viscera, and diarrhoea or haemorrhage. Alternatively, a patient can present with established pulmonary or widespread dissemination. Such patients are usually leukaemic, or are severely immunosuppressed. Neutropenia is often seen. Once infection has spread beyond the original site, mucuromycosis is almost invariably fatal with or without treatment. Laboratory diagnosis The diagnosis is suggested by the combination of infection and extensive infarction, particularly if it occurs in any of the sites men- tioned. The organisms can be difficult to culture, even from biopsy, and histology is often the quickest way of establishing the diagnosis. Serology is frequently negative. Treatment Treatment should be initiated as soon as

possible and extensive sur- gical debridement combined with intravenous amphotericin B in maximum daily dosage offers the best chance of success. Local instil- lations of amphotericin B might also be used where appropriate (such as nasal sinuses). Some physicians also recommend anticoagulation with heparin to forestall thrombosis. Despite therapy, the mortality remains high. Liposomal amphotericin B also has been used with some success is cases of mucormycosis. Rhinosporidiosis Rhinosporidiosis is an infection found in India, Sri Lanka, parts of East Africa, and South America. It is characterized by polypoid growth from the nose or conjunctiva. The causative organism can be demonstrated in tissue and consists of aggregates of large sporangia containing spores in various phases of development. However, they have never been successfully cultured and they appear to be related genetically most closely to aquatic protista, members of the Mezomycetozoa, and not fungi. The treatment is surgical excision. Otomycosis and oculomycosis External otitis is often multifactorial, but in some cases dense fungal colonization can contribute to the picture. In severe cases, the ex- ternal ear might be plugged by a dense mat of mycelium. Aspergillus species are the most common organisms cultured, particularly A. niger, but candida, penicillium, and mucor might all contribute. Intensive ear toilet can eradicate the infection without recourse to antifungal agents. Infections of the eye, particularly the cornea, caused by fungi (oculomycosis) are rare. They often follow penetrating injuries to the globe or contamination of lacerations. An opacity develops within the cornea with associated pain and chemosis. An exudate is usually present in the aqueous humour. Prompt treatment with intensive topical instillation of drugs containing an antifungal drug such as

section 8 Infectious diseases 1356 miconazole or econazole is necessary every 2 to 4 h. Perforation of the eye can occur in advanced cases. Approaches to management of fungal infections Antifungal agents can be considered in four main groups: the poly- enes, azoles, morpholines, and allylamines, and an assortment of unrelated drugs with specific activity. Polyenes The polyene antifungals are macrolide substances derived origin- ally from species of Streptomyces. They include amphotericin B, natamycin, and nystatin. More recent additions to this group are partricin and mepartricin. Amphotericin B is the only one widely used as a parenterally administered drug. Nystatin and natamycin are purely topical. Amphotericin B is metabolized in the liver with low penetration of body cavities, cerebrospinal fluid, and urine. The polyenes have broad activity against a wide range of fungi. The mode of action of the polyenes appears to involve inhibition of sterol syn- thesis in the fungal cell membrane. The combination of an amphotericin B with a lipid, for in- stance a liposome, has been proposed as a means of reducing the nephrotoxicity of this drug. Three commercial lipid amphotericins are available: AmBisome (a true liposome), amphotericin B lipid complex—ABLC or Abelcet (a ribbon-like lipid binding amphotericin B), and amphotericin B colloidal dispersion (ABCD) (a dispersion of lipid discs). Azoles The imidazoles are synthetic antifungal agents. They include miconazole, clotrimazole, econazole, isoconazole, ketoconazole, tioconazole, and bifonazole. The triazole series contains two po- tent oral agents, fluconazole and itraconazole. Voriconazole, posaconazole, and isavuconazole are newer additions. Most are used topically except for ketoconazole (oral), itraconazole (oral), voriconazole (oral and intravenous), posaconazole (oral and intravenous) and isavuconazole (oral and intravenous. These are metabolized in the liver and, like amphotericin B, affect fungal cell- membrane synthesis and penetrate cerebrospinal fluid and urine in low concentrations. The imidazoles have a broad spectrum of activity against many fungi, particularly those causing superficial infectiond. Fluconazole is less active against moulds and there are instances of both primary (Candida krusei, C. glabrata) and sec- ondary resistance to this compound. New triazoles, voriconazole,

posaconazole and isavuconazole, are now available; voriconazole is an effective treatment for invasive aspergillosis. The allylamines such as terbinafine are primarily active against superficial fungi, but in vitro appear to have fungicidal activity at low concentrations. Other antifungals in this category include flucytosine, which is a synthetic pyrimidine analogue. Given either intravenously or orally it is mainly useful for chromomycosis and certain yeast infections. Drug resistance is a major problem with flucytosine, particularly with cryptococcus. The drug shows several modes of action including disruption of RNA transcription following up- take by the cell. Caspofungin, an echinocandin, is an effective treatment for deep candida, including fluconazole-resistant, in- fections. Newer echinocandins are anidulafungin and micafungin. Griseofulvin is derived from a species of penicillium. It can be given orally and is only useful against dermatophytes. It is best absorbed when given with a meal and selectively accumulates in stratum corneum in concentrations approximately 10 times greater than serum levels. Griseofulvin acts by inhibiting intracel- lular microtubule formation. Management of superficial infections Specific details of therapy are included under the separate diseases. Benzoic acid compound (Whitfield's ointment), which contains 2% salicylic acid and 2% benzoic acid, acts as a keratolytic agent by causing exfoliation of the superficial layers of the stratum corneum. Other topical agents with only weak antifungal activity include gentian violet (candidiasis or dermatophytosis); Castellani's paint, which contains magenta and resorcinol (candidiasis or dermato- phytosis); and brilliant green (dermatophytosis). Selenium sul- phide (2%) remains a highly effective method of treating pityriasis versicolor by application once daily for 2 weeks. The more specific antifungals such as the polyenes, amphotericin B, nystatin, and natamycin (candidiasis) or the imidazoles (can- didiasis, dermatophytosis, and pityriasis versicolor) are highly effective and probably quicker than the keratolytics or dyes, al- though more expensive. Local irritation can be a problem, par- ticularly with Whitfield's ointment, which is usually given as a half-strength preparation. Allergic contact dermatitis is rare but has been recorded from some imidazoles (miconazole, clotrimazole, tioconazole) and tolnaftate. Topical terbinafine is highly active in tinea pedis with cures being effected with less than 1 week of therapy. Terbinafine or itraconazole are more effective in many forms of dermatophytosis requiring oral therapy than griseofulvin. In onychomycosis they are preferred. Terbinafine has occasional side effects, mainly related to gastrointestinal intolerance, although it might also cause transient loss of taste. It is given in daily doses of 250 mg. Itraconazole is usually given in 'pulses' (e.g. 200 mg twice daily for 1 week monthly). Itraconazole likewise can cause gastro- intestinal discomfort and nausea. Both drugs rarely cause hepatic injury, with a frequency of less than 1 in 70 000 to 1 in 120 000. Fluconazole is also effective in dermatophytosis and is given in weekly doses of 150–300 mg. Griseofulvin is still the principal treat- ment for tinea capitis (10–20 mg/kg per day). In onychomycosis caused by dermatophytes both terbinafine and itraconazole lead to remission of toenail infections in only 3 months. Terbinafine is used on a daily basis, whereas itraconazole is given in a pulsed regimen, 200 mg twice daily for 1 week every month for 3–4 months. There is one study which shows better responses with terbinafine for toenail disease. Amorolfine, a morpholine drug, is used in the topical treatment of nail disease where there is less than complete involvement of the nails. It can be given together with other drugs, such as terbinafine. Management of deep mycoses Very few drugs are effective in systemic fungal infections, and those that are used should always be accompanied by supportive measures and, if possible, an attempt to eliminate any predisposing conditions. For instance, if their condition permits, patients who have devel- oped a candidaemia while a central venous line is in place should be managed by removal of the line. However, fluconazole is also usually

8.7.1 Fungal infections 1357 given as well. In the patient with neutropenia, a positive blood culture would be regarded as evidence of dissemination and antifungal therapy would be required. Amphotericin B is given intravenously in a 5% dextrose infusion not containing additional drugs, if possible. A test dose of 1–5 mg is given over 2 h and this is followed by gradually increasing doses over the next 3–9 days to the normal maximum of 0.6–1.0 mg/kg body weight daily depending on the infection. In some cases, this slow approach might help the patient to tolerate the drug better, or may define the dose at which side effects such as pyrexia start. In severely ill patients, half of the full dose can be given 4 h after a test dose of 5 mg, usually under hydrocortisone cover. The full dose is given 24 h later. Side effects include thrombophlebitis, nausea, hypotension, and pyrexia. Renal clearance might fall in the initial period but this usually returns to normal after a tem- porary halt in therapy. More permanent renal tubular damage can follow a total dose of 4 g or more. Amphotericin B does not pene- trate urine, cerebrospinal fluid, or peritoneal fluid in significant concentrations. Local instillations (such as the peritoneum) can be used, but can be highly irritant. Amphotericin B is normally given until clinical or mycological cure is induced. This is often difficult to judge accurately and in many of the mycoses caused by the systemic pathogens a course of at least 2 g is often used on an empirical basis. In the opportunistic infections, lower total doses are probably effective, and the length of treatment should depend on the clinician's judgement. This approach is not necessary with the lipid-associated amphotericin B formulations, which can be given without the slow build-up. The initial dose is usually 1 mg/kg, but standard daily doses of 3 mg/kg are common. Patients are less likely to develop renal impairment although it can occur. There have been a few clinical trials comparing these formulations with amphotericin B and these show equal efficacy with less toxicity; however, these for- mulations are expensive. The main lipid-associated formulations are given earlier. The azole drugs are also used in systemic mycoses. Fluconazole is given in systemic candidiasis, urinary tract infections, and as a long- term suppressive, in addition to primary therapy, in cryptococcosis in patients with AIDS. Side effects are uncommon, although it can cause nausea and vomiting. Fluconazole can be given orally or intravenously. It penetrates urine in effective concentrations. Its daily dosage varies from 100 to 200 mg for oropharyngeal infections to 600 to 800 mg for disseminated candidiasis. It is highly active in can- dida infections. It can also be used in some endemic mycoses such as histoplasmosis. Resistance to fluconazole has mainly been re- corded with oropharyngeal candidiasis, principally in HIV-positive patients, although it can occur with other candida infections; for example, C. krusei and C. glabrata are often primarily resistant to this drug. Itraconazole has been evaluated in a variety of systemic mycoses from aspergillosis to cryptococcosis. Its active range includes histoplasmosis, sporotrichosis, chromoblastomycosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis. Itraconazole is used as an oral preparation, but an intravenous formulation is now available. Oral absorption is often defective in individuals with AIDS and patients after bone marrow transplantation and in these groups the mean daily dosage is doubled (200 mg). An itraconazole suspension is also available for treatment of oral infections. Voriconazole is now the treatment of choice for many cases of invasive aspergillosis and for some other systemic mycosis. Long-term administration might lead to photosensitivity and increased incidence of skin cancers. The indications for posaconazole include fluconazole unresponsive infections but it also appears be effective in some mould infections including some cases of fusarium infection as well as prophylaxis in neu- tropenic patients. Flucytosine (5-fluorocytosine) is an effective oral and intravenous antifungal agent that is primarily active against yeasts such as candida and cryptococcus. It enters urine, cerebrospinal fluid, and peritoneal fluid. Its excretion is reduced in renal failure and the daily dose should be reduced accordingly and blood levels moni- tored. The main disadvantage

of flucytosine is the development of either primary or secondary drug resistance in a significant number of isolates, and when given in toxic doses it may cause bone marrow depression. The serum level should not be allowed to rise above 100–120 µg/ml. Combination amphotericin B and flucytosine therapy might offer an alternative but effective method of treatment. Theoretically, as the drugs synergize, the dose of amphotericin B may be re- duced. In cryptococcal meningitis, combination therapy using a dose of 0.3–0.6 mg/kg body weight of amphotericin B with the normal dose of flucytosine is more effective at sterilizing the cere- brospinal fluid and preventing relapse. In other forms of systemic infection such as candidiasis there is little evidence that it is more effective than amphotericin B alone, although this might be the case. Combinations of other drugs have not been critically evalu- ated in vivo. Caspofungin is used in fluconazole-resistant deep candidiasis. FURTHER READING General Dismukes WE, Pappas PG, Sobel J (2006). Clinical mycology. Oxford University Press, New York, NY. Kibbler CC, MacKenzie DWR, Odds FC (1996). Principles and prac tice of clinical mycology. John Wiley & Sons, Chichester. Merz W, Hay RJ (eds) (2005). Mycology. Topley and Wilson's micro biology and microbial infections, 10th edition, Vol. 4. Arnold, London. Midgley G, Clayton YM, Hay RJ (1997). Diagnosis in colour: medical mycology. Mosby-Wolfe, London. Dermatophytosis Aly R (1994). Ecology and epidemiology of dermatophyte infec- tions. J Am Acad Dermatol, 31, S21–5. Hay RJ (2005). Fungal infections. In: Bos JD (ed) Skin immune system (SIS), pp. 593–604. CRC Press, Boca Raton, FL. Hay RJ, et al. (1996). Tinea capitis in south-east London—a new pattern of infection with public health implications. Br J Dermatol, 135, 955–8. Munoz-Perez MA, et al. (1998). Dermatological findings correlated with CD4 lymphocyte counts in a prospective 3-year study of 1161 patients with human immunodeficiency virus disease predom- inantly acquired through intravenous drug abuse. Br J Dermatol, 139, 33–9.

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