Review Article

Systemic zygomycosis

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Introduction

Two families of the class of fungi known as Zygomycetes contain most of those members which are reported to cause human disease. The Entomophthoraceae are particularly associated with infection of the skin and subcutaneous tissue, whereas the Mucoraceae typically cause systemic disease. The species most often associated with such systemic infections include *Rhizopus oryzae*, *Rhizopus rhizopodiformis*, *Absidia corymbifera* and *Rhizomucor pusillus*; a number of other species are also occasionally implicated (Scholer *et al.*, 1983), and it is clear that the number of identified pathogenic species is increasing.

In clinical nomenclature, there is a terminological quagmire, within which 'mucormycosis', 'phycomycosis' and 'zygomycosis' are sometimes used as if they were synonymous (Medical Research Council, 1977). 'Phycomycosis' appears to have been rendered obsolete by taxonomic changes (Ajello *et al.*, 1976; Emmons *et al.*, 1977), though it was the term preferred by the nomenclature committees of the British Society for Mycopathology (Medical Research Council, 1977) and the International Society for Human and Animal Mycology (Vanbreuseghem *et al.*, 1980), as well as the authors of a standard text in mycology (Emmons *et al.*, 1977). Other major texts, however, prefer 'mucormycosis' (Rippon, 1982) or 'zygomycosis' (Chandler *et al.*, 1980). The organisms causing cutaneous and subcutaneous infections can often be identified by culture, and it may then be logical to refer to the resulting clinical condition as 'entomophthoramycosis' or 'basidiobolomycosis'. 'Mucormycosis' should strictly be limited to cases proven by culture to be caused by a member of the Mucorales (Meyers *et al.*, 1979; Hawksworth *et al.*, 1983), but the term is established by long usage, and is customary where a diagnosis by biopsy only is available. This usage is potentially misleading, for

zygomycetes not within the order of Mucorales can cause systemic zygomycosis (King & Jong, 1976; de Aguiar *et al.*, 1980; Scholer *et al.*, 1983). Deep infection is often only diagnosed on histological examination: the species cannot then be identified by any method in general use, and the genus can only be guessed at. It is, in such circumstances, not possible to be sure of anything other than that a zygomycete is present, and so the term 'zygomycosis' is safest. When a suitable adjective, such as 'systemic' or 'subcutaneous' is appended, all examples can be unambiguously labelled (Ajello *et al.*, 1976).

The Zygomycetes are typically found in soil and dung (Emmons, 1962). Members of the genera associated with human disease are part of the soil mycoflora in many parts of the world (Warcup, 1951; Miller *et al.*, 1957; Moubasher & Abdel-Hafez, 1978), including the United Kingdom (Warcup, 1951; Nichols, 1956); they are frequent contaminants of animal fodder (Ainsworth & Austwick, 1955) and of tobacco (Papavassiliou *et al.*, 1971). Their spores are widespread in the air (Agarwal *et al.*, 1969; Hudson, 1973; Sorensen *et al.*, 1974), are present in house dust (Davies, 1960) and were found in the atmosphere in a ward in a London teaching hospital (Noble & Clayton, 1963). They may be cultured from the sputum of a minority of healthy men (Kahanpää, 1972; Comstock *et al.*, 1974). Pathogenic species were found in the warm effluent from a power station and in the soil of the immediate vicinity, though no significant associated increase in the air spore count could be detected (Rippon *et al.*, 1980). Zygomycetes do not often cause human disease; their most common effects on our lives result from their ability to cause decay in many kinds of fruit and vegetables (Harter & Weimer, 1922).

They are facultative necrotrophs, able to invade and kill living tissue, and to then withdraw nutrients from it (Cooke, 1977). They require previous damage to the skin of most fruits, either by trauma (Harter & Weimer, 1922) or initial attack by another agent (Stevens, 1914), before they can invade. Intact peach

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skin may be breached (Harter & Weimer, 1922), and economically significant decay may result (Heaton, 1980). They may harm other soft fruit crops, such as strawberries (Stevens, 1914), but they can also cause significant post-harvest loss of thick-skinned fruit, such as Cantaloupe melons (Wade & Morris, 1982). They are often found in peanuts (Moubasher *et al.*, 1979), and may reduce the useable oil content of cotton seeds (Abdel-Rahman, 1981). They are even present in dried pasta products (Christensen & Kennedy, 1971). Various Zygomycetes are used, often as components of mixed cultures, in several culinary processes in the Far East and the Indian subcontinent. They are used to promote the fermentation of various substrates, including soybeans and rice, to foods and drinks which are more palatable or interesting than the original material. Some of these techniques even increase the nutritional value of the raw material by making its components more readily digestible (Hesseltine, 1965; Fukushima, 1981).

Systemic disease is not confined to man, and may arise in a variety of domestic animals (Ainsworth & Austwick, 1955), including sheep (Angus *et al.*, 1971), cattle (Spratling *et al.*, 1968; Nielan *et al.*, 1982), pigs (Mahanta & Chaudhury, 1985), dogs (Ader, 1979) and cats (Ader, 1979; Loupal, 1982), and has been described in non-human primates (Migaki *et al.*, 1982). One feline case was mistaken for rabies (Ravisse *et al.*, 1978). Ader (1979) reviews cases in a variety of more exotic species, including birds, reptiles, amphibians and fish.

The four main systemic forms of the disease in man are the rhinocerebral, pulmonary, gastrointestinal and disseminated types. There is also a miscellaneous category of involvement of single organs not within the main categories (Baker, 1957; Lehrer *et al.*, 1980). Systemic zygomycosis is usually an opportunistic infection, and each of the main forms is associated with a characteristic group of underlying conditions.

Geography and incidence

Although the earliest recorded cases are of European origin (Hutter, 1959; Rippon, 1982), the majority of modern published reports are North American. These began with three classic cases described by Gregory *et al.* in 1943, and now include many substantial series (Straatsma *et al.*, 1962; Meyers *et al.*, 1979; Blitzer *et al.*, 1980; Marchevsky *et al.*, 1980; Abedi *et al.*, 1984). Systemic zygomycosis is clearly relatively common in Mexico (Rangel-Carrillo *et al.*, 1982; del Real Mora, 1983; Rangel-Guerra *et al.*, 1985), and not infrequent in Japan (Hotchi *et al.*, 1980) and Southern Africa (Neame & Rayner, 1960; Deal & Johnson, 1969; Dannheimer *et al.*, 1974; Lawson & Schmaman, 1974). Reports have come from many other countries,

especially India, usually of single cases. European publications follow this latter pattern, with the exception of a Swiss report of four cases (Stahel *et al.*, 1983), a Czech report of 11 cases (Vorreith, 1969), and four cases in a Spanish hospital, presented in two overlapping reports (Gutierrez Diaz *et al.*, 1981; del Palacio Hernanz, 1983).

Symmers (1966) has seen 'many' examples in referred histological material originating within the British Isles, but does not describe them in detail. Detailed reports are all of single cases (Kurrein, 1954; La Touche *et al.*, 1963; Winston, 1965; Hanley, 1978; Helenglass *et al.*, 1981; Benbow *et al.*, 1985; Flood *et al.*, 1985).

It is the general experience that the incidence of systemic zygomycosis is increasing, though the disease remains a minority of opportunistic infections. This increase may be a consequence of the increased use of antibiotics, the development of more potent chemotherapeutic agents, and their devolvement in an increasing number of conditions (Meyer *et al.*, 1972). It is clear that particular susceptibility occurs during periods of leukopenia in treated leukaemics, and in those with diabetes mellitus while they are acidotic. Modern supportive techniques in haematology are able to maintain severely leukopenic patients for longer, and diabetics are able to survive a greater number of ketoacidotic episodes. In both groups, therefore, each individual sufferer may be susceptible to opportunistic infection for a greater total amount of time.

Clinical forms

Rhinocerebral zygomycosis

This type, with its association with diabetes mellitus, is the most characteristic form (Gregory *et al.*, 1943; Pillsbury & Fischer, 1977; Meyers *et al.*, 1979; del Real Mora *et al.*, 1983; Abedi *et al.*, 1984). It usually, but not always, occurs when diabetic control is poor, and acidosis is an important predisposing factor (Baker, 1960). There is destructive inflammation within the nasal cavity, with erosion of the bony walls of the nasal sinuses. Palatal necrosis may occur, and the lesion has usually penetrated to the cranial cavity by the time its significance has been realised. The fungus has a predilection for growth within blood vessels, and so this leads to infarction and fungal invasion of the frontal lobes. Less common consequences of this cerebral involvement include cerebral abscess (Berthier *et al.*, 1982), intracerebral haemorrhage (Ho, 1979) or subarachnoid haemorrhage (Baker, 1957). Further spread to the tissues of the orbit is also usual, either from the cranium, via the lacrimal duct, or by direct invasion (Diamond & Proppe, 1982), and in a few

cases has lead to severe disruption of the globe (Blatrix *et al.*, 1970; Albert *et al.*, 1979).

This progression of lesions gives a characteristic clinical picture, with swelling and distortion of the face, marked proptosis and ptosis and early visual loss, all typically unilateral (Fleckner & Goldstein, 1969; Pillsbury & Fischer, 1977; Diamond & Proppe, 1982). There is often severe unilateral facial pain, sometimes initially believed to be odontogenic (Diamond & Proppe, 1982; Webb *et al.*, 1984), together with a persistent serosanguinous nasal discharge (Smith & Kirschner, 1958; Ferry & Abedi, 1977). Examination of the nasal cavity, or a palatal lesion if one exists, usually reveals a black crusting ulcer (Smith & Kirschner, 1958; Pillsbury & Fischer, 1977). Neurological signs are often present, but are usually non-specific and masked by the underlying condition, or misinterpreted because of it. Multiple cranial nerve defects may occur because of involvement at the orbital apex (Diamond & Proppe, 1982), but local tissue destruction in the face and orbit may complicate their interpretation. Cavernous sinus thrombosis is a recognized complication (Ferry & Abedi, 1983; Meyers *et al.*, 1979; Anaissie & Shikhani, 1985), but internal carotid artery thrombosis is much more characteristic, and typically occurs in over a third of cases (Landau & Newcomer, 1962). It is usually unilateral, but may be bilateral (Wilson *et al.*, 1979).

Rhinocerebral zygomycosis is not limited to those with diabetes mellitus, and may, for example, follow the immunosuppression of anti-tumour chemotherapy. Such patients are, however, more likely to progress to the disseminated form, and the prognosis is correspondingly poorer. The craniofacial signs remain the same.

Pulmonary zygomycosis

Pulmonary zygomycosis is the predominant form complicating haematological malignancy (Keye & Magee, 1956; Hutter & Collins, 1962; Meyer *et al.*, 1972), and is thus more often a precursor of disseminated disease than is the rhinocerebral form. It typically occurs in the patient who has been treated with chemotherapy, and who is already critically ill (Hutter & Collins, 1962). The clinical findings are non-specific, and many cases remain unsuspected until necropsy (Mills & Wolfe, 1980). Retrospective examination of the notes and radiographs of such individuals reveals that death typically followed a rapidly progressive, but patchy, pneumonic process. When other conditions, such as diabetes mellitus or chronic renal failure underlie this form of the disease, the disease may remain more localized, but its features are still non-specific, with cough and chest pain; radiological findings suggest pulmonary infarction or focal pneumonia (Bigby *et al.*, 1986). A solitary lesion is

sometimes seen. In a number of cases, death has followed infiltration of a major vessel, such as the superior vena cava (Helenglass *et al.*, 1981; Marwaha *et al.*, 1985) or a pulmonary artery (Reich & Renzetti, 1970; Johnson & Baldwin, 1981).

Gastrointestinal zygomycosis

Malnutrition is often associated with this form, and a considerable proportion of cases have occurred in neonates and infants (Neame & Rayner, 1960; Michalak *et al.*, 1980). Published cases of gastrointestinal zygomycosis suggest a particular association with southern Africa (Neame & Rayner, 1960; Deal & Johnson, 1969; Lawson & Schmaman, 1974; Gwavava & Gelfand, 1983), a finding which might suggest some subtle difference in the predominant organisms, but which is more probably the consequence of the juxtaposition of a malnourished population with sophisticated modern diagnostic services. Gastrointestinal zygomycosis may also occur in diabetes, and like the pulmonary form, there may be few clues to the specific diagnosis of zygomycosis. The most usual site of involvement is the stomach (Hutter, 1959; Lawson & Schmaman, 1974), where there may be a large necrotic ulcer; presentation may be with gastric perforation (Michalak *et al.*, 1980). Large intestinal disease causes a severe diarrhoea with plentiful blood and mucus in the stool (Neame & Rayner, 1960; Agha *et al.*, 1985).

Disseminated zygomycosis

This form, like the pulmonary type, usually occurs in those with haematological malignancy, but may on occasion complicate other diseases, including contaminated skin wounds. Of particular interest are those nosocomial cases which followed the use of contaminated dressings (Dennis *et al.*, 1980; Gartenberg *et al.*, 1978).

Disseminated zygomycosis in leukaemics usually follows chemotherapy, and may in many cases only be relevant in that it hastens an already imminent death. Other cases occur in patients with a better prognosis, and appropriate therapy may prolong life. A diversity of non-specific symptoms occurs, but these are often overshadowed by the poor general condition of the patient.

Miscellaneous forms of systemic zygomycosis

Zygomycosis of single organs or single body systems, apart from those discussed already, is rare. When zygomycosis involves the brain alone, the underlying cause is often intravenous drug abuse, usually with heroin (Hameroff *et al.*, 1970; Masucci *et al.*, 1982; Pierce *et al.*, 1982) or, rarely, amphetamines (Micozzi

& Wetli, 1985). The clinical, radiological and pathological findings are those of multiple cerebral abscesses.

A rhinofacial form of zygomycosis, usually caused by a member of the Entomophthorae, typically progresses slowly (Emmons *et al.*, 1977), and is best classified with the subcutaneous zygomycoses. A syndrome intermediate between it and classical rhinocerebral zygomycosis has recently been described, wherein a more aggressive nasal zygomycotic osteomyelitis presents with multiple cranial nerve palsies of sudden onset, but with characteristic early sparing of the VIIIth nerve (Bahna *et al.*, 1980).

Involvement of the heart is unusual, and may be endocardial, myocardial or both. Solitary cardiac involvement seems limited to endocarditis complicating open heart surgery (Virmani *et al.*, 1982). Solitary renal zygomycosis is even rarer, and has only been discovered on examination of nephrectomy specimens (Prout & Goddard, 1960; Flood *et al.*, 1985). Isolated bony involvement is also very unusual (Echols *et al.*, 1979).

Wound infections with Zygomycetes may also occur. Examples have been described at the site of repeated injections (Symmers, 1968), in needle biopsy tracts (Gartenberg *et al.*, 1978; Dennis *et al.*, 1980), adjacent to colostomies (Wilson *et al.*, 1976) or in surgical incisions (Gartenberg *et al.*, 1978). Other examples have complicated accidental peripheral trauma (Boyce *et al.*, 1981; Potvliege *et al.*, 1983) and diabetic leg ulcers (Tomford *et al.*, 1980). Some of these infections have been indolent, with a well-defined granulomatous response (Symmers, 1968), whereas others have caused extensive local tissue destruction (Wilson *et al.*, 1976; Tomford *et al.*, 1980).

Other underlying conditions

The major underlying causes have already been discussed. These have been reviewed by McNulty (1982), who also describes other important predisposing states, including antibiotic or steroid usage, chronic renal failure, pancreatitis, burns, malnutrition and trauma. Single cases and small series are associated with many other conditions.

Many infections are nosocomial, as with any opportunist. A number of cases have followed the use of contaminated dressings (Gartenberg *et al.*, 1978; Bottonne *et al.*, 1979; Dennis *et al.*, 1980), and may be associated with the sites of injection (Symmers, 1968), needle biopsy (Gartenberg *et al.*, 1978; Dennis *et al.*, 1980) or cannula insertion (Fisher *et al.*, 1980). A few cases of the rhinocerebral form appear to have been precipitated by dental extraction (Eilderton, 1974; Ristow *et al.*, 1979), though it is difficult to be sure that facial pain caused by pre-existing zygomycosis was not misinterpreted. Rhinocerebral or pulmonary

zygomycosis may result from contamination of air conditioning (England *et al.*, 1981; del Palacio Hernandez, 1983).

Transplant patients form another important subgroup, and a number of cases have followed renal transplantation (Gallis *et al.*, 1975; Hammer *et al.*, 1975; Abedi *et al.*, 1984; Carbone *et al.*, 1985). Cardiac (Schober & Herman, 1973) and bone marrow (Myskowski *et al.*, 1983) transplantation are also risk factors.

Zygomycosis is not included among the fungal infections associated with acquired immunodeficiency syndrome (Jaffe *et al.*, 1983), and no examples were found among the infectious complications of that disease in a recent major series (Gold & Armstrong, 1984). A suggested association with the acquired immunodeficiency syndrome in two recent cases (Micozzi & Wetli, 1985) is clearly entirely speculative.

Several of the reported cases have been in people without any apparent pre-disposing condition. These have usually suffered from the rhinocerebral form (Muresan, 1960; Baum, 1967; Blodi *et al.*, 1969; Kurrasch *et al.*, 1982), though the pulmonary (Record & Ginder, 1976) and gastrointestinal (Horowitz *et al.*, 1974) varieties have also been seen in previously healthy people. The significance of such cases is not easily understood, for few appear to have been followed-up for a significant period, and little attention has been paid to the more subtle defects of leucocyte function that may arise from specific genetic anomalies. Blankenberg & Verhoeff's (1959) report is interesting, for they saw localized pulmonary zygomycosis in a girl who was otherwise healthy at initial presentation, but who was found to have diabetes mellitus one year later.

Diagnosis

Confirmation of the presence of zygomycosis should ideally be by culture (Smith, 1984), but this is often not possible. Even with the characteristic appearances of the rhinocerebral form, the significance of the changes is often not appreciated, and any material removed by the surgeon placed in histological fixative without reserving a portion for culture. Attempts to culture material from necropsy specimens often fails because of bacterial overgrowth, and if a zygomycete is grown when its presence was not anticipated, it may be discarded as a contaminant (Sands *et al.*, 1985).

Cultures of sputum (Bogard, 1972; Bhaduri *et al.*, 1983), bronchial brushings (Fahey *et al.*, 1981) and stool (Agha *et al.*, 1985) have been used to confirm the presence of the pulmonary and gastrointestinal forms, though the risk of contamination makes interpretation difficult. Blood cultures have on rare occasions been positive (Bhaduri *et al.*, 1983).

Histological examination is therefore of greater

significance than it is with many other infections, both because it may be the only means of diagnosis and because it may be needed to confirm that a positive culture is significant. It has the further advantage that it may provide faster confirmation of this rapidly progressive disease than is possible with culture. Microscopic examination of crushed tissue may provide strong evidence of the correct diagnosis within a few hours (Meyers *et al.*, 1979).

In tissue, the Zygomycetes have hyphae which are of variable diameter, though they are characteristically broad. Septa are scanty or absent, and the hyphae divide at irregular intervals at an angle of approximately 90°. These features generally distinguish them from the slender hyphae of *Aspergillus* species, with their regular dichotomous branching and frequent septation, though zygomycetes growing within a confined space may somewhat resemble aspergilli. The fungus is usually visible on routine haematoxylin and eosin stains, though the extent of the eosinophilic hyphae, embedded within eosinophilic thrombus or necrotic tissue, is much more easily appreciated using periodic acid-Schiff or methenamine silver stains.

Radiologically, opacification of the nasal sinuses without fluid levels, irregular erosion of their bony walls and nodular soft tissue thickening are a combination which is highly suggestive of rhinocerebral zygomycosis (Green *et al.*, 1967). Internal carotid thrombosis is a frequent angiographic finding (Lazo *et al.*, 1971), and obstruction of smaller, more distal vessels may be observed (Courey *et al.*, 1972). Computerized axial tomography (CT) may demonstrate that the lesion crosses fascial planes, and the carotid vascular bundles may become indistinct (Bohman *et al.*, 1981; Raji *et al.*, 1981). CT scans of the orbit may be more characteristic, however, with distortion and displacement of the extraocular muscles and enlargement of the optic nerve (Centeno *et al.*, 1981; Diamond & Proppe, 1982). Cerebral changes resemble infarcts or abscesses. CT scans may be particularly useful in the assessment of therapeutic response (England *et al.*, 1981). Radioisotope brain scans show increased uptake in the characteristic sites in the frontal lobes and the basal zones (Zwas & Czerniak, 1975).

Chest radiographs usually show either diffuse shadowing or focal lesions (Bartrum *et al.*, 1973), though well-developed zygomycotic pneumonia may be invisible on repeated radiographic examination (Aderka *et al.*, 1983). Focal lesions may be either single or multiple (Pagani & Libshitz, 1981). Such changes are non-specific, but in the right context, they would justify commencement of antifungal therapy (Libshitz & Pagani, 1981). Barium studies of the intestines have occasionally been useful (Lyon *et al.*, 1979; Agha *et al.*, 1985), and typical hyphae have been seen on subsequent endoscopic biopsy.

Serological changes occur in infected laboratory animals, and so attempts have been made to develop tests to diagnose human disease (Jones & Kaufman, 1978; Yankey & Abraham, 1983). Such tests remain too insensitive, and too prone to cross-reaction, to allow confident diagnosis of human disease (Lehrer *et al.*, 1980). However, serological confirmation has been claimed to have been useful in a few recent cases (Valicenti & Conti, 1980; Pierce *et al.*, 1982; Vincent *et al.*, 1984).

Treatment and prognosis

Rapid and effective control of the underlying condition is, if feasible, an important and often crucial prerequisite to therapeutic success (Blitzer *et al.*, 1980). Indeed, cases complicating diabetes mellitus have recovered with no other therapy (Harris, 1955). The only anti-fungal agent with a proven usefulness against zygomycosis is amphotericin B (Blitzer *et al.*, 1980; Eng *et al.*, 1981), and even with this drug, sensitivity is highly variable (Watson & Neame, 1960; Utz, 1980). Resistance is rapidly inducible, at least *in vitro* (Leathers & Sypherd, 1985). The drug should be used promptly, and the dose should be increased to its maximum level as soon as possible. The total dose that may be given is limited by the predictable onset of renal failure. Newer agents, such as ketoconazole, are of no value (Medoff & Kobayashi, 1980), and a claim that exposure to hyperbaric oxygen is beneficial seems premature (Price & Stevens, 1980).

Surgical debridement of necrotic tissue is also important (Ferry & Abedi, 1983; Blitzer *et al.*, 1980). It may be necessary to remove the orbital contents (Lazzaro & Sloan, 1982), with much of the nose, nasopharynx and the face (Eden & Santos, 1979; Rangel-Guerra *et al.*, 1985). Where appropriate, lung or gut resection may be valuable (Eden & Santos, 1979; Gribetz *et al.*, 1980; Wright *et al.*, 1980). Adequate surgery to the face may leave a substantial defect, and since such patients may have, on recovery, a good life expectancy, there is a major challenge to the skills of prosthetists (Kurrasch *et al.*, 1982). Cures have followed medical treatment alone (Hauch, 1977; Hamill *et al.*, 1983), but adequate debridement as well provides a much better prognosis (Anaisie & Shikhani, 1985).

Systemic zygomycosis has a considerable mortality in all groups, even with treatment. When disease is limited to the head, the mortality of those with diabetes mellitus is about 40%, and rises to 80% where the underlying condition is a haematological malignancy (Blitzer *et al.*, 1980). The best prognosis is in that small group who were previously well, but even in this relatively favourable circumstance, about a fifth will die. Internal carotid thrombosis is an indicator of

poor prognosis (Anaissie & Shikhani, 1985).

A few may develop a more chronic condition, with persistent signs over several weeks or months (Helderman *et al.*, 1974; Finn & Farmer, 1982). In some cases, this is related to the species involved, but chronicity may follow infection with a type which is usually aggressive (Symmers, 1968; Leong, 1978). An early, apparently spontaneous, 'cure' (Hoagland *et al.*, 1961) was followed by fatal recrudescence some years later (Ferstenfeld *et al.*, 1977).

Experimental studies

This unusual disease, with its striking association with diabetes mellitus, has long attracted the interest of those wishing to study opportunistic infection. The rarity of the disease is in marked contrast to its devastating nature once established, and to the frequency of the causative organisms in the environment.

Clinical observations of leukaemics suggest that the primary disease is a less important factor than leucopenia following therapy (Hutter, 1959; Baker, 1962). Further, mice with inherited lymphocyte deficiency (Corbel & Eades, 1976), or experimentally rendered lymphopenic (Corbel & Eades, 1975), are no more susceptible than their normal counterparts to experimental infection. Most human cases have followed non-specific causes of immunosuppression, but may complicate inherited defects of neutrophil killing mechanisms (Bruun *et al.*, 1976; Marx *et al.*, 1982).

Zygomycete hyphae produce a chemotactic agent *in vitro* (Chinn & Diamond, 1982), and neutrophils become attached to them, causing damage demonstrable on electron microscopy (Diamond *et al.*, 1978). Neutrophils reduce uptake of radioactive metabolic substrates by Zygomycete hyphae *in vitro* (Diamond *et al.*, 1982), an effect reduced by inhibitors of both oxidative and non-oxidative microbicidal activity (Diamond & Clark, 1982). Normal monocytes have a similar inhibitory effect on hyphal metabolism to that of neutrophils (Diamond *et al.*, 1982), but those from patients with chronic granulomatous disease of childhood are ineffective, suggesting that the oxidative mechanisms of microbe damage (Ramasarma, 1982) are more important than the non-oxidative ones. Macrophages from diabetics bind zygomycete hyphae less avidly than do those from normal patients (Waldorf *et al.*, 1984a). Isolated lymphocytes, on the other hand, have no effect on the metabolism of the cultured hyphae (Diamond *et al.*, 1982).

Systemic zygomycosis complicates diabetes when control is poor, particularly in phases of acidosis; hyperglycaemia is probably less important (Baker, 1960). This phenomenon has long been studied in animals rendered diabetic by the administration of

alloxan (Bauer *et al.*, 1955). It can be shown that the inflammatory response is qualitatively similar in diabetic mice, but less intense (Sheldon & Bauer, 1959). Subcutaneous injection of cultures in healthy mice leads to focal granulomatous inflammation; subsequent induction of diabetes by alloxan permits recrudescence of active mycosis (Sheldon & Bauer, 1958). Acidosis may be a component of other predisposing states in humans, including renal failure (McNulty, 1982) and chronic salicylate poisoning, (Espinoza & Halkias, 1983).

Iron is known to be necessary for fungal growth, and serum from iron-deficient patients is less able to support fungal growth than that from those with normal iron saturation (King *et al.*, 1975). Transferrin releases iron as the pH drops (Lestas, 1976; Artis *et al.*, 1982), and acidosis may therefore modify conditions to encourage fungal growth; serum from patients with diabetic ketoacidosis will only fail to support hyphal growth if its iron saturation is low (Artis *et al.*, 1982). Further, there is a well-recognized phagocytic and microbicidal defect in diabetes mellitus (Bybee & Rogers, 1964; Bagdade, 1976).

Steroid-induced susceptibility may also be experimentally investigated (Bauer *et al.*, 1957; Baker & Linares, 1974). Cortisone administration enhances spore germination (Waldorf *et al.*, 1984b), and greatly reduces the lethal dose (Kitz *et al.*, 1983).

Spore germination must precede hyphal growth. The organs in which invasive hyphal growth occurs correlate poorly with the sites of maximum spore deposition following intravenous injection (Smith & Jones, 1973), suggesting that local tissue factors are significant. The relation between Zygomycete spore germination and immunosuppression has been less extensively studied than the interaction between hyphal growth and underlying immune defects. Recent experimental studies are therefore important, for they show that spores germinate with much greater facility in diabetic animals (Waldorf *et al.*, 1984a), or in those given steroids (Waldorf *et al.*, 1984b).

Our primary defences, therefore, are the phagocytes, which may have two opportunities to repel any zygomycotic invasion. They may prevent spore germination, and if this fails, they can inhibit hyphal growth.

Conclusion

Systemic zygomycosis is relatively uncommon in the United Kingdom, though in other parts of the world it causes a substantial minority of opportunistic fungal infections (Bodey, 1966; Hart *et al.*, 1969; Marchevsky *et al.*, 1980). The first case recognized in this department was found at necropsy in 1984 (Benbow *et al.*, 1985), and four cases were seen in 1985 (unpublished

observations). This increase reflects world-wide experience; systemic zygomycosis may remain unusual, but is no longer a rarity. It can be cured in a proportion

of sufferers if recognized early in its development. Diabeticians, oncologists, haematologists and general physicians must beware its devastating potential.

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