Fungal pathogens in humans essay

Though there are well over seventy thousand true fungal species that inhabit this planet, very few of these cause diseases in humans, called mycoses. Many more fungal diseases are associated with various plants and other animals.

Mycoses in humans can range from superficial infections to deep-seated systemic infections that are life threatening. The superficial mycoses follow a similar pattern to most bacterial and viral diseases: incubation period is relatively short, onset of disease is sudden and symptoms decrease in severity over time, often with spontaneous healing. Deep-seated mycoses, however, show similarities to aberrant bacterial diseases such as leprosy and tuberculosis: incubation is short, onset of symptoms is varied, and symptoms increase in severity, often resulting in death (Ainsworth 1952). The types of mycoses can be broken into three major groups: cutaneous infections (affecting the outer layers of skin), subcutaneous infections (affecting the tissue below the skin) and systemic (affecting multiple organs in the body). These infections differ from one another in severity of symptoms and mode of transmission, and cause a wide variety of diseases in humans.

This paper does not attempt to cover all human mycoses, but rather those that are interesting from a mycologist’s perspective. Cutaneous Infections Cutaneous fungal infections are those that involve the outer layers of the skin and cause an inflammatory or allergic response. Most cutaneous infections are caused by specialized fungi that thrive on keratinised tissues such as skin, hair, and nails (Kendrick 2000). These organisms are a taxonomically related group of fungi called the dermatophytes. There are approximately forty species of dermatophytes grouped into three genera:

Epidermophyton, Microsporum and Trichophyton. Those with sexual stages have teleomorphs in Nannizzia or Arthroderma (Cole and Hoch 1991).

Dermatophytes are also classified on the basis of the environment in which they are often found. Geophillic strains are able to grow and strive in soil, surviving with a saprophytic mechanism, but these can also be isolated from the hair of some animals. Zoophillic dermatophytes such as Microsporum canis, found on cats, usually parasitize animals other than humans, but some have been found in human infections as well (Campbell and Stewart 1980). Anthropophillic strains are primarily parasitic on humans, and account for slightly less than half of the known dermatophytes (Cole and Hoch 1991). The mechanism of transmission of the fungus is dependent on three different types of spores.

In a saprophytic environment, dermatophytes will produce either large multiseptate macroconidia or unicellular globular microconidia, depending on the organism (Ainsworth 1952). Once the fungus is established as a parasite, it produces only arthroconidia, which are thick walled and may be covered in spine-like projections. This type of spore is spread from person to person on dead skin and fallen hairs (Cole and Hoch 1991). There must be some evolutionary advantage to producing arthroconidia that accompanied the dermatophyte’s progression from geophillic to zoophillic or anthropophillic. The initial association with animals probably occurred in soil-inhabiting rodents. The saprophytic conidia of the soil dermatophytes are quite numerous, and would have been the mode of transfer to the rodents.

Once the transition to a parasitic mode of life was established, the fungus could afford to produce the less abundant arthroconidia. Now it could depend on the common rodent-to-rodent contact for spore dispersal instead of producing several propagules in hopes that one may attach to a patch of fur. One of the most prevalent dermatophytoses is tinea capitis, or ringworm of the scalp. Deriving its name from its similarity in appearance to the marks in cloth made by the moth Tineola biselliella, tinea was first recorded in 1686 in the Philippines (Ainsworth 1952). It is often found in young children, as they are known to be missing several fatty acids that are known fungicides and often play close to one another, allowing for infection to spread rather easily. Poor nutrition, inadequate hygiene, and living with infected pets are also factors increasing the spread of ringworm (Wisuthsarewong et al.

1996). The disease is identified by hairs broken off a few millimetres above the scalp, progressing in a ring-like fashion as the fungal hyphae grow out to attain more resources (Ainsworth 1952). Tinea capitis is normally caused by Trichophyton tonsurans or Microsporum audouinii, which often stimulate epithelial cells to divide more often than usual, increasing the amount of keratin available to the fungus (Kendrick 2000). There are three identified forms of infection in Tinea capitis. Endothrix infection begins by penetration of the hair, then the hyphae grow up the interior main axis of the hair, where hyphal segments fragment into arthroconidia.

Growth near the root can also produce a fringe of delicate hyphae surrounding the root called Adamson’s Fringe (Campbell and Stewart 1980). In favus infection, there is endothrix-style growth, but arthroconidia do not form. Finally, ectothrix infection begins as in endothrix, but the hyphae

extend back out through the hair cuticle and form a mass of arthroconidia both within and around the hair shaft (Patterson and McGinnis 2003). Due to these obvious morphological differences in dermatophytes, microscopic examination can aid in the identification of the fungal species involved.

Another method of identifying a case of dermatophytosis is the Wood's Lamp test, used quite frequently by public health officials . In this test, an ultraviolet lamp is shone over a suspected area of Tinea capitis infection. If hairs glow a bright green colour, it is a sign of infection, since the fungal by-products tend to fluoresce (Wisuthsarewong et al. 1996).

This is not a completely reliable identification method, however, since some dermatophytes do not glow. Following a procedure called hair baiting, detailed by John Rippon from the Pritzler School of medicine, I attempted to isolate Trichophyton tonsurans from soil. According to Rippon (1974), placing human hair on soil from a nutrient-rich area (such as a flower bed) can produce a vast number of keratinophillic fungi. After two weeks of incubation, I examined the hair under an ultraviolet light, finding a few small patches of bright green fluorescence. Examination under a microscope did not show any noticeable hyphal growth, but without proper dyes, an endothrix infection may have been undetected. Dermatophytoses are also found on other parts of the body.

Tinea pedis (athlete's foot) and tinea cruris (jock itch) are often caused by Epidermophyton fluccosum (Kendrick 2000). Chronic ringworm of the body (Tinea imbricata) is found in Polynesians, caused by Trichophyton concentricum. Despite the various forms of dermatophytoses, the clinical

manifestations are all due to irritants they produce, such as proteases, peptidases, and elastases, making the condition a form of toxic dermatitis (Kendrick 2000). Subcutaneous InfectionsSubcutaneous mycoses include a variety of infections characterized by the development of a large lesion at the point where the fungus enters the body, with little spreading from this site (Rippon 1974). Unlike many other modes of infection, whose primary mode of entry is through the inhalation of spores, subcutaneous infections result from traumatic implantation of the fungus into the skin (Cole and Hoch 1991).

Since the fungi that cause these infections are saprobic, generally living on soil, this implantation occurs when spores or fungal tissues enter the skin through a cut or a prick from a thorn (Kendrick 2000). Once in the body, the fungus adapts to its environment, often changing its morphology from a mycelial form to several single-celled yeasts, a condition called dimorphism (Kendrick 2000). Not all species that cause subcutaneous mycoses show the same degree of virulence and not all change their morphology, making this a quite diverse group. The degree and type of dimorphism exhibited by these organisms depends both on the individual species as well as the condition of the host’s immune system. Some species adapt to their environment quite easily and form rapidly dividing yeasts that can spread infection quite easily.

In a host with an immune deficiency, however, the same fungus may remain mycelial in morphology since there is no need to produce an army of yeast to defend against the immune system (Rippon 1974). There is relatively little literature pertaining to subcutaneous mycoses since they occur mostly in tropic environments, and very seldom appear in North America (Campbell

and Stewart 1980). Eumycetoma is a subcutaneous fungal infection caused by Madurella mycetomatis, endemic almost exclusively in Sudan (Ahmed et al. 2002). After the initial implantation of the fungus, Madurella remains inactive until another stress such as a cut or thorn prick occurs.

After this time, a large lesion forms on the skin at the point of injury, under which a large swelling tumour develops. It often ruptures and the hyphae (rarely yeast in this case) burrow back down into the damaged tissue (Rippon 1994). Though very debilitating, Eumycetoma does not spread to internal organs and rarely causes death (Ahmed et al. 2002). Chromomycosis is another subcutaneous infection isolated from the soil rich with decaying vegetation and rotting wood. The disease is usually caused by the fungus Phialophora verrucosa, but there are many other fungal species involved.

The name of the disease is taken from the richly pigmented mycelia, spores, and sclerotic cells of the causative fungi. The clinical manifestation of the disease is similar to Eumycetomas, with lesions appearing at the site of fungal penetration (Sugar and Lyman, 1997). Instead of forming tumours, however, Chromomycosis produces raised lesions with a scaly, dull, and red to greyish surface, which may become secondarily infected by other bacteria (Rippon 1974). Again, there have been no deaths associated with this infection, as it is not likely to spread to other regions of the body. Systemic Infections Systemic infections result from inhalation of spores produced by the fungi that often live in soil or rotting vegetation.

Unlike subcutaneous diseases, these infections have the ability to spread to several organs in the body. The systemic infection Histoplasmosis is caused by the ascomycete Histoplasma Capsulatum. It is endemic in specific geographical areas, such as the Ohio and Mississippi River valleys (Kern 1985). Infection is established after the inhalation of microconidia and hyphae.

After this, most people (approximately 90%) do not show any symptoms. Those that do become ill complain of mild, non-specific symptoms such as fever, chills, headache, chest pain, weight loss and arthritis. Occasionally, the lung infection can become chronic, and the fungus forms small nodules in the lungs called histoplasmomas (Campbell and Stewart 1980). These nodules degrade the outer layers of the lung, and often resemble tuberculosis in appearance and symptomatology. Inflammation of the membranes covering the heart (pericarditis) and fibrosis of major blood vessels are also associated with this disease (Klein 2000).

Though there have been reported cases of spontaneous recovery of chronic pulmonary histoplasmosis, prognosis is rather grim-many chronic patients die within a few weeks to a few months (Ainsworth 1952). An interesting aspect of Histoplasma is that it lives a double life: one as a soil-dwelling mycelial saprobe and another as a pathogenic yeast living in mammalian tissues. This mycelial form is found in soil enriched with bird and bat droppings, and produces infections spores (Klein 2000). When the soil is disturbed, spores are inhaled into the respiratory tract, and the temperature change from twenty-five degrees Celsius to the mammalian body temperature of thirty-seven degrees Celsius stimulates the growth of the

yeast form (Magrini and Goldman 2001). In an attempt to destroy the foreign yeast, the host’s macrophages and other cells of the reticulo-endothelial system engulf them (Klein 2000).

Unfortunately for the human, the yeasts survive and proliferate within the normally hostile environment of the phagolysosomes, cells formed by fusion of phagocytic vesicles with lysosomes (Sebghati and Goldman 2000). The yeast cells secrete enzymes that establish a more basic environment than usually present in the phagolysosomes, deactivating many lysosomal enzymes requiring a low pH (Klein 2000). Another way the host’s cells defend themselves is by withholding required nutrients such as iron and calcium from the intruders, sequestering them in the phagolysosomes (Weinberg 1999). In fact, there is a very low concentration of calcium in the very cells Histoplasma yeasts choose to call home.

The yeasts are able to grow in a calcium-deprived environment by secreting a 7. 8 kilodalton calcium binding protein (CBP). This knowledge has allowed researchers to isolate the CBP1 gene and they found that by disrupting it in fungal cultures, the yeasts lost their ability to survive in a calcium-limited environment. Interestingly, the saprophytic (mycelial) form of Histoplasma cannot survive without high levels of calcium in the environment, and does not secrete CBP (Magrini and Goldman 2001). The organism must have the CBP1 gene, but it is “ turned off” in the mycelial form.

A probable reason for this missing protein is that the organism is conserving energy and resources, only producing CBP when conditions are guaranteed to be low in calcium. Thus, it is apparent that the evolution of the parasitic

yeast form from the mycelial form was dependent on the incorporation of the CBP1 gene into the fungal genome. How CBP links the two phenotypes is at the moment unknown, but it remains that calcium acquisition is an important strategy for microbial survival in the intracellular compartments. Histoplasmosis is an example of an endemic disease, one that is able to produce an invasive infection in healthy individuals as the fungus is sufficiently virulent that it does not require help breaching the host's immune system (Patterson and McGinnis 2003). Another example of this type of systemic infection is Blastomycosis, caused by Blastomycetes dermatidis, also a thermally dimorphic ascomycete.

There are two forms of the disease: a cutaneous infection caused by direct contact with fungal spores through a cut, and a pulmonary infection from the inhalation of spores. Both of these infections may lead to a systemic disease, affecting a number of organs such as the brain and kidneys (Kern 1985). Another type of systemic fungal infection is opportunistic meaning the fungus is not able to harm individuals with healthy immune systems. AIDS and chemotherapy patients, as well as organ transplant recipients and others with lowered immune defences are at a high risk of developing this sort of uncommon invasive infection. For example, the mainly conidial Aspergillus causes a widely varied disease called Aspergillosis in immunocompromised individuals (Denning et al. 1991).

Aspergillus is a rather ubiquitous fungus, commonly isolated from soil, plant debris, and indoor air environments. Out of 185 recorded Aspergillus species, only 20 cause opportunistic infections in man, with Aspergillus fumigatus being the most commonly isolated species. Aspergillosis may at first present

as a bronchopulmonary infection as Aspergillus colonizes in bronchial and lung tissue (Denning et al. 1991). The presence of Aspergillus in healthy individuals is not uncommon; in fact, many people have sustained microscopic pulmonary lesions identifiable only by biopsy, and have never suffered from any symptoms (Campbell and Stewart 1980). In immunocompromised individuals, however, the fungus tends to reside in larger lesions produced by prior infections such as tuberculosis or pneumonia and dissolves the already raw lung tissue.

This results in airway obstruction, coughing, and chest pain. The disease occasionally disseminates to other organs such as the heart, kidneys, and brain (Denning et al. 1991). While the initial infection is indeed caused by inhalation of spores, Aspergillus is not dimorphic like many other systemic disease-causing fungi. It grows in a mycelial form in the soil as well as in the human body (Patterson and McGinnis 2003). As with many other systemic diseases, Aspergillosis is most often fatal, and the host’s immune system is too badly damaged to repair the body.

Candidiasis Perhaps one of the best-known fungal is candidiasis, otherwise known as “ thrush”, “ monilla”, or a “ yeast infection”. The spectrum diseases caused by the fungus Candida is quite extensive, ranging from simple colonization of mucosal membranes to multiple organ invasion (Sugar and Lyman 1997). Due to the large range of infections caused by members of Candida, it cannot be classified as strictly cutaneous, subcutaneous, or systemic. Though members from several species of the genus have been recovered in human infection, the most common medically important member is Candida albicans.

This organism is a normal inhabitant in the intestines and mucotaneous regions of healthy individuals. The fungal cells only become problematic when they congregate in one area, sparking an immune response from the host. Candidiasis is thus categorized as an endogenous disease (arising from the host), but also can be obtained exogenously from catheters, prosthetic devices, or through person-to-person contact. Generally, mild diseases such as oral candidiasis (thrush) or vaginitis occur in otherwise healthy individuals with a slight drop in immune system performance. In pregnant women, the likelihood of vaginal candidiasis is high since there is an increase in glycogen levels in mucosal tissues, which stimulates overgrowth of Candida. This infection may be passed as thrush to her baby following birth, before the natural flora of protective bacteria is established (Kendrick, 2000).

In the same way, adults taking antibiotics for a bacterial infection are quite susceptible to candidiases, since the lactobacilli that regularly keep this fungus in check are also destroyed along with the harmful bacteria (Kendrick 2000). Infections of the mucotaneous regions are usually identified by large white patches of yeast, white blood cells, debris, and bacteria. Candida albicans can adhere to host tissues using specialized proteins called adherins and produces aspartyl proteases and phospholipase enzymes, causing mild to severe swelling, itchiness and redness in the infected areas (Cole and Hoch 1991). Like opportunistic systemic diseases, Candida can also prey on those with weakened immune systems, causing chronic bronchial pulmonary or alimentary candidiasis.

These diseases are almost never seen in healthy people because the fungus is not strong enough to overcome a healthy immune system. The ability for

yeasts to survive most of their lives in the human body arises from their ability to undergo morphological changes in certain conditions. Typically, C. albicans grows as single ellipsoidal cells called blastospores (blastoconidia). In the presence of inducing signals in the environment, the fungus can assume a filamentous form in which cells remain attached to each other after dividing, forming long branching strings of connecting cells (Hoffman 1992).

This filamentous form can assume the form of pseudohyphae in which cells are elongated but still ellipsoidal, or true hyphae where highly elongated cells forming the filament are cylindrical and separated by perpendicular septal walls (Braun and Johnson 1997). The morphological change is thought to contribute to colonization and dissemination within host tissues and promote infection. The main cause of filamentous growth in C. albicans is a shortage of food. Since these tiny cells cannot move, they grow toward a new food source by attaching to one another in a filament (Hoffman 1992).

In the lab, high temperature, serum, high carbon dioxide to oxygen ratio, and neutral pH cause blastospores to sprout hyphae (Braun and Johnson 1997). One of the key genes responsible for filamentous growth is TUP1, first isolated from Saccaromyces cerevisiae, which until 1992, was not thought to have a filamentous form at all (Hoffman 1992). By isolating and disrupting TUP1, researchers have observed constitutive filamentous growth. This discovery leads to possible modes of treatment, perhaps by supplementing an infected individual with a compound that stimulates transcription of TUP1, in hopes to prevent filamentous growth (Braun and Johnson 1997).

Treatment of Human Mycoses There are several drugs available to treat fungal infections in humans.

Until quite recently, however, diseases such as Histoplasmosis, Aspergillosis, and Blastomycosis were almost always fatal (Kendrick 2000). Nyastatin, produced in 1950, was one of the first successes in treatment of superficial and oesophageal candidiasis (Kendrick 2000). Amphotericin and Ketoconazole are useful in treating deep-seated systemic mycoses, but have several unpleasant side effects, and should only by administered as a last resort. Dermatophyte infections can also be treated using Canestin, Griseofluvin, Tolnaftate, and most recently, Terbinafine, with relatively mild side effects (McClellan et al. 1999). Some mycoses can also be prevented by diet and lifestyle changes.

For example, candidiasis can be prevented by keeping skin dry and wearing loose clothing, as fungal growth is encouraged by moist conditions. Also, several studies have shown that eating yoghurt every day will restore the natural flora of lactobacilli in the body, preventing yeast infections (Lewis 1992). Conclusions Despite the array of possible mycoses with which humans have been afflicted, severe systemic and subcutaneous diseases are still quite rare in North America. Due to the increasing number of immunocompromised individuals, however, rare fungal diseases once found only in other animals are causing complications and death in these people.

The ability of kingdom Eumycota to thrive in both saprophytic and parasitic environments and change its morphology has contributed greatly to the success of fungi on Earth. As we continue to observe the evolution of

saprophytic fungi to parasitic organisms, we must expect to see more mycoses affecting humans-we simply present an environment too ideal to pass up.