The living world is divided into the five kingdoms of Planta, Animalia, Fungi, Protista and Monera. So note: fungi are unrelated to the Monera, or bacteria. In general, fungi are eukaryotes, heterotrophic, unicellular to filamentous, bear spores and have a rigid cell wall, akin to plants. They reproduce by sexual and asexual means. They are insensitive to antibacterial antibiotics – an important point, and one reason why it is important to recognize when an infection is fungal in origin. Fungi are non-motile, unlike many bacteria. The term eukaryotic means they have membrane-bound cell organelles such as nuclei, mitochondria, Golgi, an endoplasmic reticulum and lysosomes. Eukaryotes also exhibit mitosis. These features separate fungi from bacteria. Fungi are heterotrophic, meaning they lack chlorophyll – they are not autotrophic (photosynthetic) like plants and algae. As heterotrophic organisms, they absorb their nutrition either as saprophytes (from dead organic matter) or parasites (utilizing living tissue). Most fungi are saprophytes and are readily detected in lesioned tissues microscopically due to their size and distinctive appearance. A hallmark lesion is the presence of granulomatous inflammation, although the floridity of the reaction depends on the agent. Some fungi (e.g., Cryptosporidia) invoke minimal granulomatous response as part of their survival strategy. Various chemical stains are used to highlight fungi in tissues, and this may help identify the species involved. Fungal culture is a specialized and potentially risky activity. In the WSVL we have limited capability to identify fungi, and tend to send out all but the most routine samples.

**Fungal Pathogenicity**

The ability of fungi to cause disease appears largely accidental. With the exception of the **dermatophytes** responsible for ringworm, the ability to cause disease is not necessary for maintenance or dissemination. Three physiologic barriers limit fungal growth in the body:

- Body temperature. Most fungi are mesophilic. They cannot grow at 37 C.
- Redox potential. Fungi are saprophytic. Their enzyme pathways function more efficiently at the redox potential of non-living substrates than at the more reduced state of living tissue.
- Immune defenses.

The basic mechanism of fungal pathogenicity is the ability to adapt to the environment in tissues and withstand the lytic activity of the host's cellular defenses. **In general, the development of mycoses is related primarily to the immunological status of the host and environmental exposure, rather than to the infecting organism.** For most fungi, and unlike bacteria and viruses, rarely is there a single virulence factor determining the ability to cause disease. A few fungal species have the ability to cause infections in normal healthy animals. This is by virtue of:

- Unique enzymatic capacities,
- Exhibiting thermal dimorphism
- Blocking cell-mediated immune defenses
There are also opportunistic fungi which cause infections almost exclusively in debilitated patients with impaired defense mechanisms. The organisms involved are cosmopolitan and have low inherent virulence. In the wake of our medical ability to suppress the immune system, and keep immunologically fragile human and animal patients alive for extended periods, there has been an increase in fungal infections of this type, particularly due to candidiasis, cryptococcosis, aspergillosis, and zygomycosis. All told, only 200 pathogenic fungal species are recognized among the estimated 1.5 million species of fungi.

STRUCTURE OF FUNGI

Fungi have two basic growth stages. The unicellular (yeast) form is defined morphologically as a single cell that reproduces by budding. The filamentous (mold) form is due to the vegetative growth of filaments. Reproduction is by the formation of spores or conidia. Moulds produce a variety of conidia that develop on specialized hyphae. Most molds are identified by the morphology of spores and their arrangement on hyphae. A mass of hyphae collectively makes up a mycelium. There are two kinds of hyphae: septate and non-septate. Septa divide hyphae into compartments but not into cells. In some groups, nuclei and/or cytoplasm flow through pores in the center of septa. As pathologists, we use the shape, size, branching pattern and septation to attempt to speciate fungi in tissue. Exact identification requires that the fungus be grown in the laboratory. With the exception of cutaneous and post-traumatic fungal infections, most mycoses occur as a result of inhalation of spores: most internal fungal infections start in the upper or lower respiratory tract. Immunologically robust individuals are constantly bombarded by fungal spores which are rapidly cleared from the upper and lower respiratory tract. Detecting an internal fungal infection should suggest either immune compromise or exposure to one of the few pathogenic fungal species, or both.

FUNGAL INFECTIONS

SUPERFICIAL MYCOSES

Ringworm of scalp, glabrous skin, and nails is caused by fungi known as dermatophytes. These possess keratinases and can use keratin as a nutrient. No living tissue is invaded, unless it is as a result of inflammation and rupture of hair follicles. Ringworm fungi and their metabolic products often induce allergic and inflammatory responses in the host. These tend to be worse in some species (dogs) than in others (man). The type and severity of the host response is often related to the species and strain of dermatophyte. Many cats carry ringworm without showing clinical signs – it is first suspected when the owner develops an infection. Dermatophytes are the only fungi with an evolved dependency on human or animal infection for survival and dissemination. Dermatophytes occur as 3 epidemiological groups: geophilic (soil inhabitants), zoophilic (parasitic on animals) and anthropophilic (parasitic on man). Ringworm often induces inflammation around hair shafts (folliculitis). Colonization of hair shafts and secretion of keratinases makes hairs fragile, resulting in hair loss (alopecia). Ringworm is a self-limiting infection lasting 1 – 4 months. It is not fatal. Geomycosis (white-nose syndrome of bats) due to the new described fungus Geomyces destructans. This has caused a die-off of multiple bat species in North America and Europe during hibernation. In addition to causing a ringworm-like disease in hair follicles, it damages the wing epidermis. This may be the basis for death, due to disruption of the physiology of hibernating bats. Another superficial mycosis is due to Malassezia species. This organism generally occurs as yeast and is a normal inhabitant of human and canine skin. In circumstances where skin is unusually moist or there are abundant long-chain fatty acids, Malassezia proliferate and exacerbate the skin disease. It commonly
complicates otitis externa in dogs with pendulous ears, and various forms of keratinizing defects of the skin (“seborrhea”).

**SUBCUTANEOUS MYCOSES**

These are chronic, localized infections of skin and subcutaneous tissue in the wake of traumatic implantation of fungi. Most are due to soil saprophytes of regional epidemiology whose ability to adapt to the tissue environment and elicit disease is variable. They are for the most part rare in Wyoming and are more common in tropical/subtropical areas. One that occasionally occurs in cats and people is **sporotrichosis**. This chronic mycotic infection affects cutaneous or subcutaneous tissues and adjacent lymphatics. It is characterized by granulomatous nodules that suppurate and ulcerate. Infections are caused by traumatic implantation of fungi into the skin or, on rare occasions, by inhalation. I am not aware of a case occurring in cats or other animals in Wyoming. Another subcutaneous mycotic infection is **chromoblastomycosis**. As the name suggests, these fungi are pigmented – the ability to form melanin in fungi is thought to be partially protective against free-radical destruction. We see this occasionally in horses, most typically in open wounds or in sarcoids that are opportunistically infected. They tend to be chronic, localized, slowly progressive granulomatous lesions. **Mycetomas** are exactly what you might think: granulomatous masses caused by various fungi (some include some of the “higher bacteria,” such as the actinomycetes). They are characterized by draining sinuses, granules and tumefaction. These are due to traumatic implantation of fungi, involving the cutaneous/subcutaneous tissue, fascia, and lower limbs, and oral cavity. Sinuses discharge serosanguinous fluid containing the granules (= fungal colonies) of varying size, color and hardness, depending on the species. These granules are the hallmarks of mycetomas.

**SYSTEMIC MYCOSES**

These are several systemic fungal infections caused by dimorphic fungal pathogens. In each case they have the ability to circumvent normal physiological and cellular defenses. They tend to be geographically restricted, so that it is often helpful to know which pathogenic fungi are endemic to the area where you work as a physician or veterinarian – or where your patient has been. The primary site of infection is generally the respiratory tract, following inhalation of conidia. In some cases they induce type 4 hypersensitivity reactions, which form the basis for clinical tests, and exacerbates the disease process. A few important ones (from a national standpoint) are addressed below. **Histoplasmosis** is an intracellular mycotic infection of the reticuloendothelial system caused by the inhalation of *Histoplasma capsulatum*. Some 95% of cases of histoplasmosis are inapparent, subclinical or benign. Of the remaining 5%, most patients (animal or human) have chronic progressive lung disease, chronic cutaneous or systemic disease, or acute fulminating disease. All stages of histoplasmosis can mimic tuberculosis. It is typically seen along the Mississippi and Ohio drainages. We’ve seen cases of a histoplasmosis-like disease in dogs and cats in Wyoming (Torrington area). **Coccidioidomycosis** is another geographically localized disease: in the US it is restricted to the south-western US. It begins as a systemic respiratory infection after inhalation of conidia. In most human and animal patients it resolves rapidly, leaving the patient with a strong specific immunity to re-infection – this is a problem in trying to make a diagnosis, since suspect cases are often test-positive due to subclinical disease. In some individuals the disease may progress to a chronic pulmonary or systemic disease involving meninges, bones, joints and subcutaneous and cutaneous tissues. **Blastomycosis** is due to the endemic dimorphic fungi *Blastomyces dermatitidis*. Outbreaks are associated with occupational or recreational activities around streams or rivers with high content of moist soil enriched with organic debris and/or rotting wood. Infection is acquired via
inhalation of the conidia, which transform into yeast forms once in the lungs. After 1 – 2 months an acute pulmonary disease indistinguishable from a bacterial pneumonia may occur. However, at least 50% of primary infections are asymptomatic. Most cases become manifest during a chronic and indolent phase that may affect the lungs, the skin, the bones, the genitourinary tract and other reticuloendothelial organs. Blastomycosis may coexist or mimic a pulmonary carcinoma, and tuberculosis.

OPPORTUNISTIC SYSTEMIC MYCOSES

Opportunistic fungal infections of the body occur almost exclusively in debilitated patients with impaired normal defense mechanisms. The organisms responsible are cosmopolitan with low inherent virulence. The increased incidence of these infections and diversity of fungi causing them paralleled the emergence of AIDS, similar immunosuppressive infections in animals, and the use of antibiotics, cytotoxins, immunosuppressive drugs and corticosteroids. A particular risk for systemic opportunistic mycoses is a low neutrophil counts (neutrophilia). Any fungus that can grow at 37°C and gain access to the bloodstream may cause disseminated infection. These infections pose problems in terms of initial clinical recognition, diagnosis and laboratory identification. The prevalence of serious fungal infections in patients increased in the wake of the emergence of HIV, especially candidiasis, cryptococcosis and aspergillosis. Candidiasis, illustrated in the lecture, is most often occurs as an oral infection (“thrush”) of AIDS patients, children and the elderly. Systemic candidiasis is seen in patients with cell-mediated immune deficiency, receiving aggressive cancer treatment, are immunosuppressed as part of transplantation therapy, or have indwelling medical devices. It is also a common infection of birds. Mucosal candidiasis affects most symptomatic AIDS patients, with one species (C. albicans) accounting for >85% of infections. One of its defense mechanisms is its ability to form biofilms, which is why they are associated with intravascular and urinary catheters. Cryptococcosis due to Cryptococcus neoformans in patients with AIDS is considered incurable, and requires lifelong therapy. An estimated 10 - 30 % of AIDS patients develop cryptococcosis, and mortality approaches 100% when untreated. AIDS is the classic setting for this fungus which has the ability to inhibit phagocytosis and survive the non-specific inflammatory immune defenses of the host. Cryptococcosis is one of the classical opportunistic fungi. a species that was hitherto considered exotic to North America emerged on Vancouver Island in the last decade, and has since spread to mainland Canada and to Oregon. This chronic, subacute to acute pulmonary, systemic or meningitic disease is initiated by the inhalation of basidiospores and/or desiccated yeast cells of C. neoformans. Primary pulmonary infections have no symptoms and are usually subclinical. On dissemination, the fungus usually shows a predilection for the central nervous system. Aspergillosis is a spectrum of diseases of humans and animals caused by members of the genus Aspergillus. These include mycotoxicosis due to ingestion of contaminated foods; allergy and sequelae to the presence of conidia or transient growth of the organism in body orifices; colonization without extension in preformed cavities and debilitated tissues; invasive, inflammatory, granulomatous, necrotizing disease of lungs, and other organs. It can cause systemic and fatal disseminated disease. The type of disease and severity depends upon the physiologic state of the host and the species of Aspergillus involved. Growth of aspergillus in the guttural pouch of horses occasionally leads to rupture of the internal carotid artery, and fatal bleeding out via the nose. We see aspergillosis on occasion as a cause of pneumonia, encephalitis, placentitis and nasal infections in animals, particularly in cattle.

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