

MID 28
Fungi – 1
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Locky Chambers
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The Professor rambled for a bit before delving into the pathogenesis of fungal infections:

Preamble: Fungal infections, which at the beginning of this century were quite rare, are now increasingly more common. This is in large part a result of the increase in number of immunocompromised individuals. Normally people have strong natural immunity to fungi: only a couple of dozen fungi out of hundreds of thousands are pathogenic. Fungi are very good at taking advantage of some abnormality in the human host and, thus, virtually every fungal infection is opportunistic.

Fungi are eukaryotic, not motile, and usually aerobic. They can exist as parasites or free living organisms and need organic sources of nourishment. They have a dense rigid cell wall made of glucan and chitin (found in crabshells). Their cell membrane contains sterols (ergosterol), making them similar enough to human cell membranes to have negative implications for the membrane destroying properties of antifungal drugs.

Fungi come in many forms but we need to know three:

- 1) yeasts – round/oval, unicellular and reproduce via budding
- 2) molds – long, floppy, fluffy colonies that microscopically can be seen as long tubular structures called hyphae and reproduce by forming spore-forming structures at the end of hyphae called conidia
- 3) dimorphs – most medically important, can change from yeast to mold and back, and grow in environment as molds and in humans as yeast

Fungi can produce toxins but this is not relevant to human infections. Fungi can produce human disease because of their sheer size (50-100 times larger than bacteria) and by eliciting an immune response as a result of them or their by products. There are three different types of fungal infections:

- 1) Superficial/cutaneous – present on skin, hair, nails
- 2) Subcutaneous – infection in tissues under the skin
- 3) Systemic – two groups: a) “true pathogens” (term is becoming obsolete) – have ability to cause disease in healthy hosts b) “opportunists” – cause disease exclusively in immunocompromised individuals

Superficial Fungal Infections: These infections are common all over the world (but with a geographic pattern) and are caused by fungi called dermatophytes, which produce keratinase. This allows them to metabolize and live on human keratin – in skin, nails, and hair. They cause inflammation but do not and can not invade deeper into the dermis. These fungi cause the *tinea* (worm) diseases: body ring worm-*tinea corporis*, athlete’s foot-*tinea pedis*, jock itch-*tinea cruris*, nails-*tinea unguum*, ring worm of scalp-*tinea capitis*. These infections are red, itchy and scaly. To diagnose one would observe the clinical findings, scrape the lesion and look under the microscope, and/or use a Wood’s lamp (UV) – colonies fluoresce.

One other important superficial infection is caused by the yeast *Malassezia furfur*. It does not even get into the keratin – more superficial than the dermatophytes. It digests the top layer of lipids and affects adolescents and adults to cause the superficial infection called *tinea versicolor* – round, hypo and sometimes hyperpigmented patches. It never penetrates the skin but can, especially nosocomially, infect the blood by contaminating lipid IV solutions.

Subcutaneous Fungal Infections: If introduced through the human skin, these fungi have the biologic ability to grow in subcutaneous tissue and sometimes can cause significant human disease. They can grow up lymphatics and into bones or joints if in the way. These infections are far more common in the developed world. There are a variety of species that cause them: in India, Africa, and the Far East, generally speaking, they cause mycetoma (Madura foot). Individuals walking barefoot may get a splinter or injury to the foot and be inoculated, and slowly the bones in the foot and the ankle joint can be destroyed.

The only subcutaneous fungal infection that we may run into is Sporotrichosis, caused by the dimorphic fungus *Sporothrix schenckii*. It needs a splinter or a thorn to introduce it into human tissue – it can only live inside the body. It travels along lymphatics and causes a combination of pyogenic and granulomatous reaction. It manifests itself as a set of ulcerating nodules along a hard cord as it slowly grows up the lymphatics. It moves from distal to proximal and can lead to bone and joint destruction. It can become disseminated almost exclusively in immunocompromised individuals. The classic clinical presentation of this is with individuals with outdoor encounters: gardeners, golfers, hunters.

Systemic Fungal Infections: These are less common but more serious. They can be divided into two families. The first family is the “true pathogens” who can infect all types of people, including those with a normal immune system. Although, very much like TB, they cause disease only in specific circumstances – of the huge number of individuals that are infected only a few get disease.

As these infections have a number of properties in common, we should think of them as a group: Histoplasmosis, Coccidioidomycosis, and Blastomycosis. First, they are all caused by dimorphs. They grow as molds in soil and reproduce there by sporulation. When they enter a human, which happens exclusively via the respiratory route, they become yeasts. They also have a restricted geographic distribution and finally, and most importantly, they all cause disease with symptoms almost indistinguishable from TB.

Histoplasmosis: This infection is caused by the organism *Histoplasma capsulatum*. This fungus really likes soils with a high nitrogen content so it is found in the Ohio-Mississippi Valley, the Caribbean, Central and South America. It is particularly endemic to chicken coops and caves due to the nitrogen in bird and bat droppings. How does it cause disease? We inhale spores, which change into yeast in the lungs, are phagocytosed by macrophages, and are disseminated hematogenously. After about 6 weeks, one can be tested for histoplasmin antigen derivative (just like TB), which is useful for diagnosing exposure but worthless for diagnosing disease. Clinically, histo also mimics TB; almost everyone who is infected with this organism has latent disease. Very few people get sick,

unless there is something else going on: can cause problems for those with an immature immune system or immunocompromised. For people with abnormal lungs, histo can cause pneumonia if inhaled into non-perfused areas. It can cause a chronic, cavitating nodular infection very similar to TB. Histo can remain latent and reactivate many years later, for example, with AIDS. This can then disseminate and cause disease in virtually every organ of the body. To differentiate between TB and Histo, one can use sputum or blood smears, and PPD.

Coccidioidomycosis: This fungus is probably the most virulent and prefers to live in hot dry weather (Arizona, Cali, Mexico, Central and South America). Unlike Histo, this dimorph turns into a spherule not a yeast in the human lung. A spherule is a giant seedpod full of thousands of yeast particles called endospores; thus, it can infect very efficiently (explains virulence). There is also a skin test for Cocci called coccidioidin. Like Histo, spores are aerosolized and inhaled. The same sequence of events as in TB and Histo will happen. However, unlike TB and Histo, the primary infection with Cocci can have symptoms because one is getting such a huge load of organisms, with the endospores disseminating in the lungs. One gets a self-limited, flu-like syndrome (sometimes called Bali Fever). However, in some people it does disseminate (more commonly in pregnant women, immunocompromised, and darker skinned people) and causes skin, bone, and CNS disease.

Blastomycosis: The fungus blastomyces dermatiditis causes this disease. Again, this fungus is a dimorph that lives in a soil as a mold and becomes yeast in the human being upon inhalation. It really likes organic debris and humidity: woodlands, beaver dams, marshes, and peanut farms (for some unknown reason); Mid-Atlantic, Carolinas, and Mississippi Valley are all Blasto country. Again, it is picked up from aerosolized spores. In its yeast form, **blasto** is much bigger than Histo and has **broad based buds** and a small capsule. The pathogenesis is basically the same as the others. The one big difference is that no one has yet discovered a characteristic protein for a skin test. So we have no idea how many people have been exposed and go on to develop disease with Blasto. We do know that with a fraction of people (immunocompromised) the disease can go on to become disseminated or can stay in the lungs to cause a TB-like disease. It likes cool surfaces so it tends to cause a lot of skin disease (skin lesions that look and behave like skin cancer), bone disease, and urinary tract disease in men.

Unofficially used from C.M.M.R.S: please examine Cowboy Fungus's **spore** bullets and observe how he **cocks** his gun, then **blasts** and **hits** the lung, skin, bone, and meninges.



