OPPORTUNISTIC AND SYSTEMIC MYCOSES

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LEARNING 0BJECTIVES:

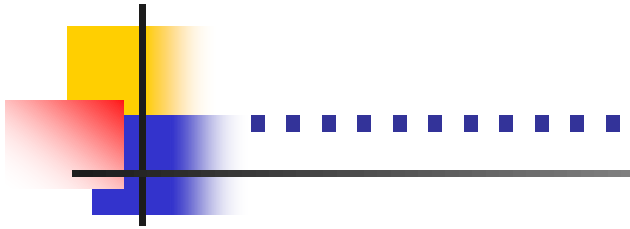
- Defining terminologies
- Aetiological agents ; entry of pathogens, Adaptation and propagation, Dissemination,
- Pathogenesis, Symptoms and epidemiology.

DEEP MYCOSES

Primary versus opportunistic mycoses:

- Deep mycoses are caused by primary pathogenic and opportunistic fungal pathogens. The primary pathogenic fungi are able to establish infection in a normal host; whereas, opportunistic pathogens require a compromised host in order to establish infection (e.g., cancer, organ transplantation, surgery, and AIDS).

- The primary deep pathogens usually gain access to the host via the respiratory tract. Opportunistic fungi causing deep mycosis invade via the respiratory tract, alimentary tract, or intravascular devices (figure 2).



- The primary systemic fungal pathogens include *Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis*.

- The opportunistic fungal pathogens include *Cryptococcus neoformans, Candida* spp., *Aspergillus* spp., *Penicillium marneffei*, the Zygomycetes, *Trichosporon beigelii*, and *Fusarium* spp.

ANATOMICALLY

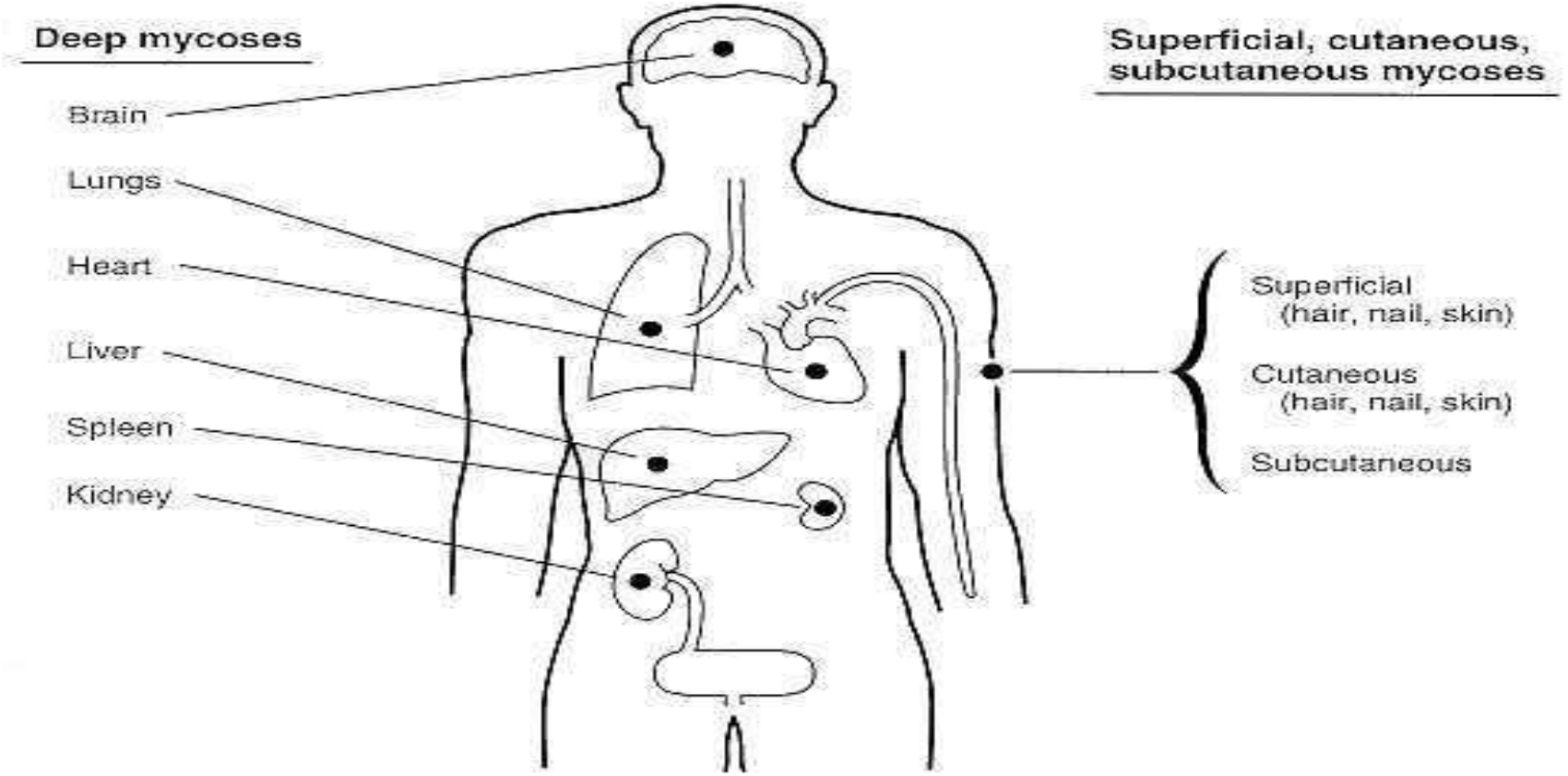


Figure 1 Principal tissue sites of deep mycoses in comparison to those of the superficial, cutaneous, and subcutaneous mycoses.

AS FOR DEEP MYCOSES

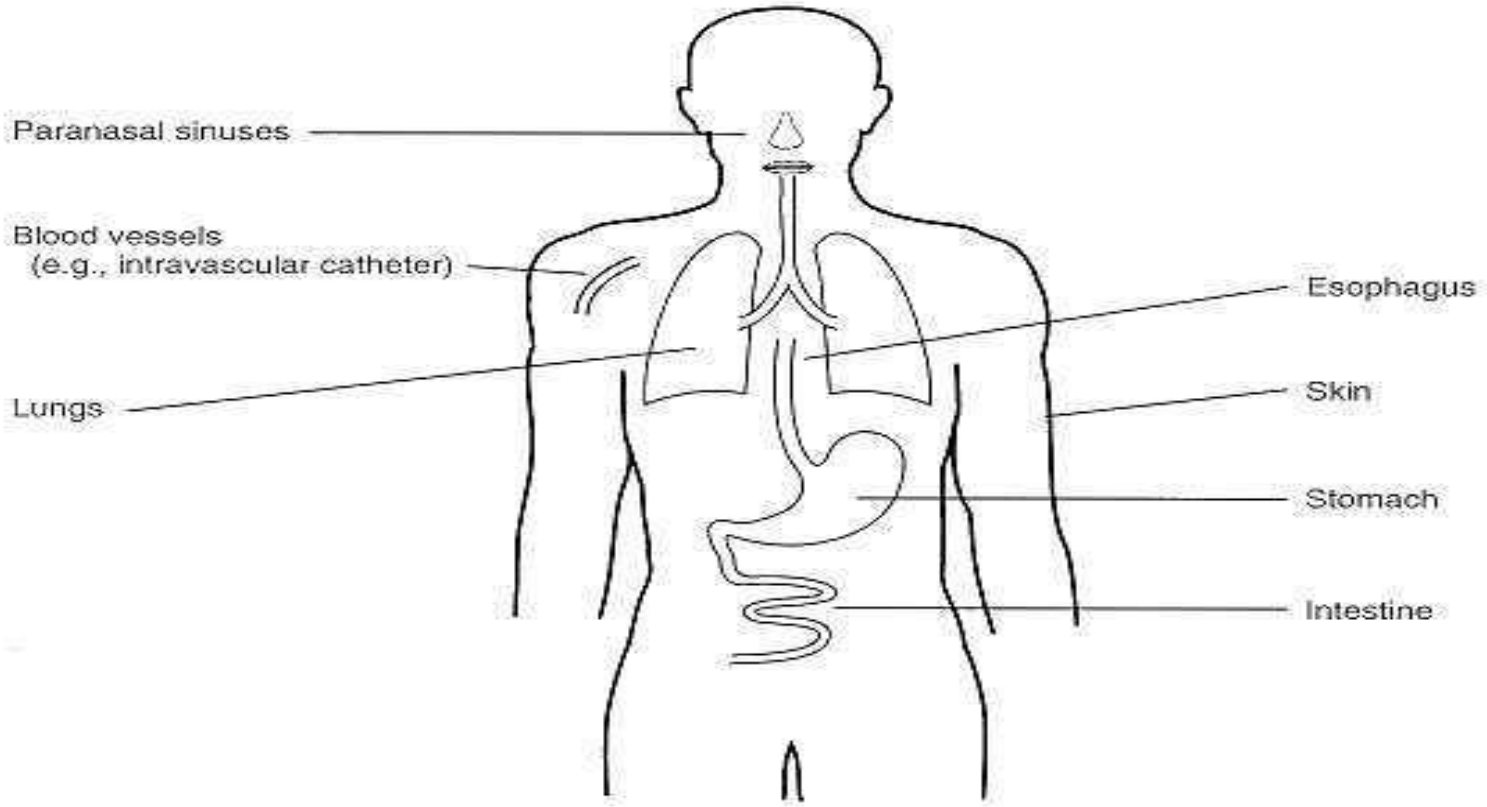


Figure :2 Portals of entry of pathogenic and opportunistic fungi causing deep mycoses.

- **Dimorphism in the Pathogenic Fungi:**
- **Fungal dimorphism** is the morphological and physiological conversion of certain fungi from one phenotype to another when such fungi change from one environment to another.

- Dimorphic fungi include *C immitis, H capsulatum, B dermatitidis, P brasiliensis, P marneffei*, and *S schenckii*, and certain opportunistic fungi such as *Candida albicans* and *Penicillium marneffei*. Various environmental host factors control fungal dimorphism.

- These factors include amino acids, temperature, carbohydrates, and trace elements (e.g. zinc). Among the primary pathogens and *S schenckii*, the morphological transformation is from a hyphal form to a yeast-like form (or spherule in the case of *C immitis*) in tissue (Fig. 75-3).

- However, the dimorphism of *Candida albicans* is somewhat different in that the organism transforms from a budding yeast-like structures (blastoconidia) to filamentous structures known as germ tubes (Fig. 75-4).

- Other filamentous structures may later develop as pseudohyphae and hyphae. *Penicillium marneffei* is unique in being the only *Penicillium* species pathogenic to humans. It undergoes dimorphic conversion in vivo to transversely dividing sausage-shaped cells.

REFER TO THIS REPRESENTATION;

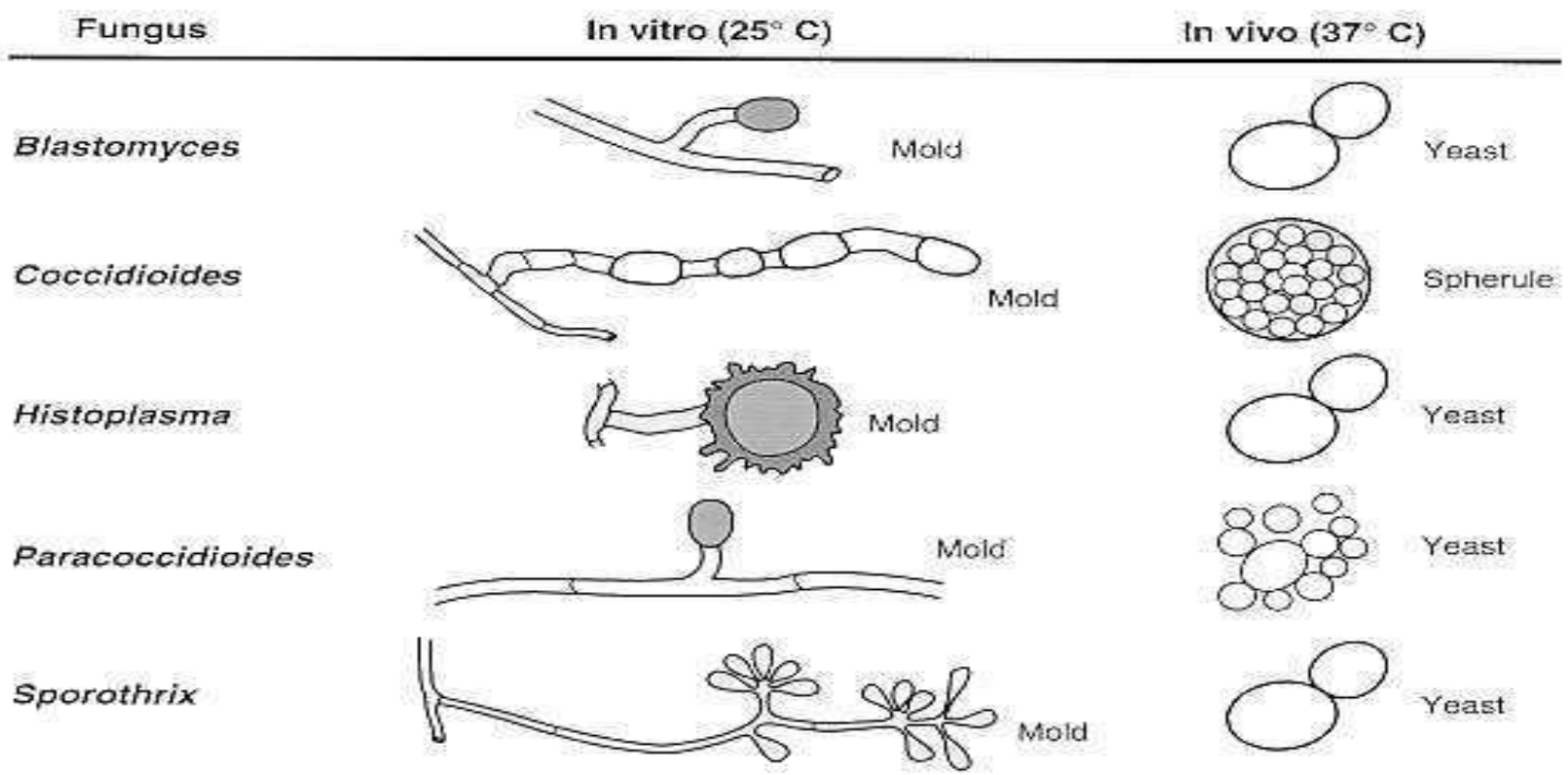


Figure 75-3 Diagrammatic representation of the saprophytic and invasive tissue forms of pathogenic fungi.

AND THIS

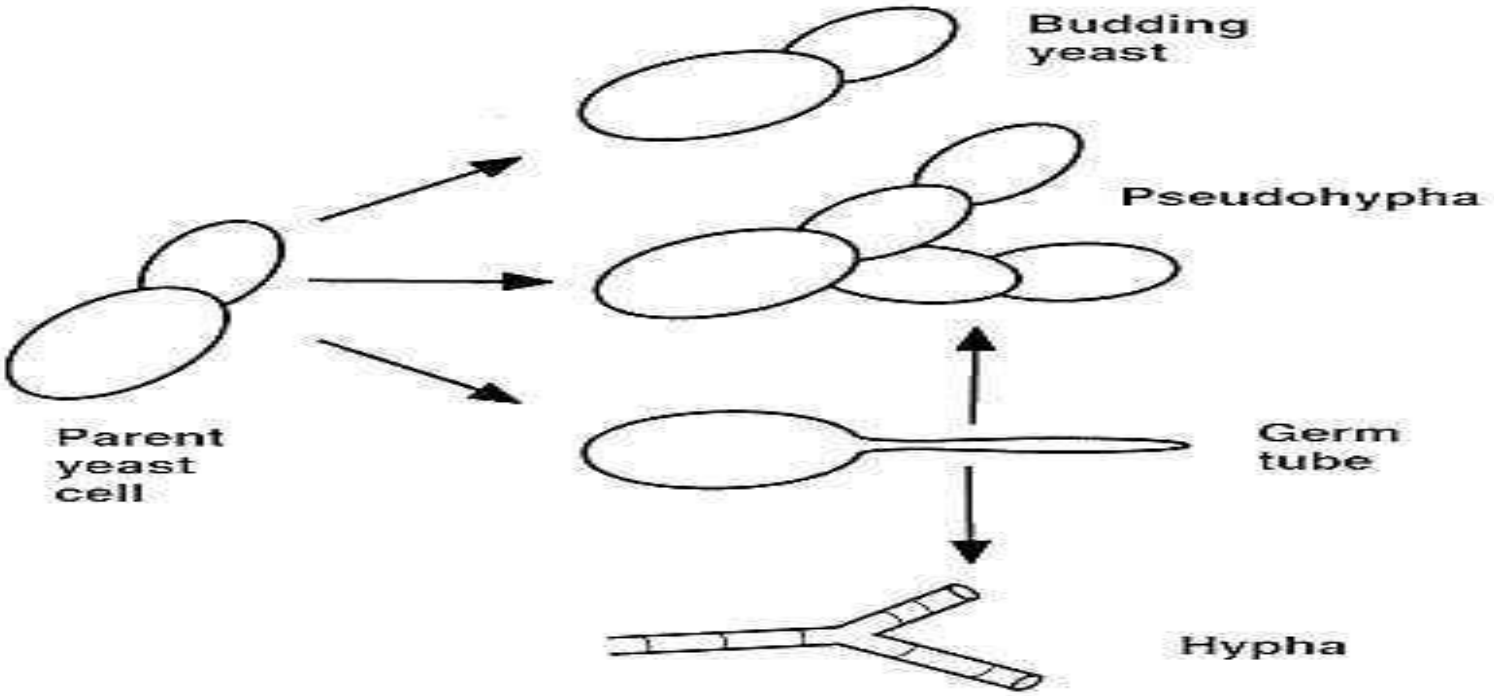


Figure 75-4 Germination of *Candida albicans*.

OPPORTUNISTIC MYCOSES

- **Candidiasis.** Candidiasis (due to *C albicans* and other *Candida* spp.) is the most common opportunistic fungal infection. *Candida albicans* is the most common cause of candidiasis. Candidiasis may be classified as superficial or deep.

- Superficial candidiasis may involve the epidermal and mucosal surfaces, including those of the oral cavity, pharynx, esophagus, intestines, urinary bladder, and vagina. The alimentary tract and intravascular catheters are the major portals of entry for deep (or visceral) candidiasis.

- The kidneys, liver, spleen, brain, eyes, heart, and other tissues are the major organ sites involved in deep or visceral candidiasis. The principal risk factors predisposing to deeply invasive candidiasis are protracted courses of broad spectrum antibiotics, cytotoxic chemotherapy, corticosteroids, and vascular catheters.

- **Aspergillosis**. Invasive aspergillosis most frequently involves the lungs and paranasal sinuses. This fungus may disseminate from the lungs to involve the brain, kidneys, liver, heart, and bones.

- The main portal of entry for aspergillosis is the respiratory tract, however, injuries to the skin may also introduce the organism into susceptible hosts.

- Quantitative and functional defects in circulating neutrophils are key risk factors for development of invasive aspergillosis.

- For example, neutropenia due to cytotoxic chemotherapy and systemic corticosteroids are common predisposing factors for invasive aspergillosis.

- **Zygomycosis.** Zygomycosis due to *Rhizopus, Rhizomucor, Absidia, Mucor* species, or other members of the class of Zygomycetes, also causes invasive sinopulmonary infections.

- An especially life-threatening form of zygomycosis (also known as mucormycosis), is known as the rhinocerebral syndrome, which occurs in diabetics with ketoacidosis.

- In addition to diabetic ketoacidosis, neutropenia and corticosteroids are other major risk factors for zygomycosis. *Aspergillus* spp and the Zygomycetes have a strong propensity for invading blood vessels.

Rhizopus:

- Although this genera can cause disease, they are also commonly found as a contaminant.
- Colonies grow rapidly and resemble cotton candy. Colonies darken with age, becoming gray or yellow-brown. The reverse is white.
- Mycelia are marked by numerous stolons connecting groups of long sporangiophores.
- Sporangiophores are usually unbranched, long, and terminate in a columella and a dark round sporangium containing oval colorless to brown spores.
- Stolons bear large rhizoids which are found immediately adjacent to the sporangiophore in the nodal position.
- Columella and sporangium collapse easily after discharging spores.

FIG. 1. *Rhizopus* in slide culture

- **Cryptococcosis**. Cryptococcosis is most typically an opportunistic fungal infection that most frequently causes pneumonia and/or meningitis. Defective cellular immunity, especially that associated with the acquired immune deficiency syndrome, is the most common risk factor for developing cryptococcosis.

- ***Penicillium marneffei***

- Endemic in southeast Asia, *P. marneffei* is known to cause a wide variety of disease among immunocompromised and, less frequently, immunocompetent patients.

- Hyphal colonies appear rapidly and white-tan, velvety, and flat, although distinct spicules of growth may protrude from the surface of the culture. Red soluble pigment is noted in maturing colonies, although this finding is not specific for *P. marneffei*.

- The mold form (grown at 25-30°) resembles an otherwise typical *Penicillium*, with septate hyphae and smooth generally smooth conidia aloft phialides which in turn are borne by metulae. The conidiophore typically carries 4-5 metulae, each of which bears 4-6 phialides.

- The yeast form (grown at 35-37°) are round to oval and are 3-7μ in diameter; yeast reproduce by fission rather than budding.

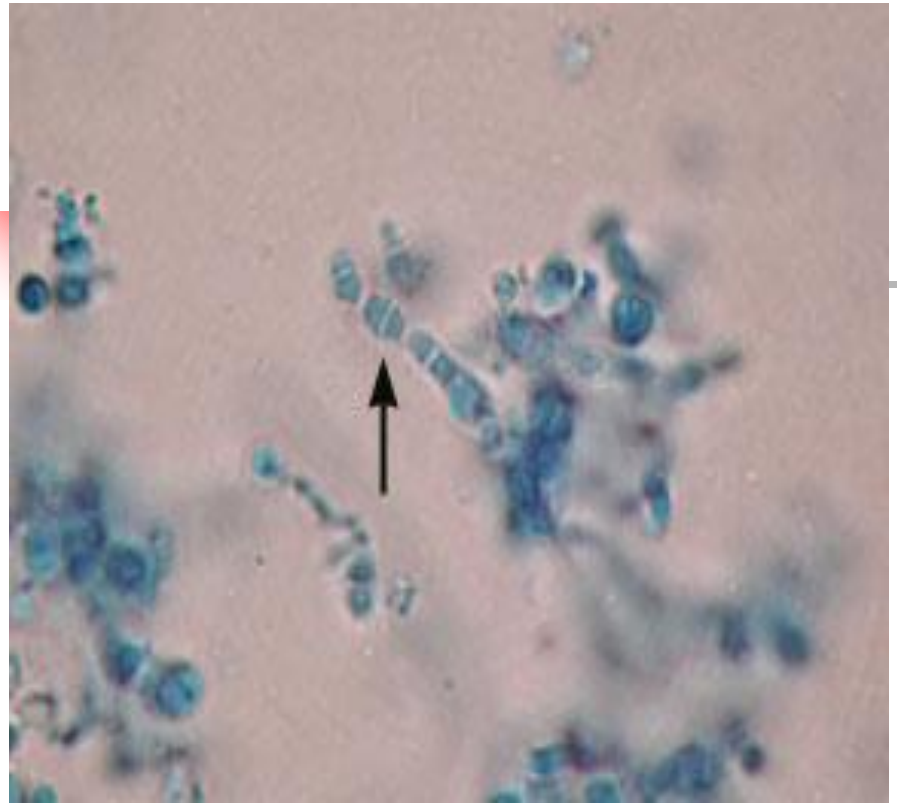


FIG. 1. *Penicillium marneffei* yeast form. An arrow indicates a yeast cell reproducing by fission.

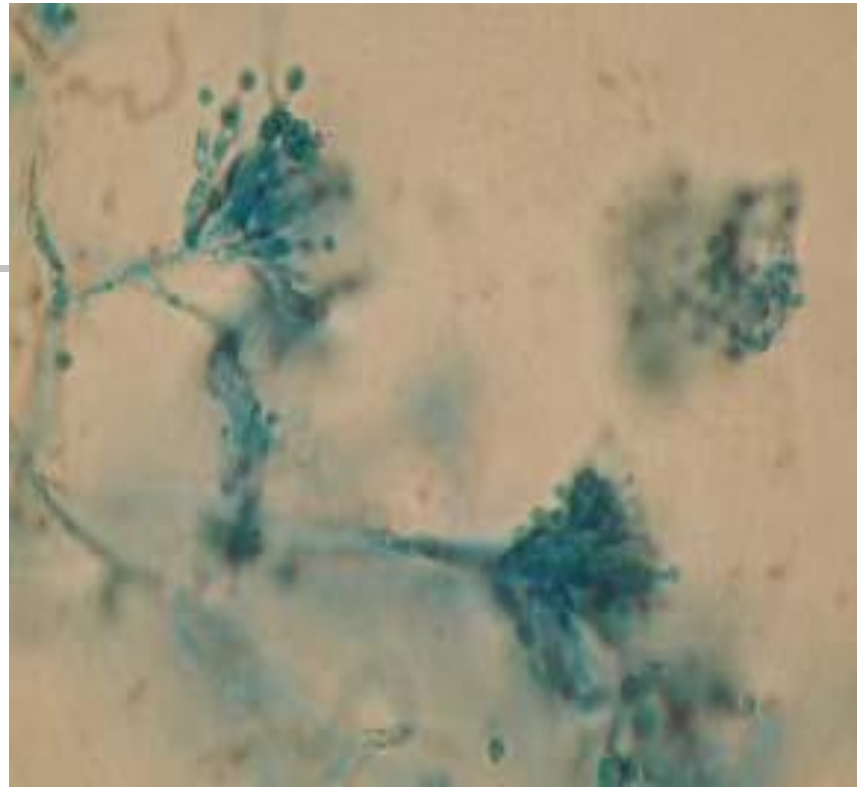


FIG. 2. *Penicillium marneffei* in slide culture. The mold form resembles other *Penicillium* species.

OTHER MEDICALLY IMPORTANT OPPORTUNISTIC FUNGI

Pneumocystis jiroveci

- Unicellular eukaryote originally classified as protozoan, but currently described with the fungi in the ASM Manual of Clinical Microbiology 7th ed; the debate continues

- Cysts contain up to 8 ovoid-to-fusiform spores
- Free trophic forms are more common in clinical specimen, are 1.5-5μ and have small nuclei (0.5-1μ)

- Diagnosis still relies on morphologic identification of the organism from respiratory specimen

- In AIDS patients, 80% of PCP can be diagnosed on induced sputum; the remainder may need bronchoalveolar lavage

- At San Francisco General Hospital & Trauma Center specimen may be examined if the patient:

  - is immunocompromised
  - has respiratory symptoms and
  - has objective evidence of lung disease

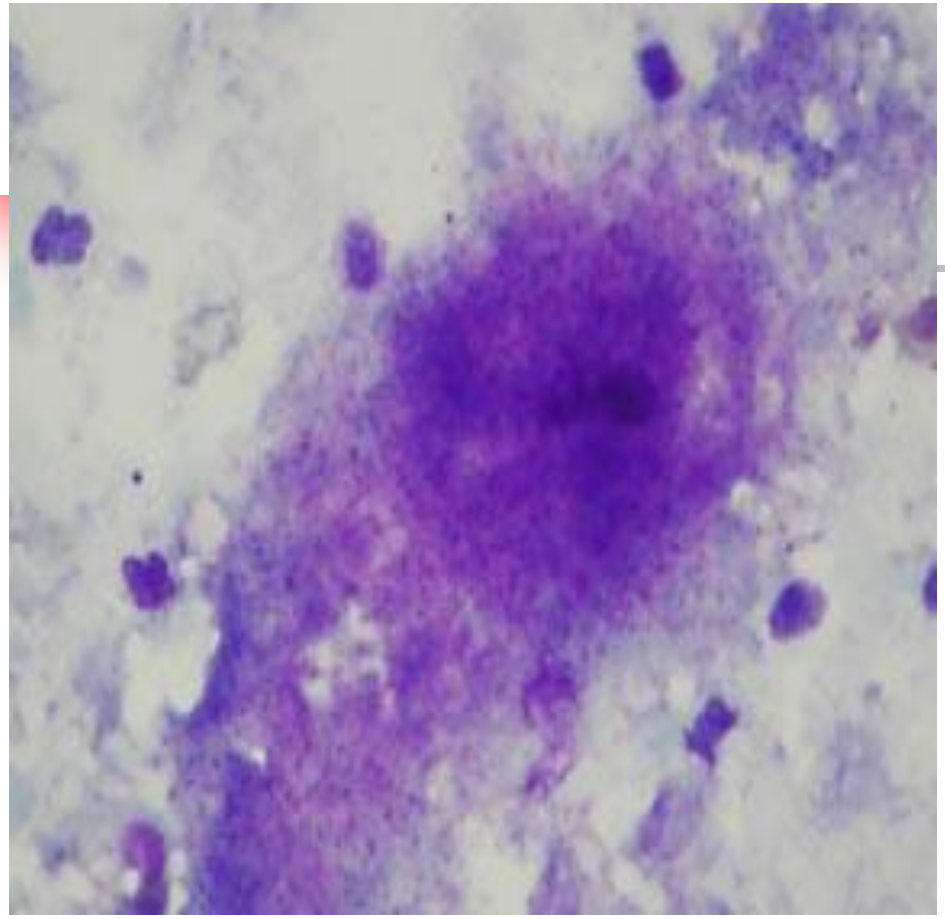
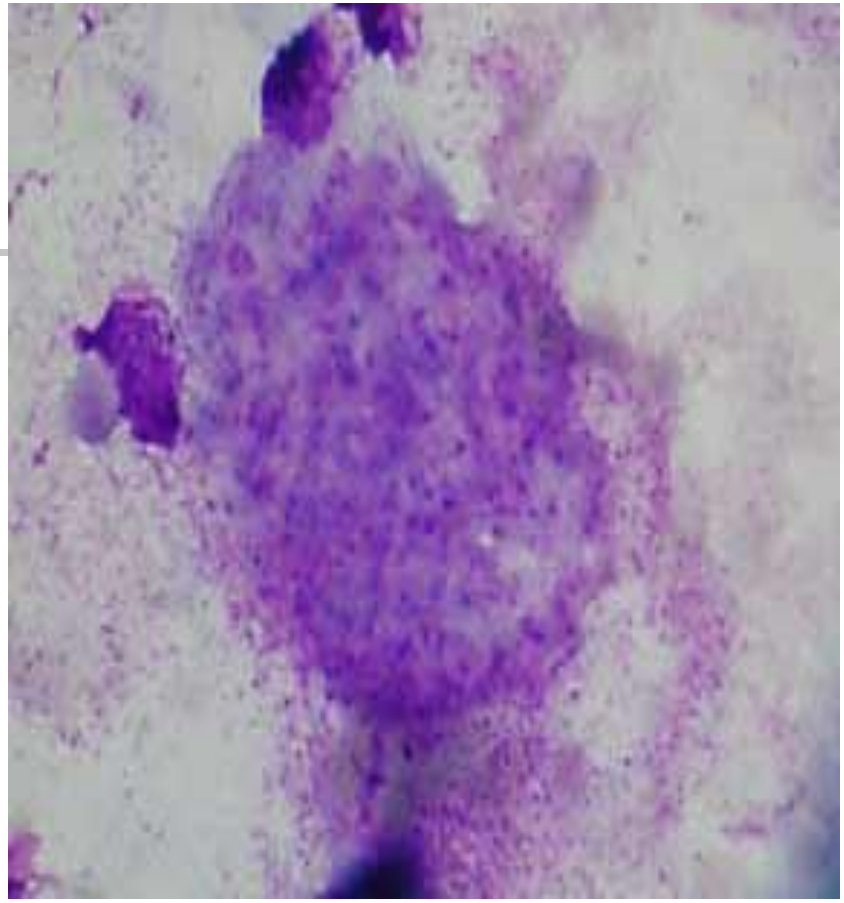


FIG. 2. *Pneumocystis* in induced sputum; wright stain stains trophozoites.



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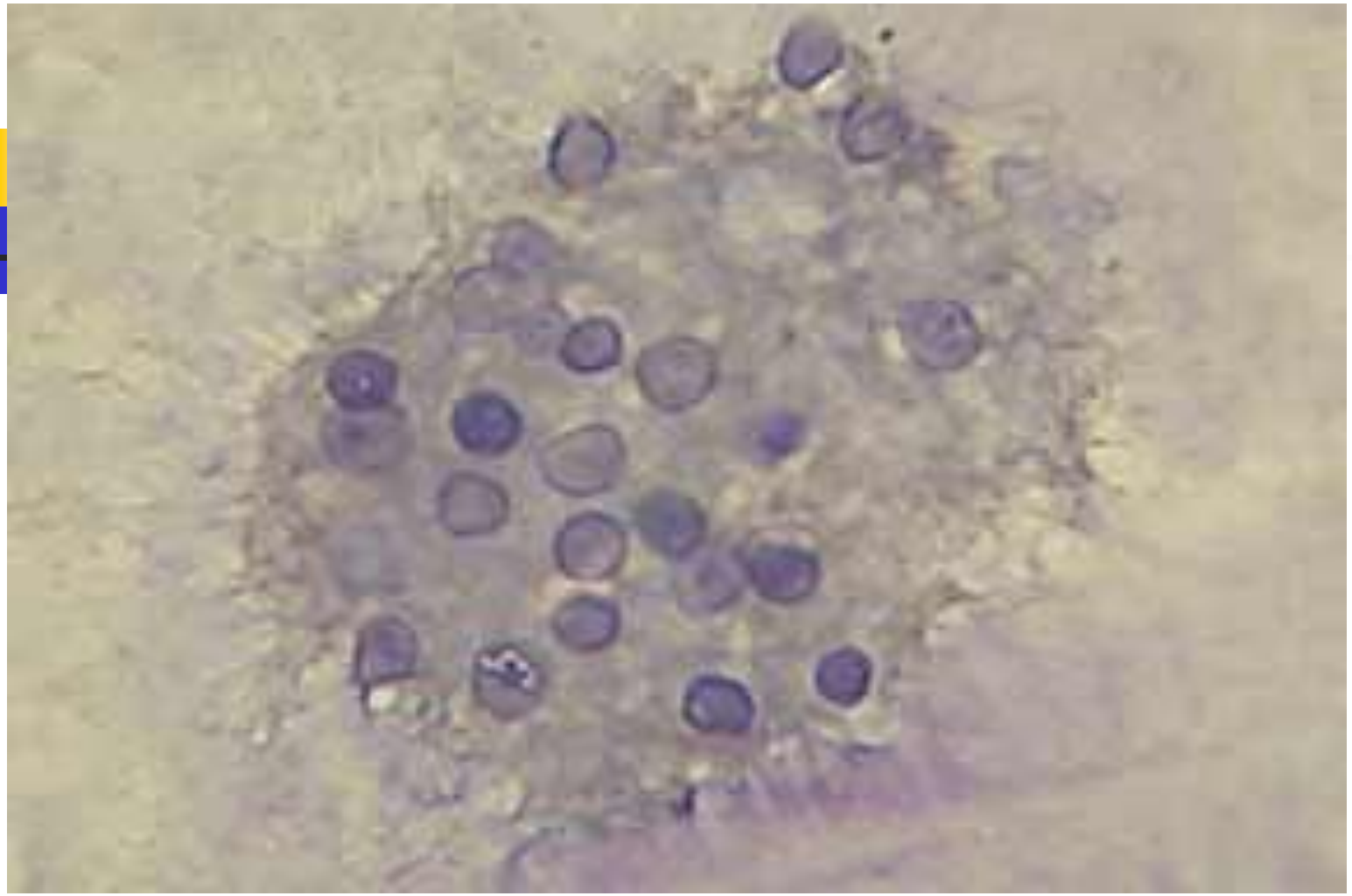
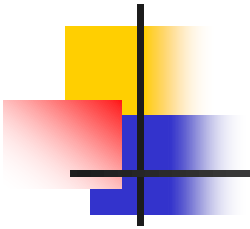


FIG. 3. *Pneumocystis* in bronchoalveolar lavage; toluidine blue highlights cyst forms.



SYSTEMIC

MYCOSES

SO; WHAT ARE THEY?

- Systemic mycoses refer to fungal infections affecting the internal organs.
- The fungi have the ability to enter the body through the lungs, through the gut, the paranasal sinuses or the skin.

- Most infections tend to originate in the respiratory tract and the fungi can then spread through the bloodstream to multiple organs including the skin,;
- often causing multiple organs to fail and eventually resulting in the death of the patient.

ADDITIONALLY……..

- Patients who are immunocompromised are more predisposed to systemic mycoses, but these infections can also develop in otherwise healthy patients.

- While potentially life threatening, most infections tend to go unrecognized, and occur as asymptomatic or sub-clinical infections.

- Of those that manifest symptoms, most occur as mild or acute self-limiting disease. Only in rare situations, does disseminated, invasive, and progressive infection occur.

AETIOLOGICAL AGENTS.....

- Fungi that can cause systemic infection in people with normal immune function as well as those who are immune compromised, include the following:

- ***Histoplasma capsulatum*** (causing histoplasmosis)
- ***Coccidioides immitis*** (causing coccidioidomycosis)
- ***Blastomyces dermatitidis*** (causing blastomycosis)
- ***Paracoccidioides brasiliensis*** (causing paracoccidiodomycosis; limited to Central and South America)
- ***Cryptococcus neofrmans*** (casuing cryptococal menningitis)

BRIEF EPIDEMIOLOGY

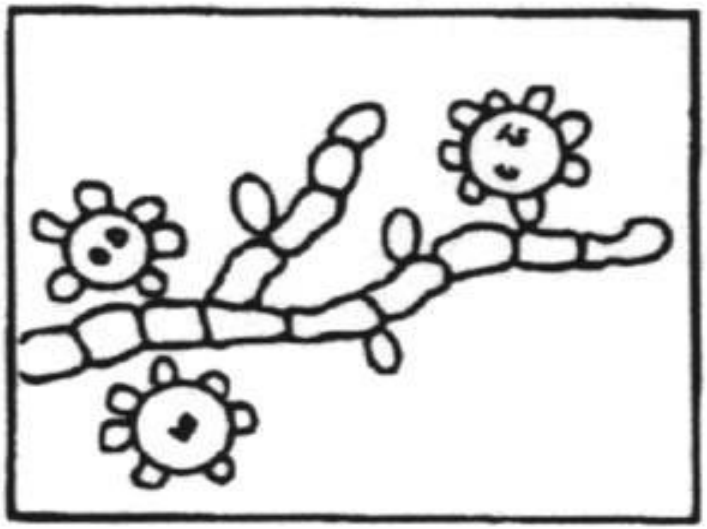
- These fungi are located in soil and in wood debris. ***Histoplasmosis*** is prevalent in Southern USA, Central America, South America, Africa and Asia.

- Both ***Coccidioides*** and ***paracoccidioides*** are prevalent in Southern USA and Central America. And *Blastomyces* is generally found in North America.

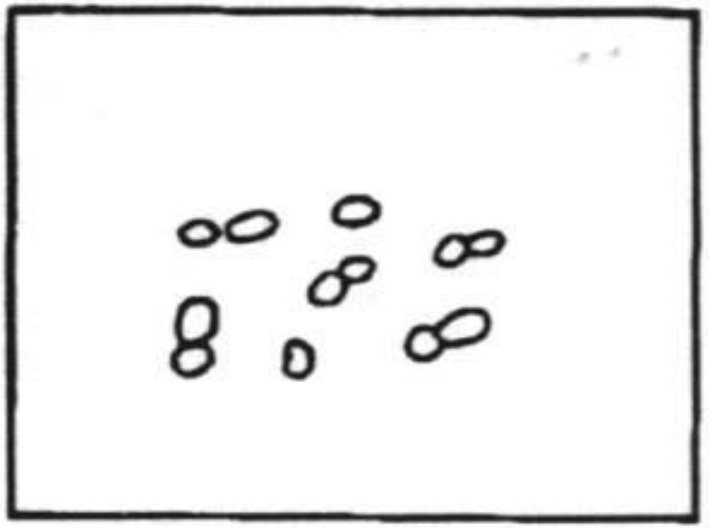
- These mycoses share the common characteristic of being caused by dimorphic pathogens; meaning, the organisms exist in two forms: saprophytic-mould phase, and the parasitic-tissue/yeast phase.

- Various factors such as temperature, atmosphere, and nutrients may have an influence on the conversion from one phase to the other. The conversion of an isolate from one phase to the other in vitro is usually required for definition identification.

DIMORPHISM

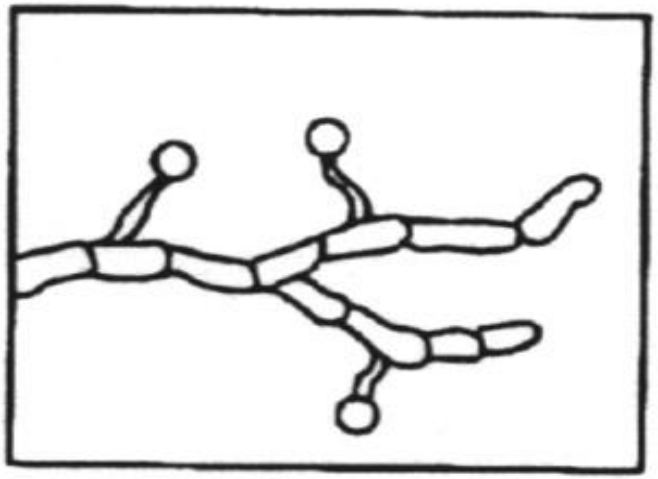


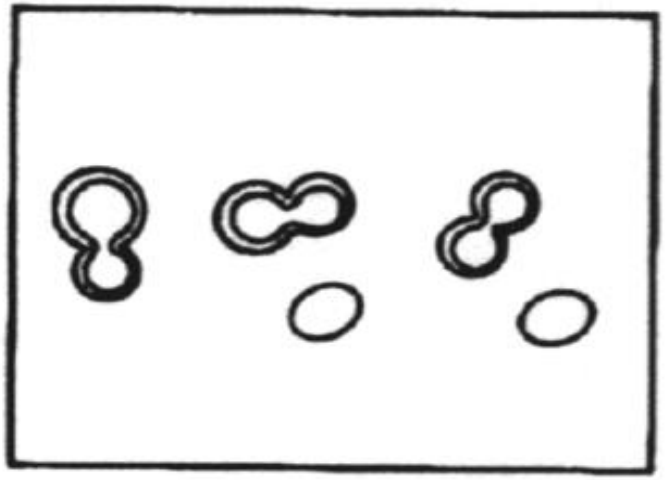
Saprobic Phase



Parasitic Phase

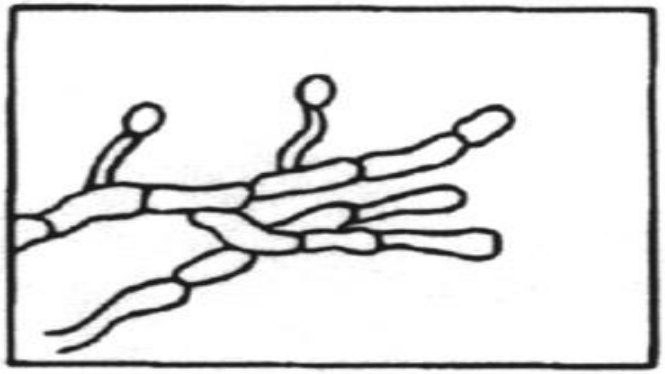
Dimorphic with mold to yeast transition when infecting susceptible species. Yeast cells are relatively small. Saprobic phase shows **tuberculate macroconidia**



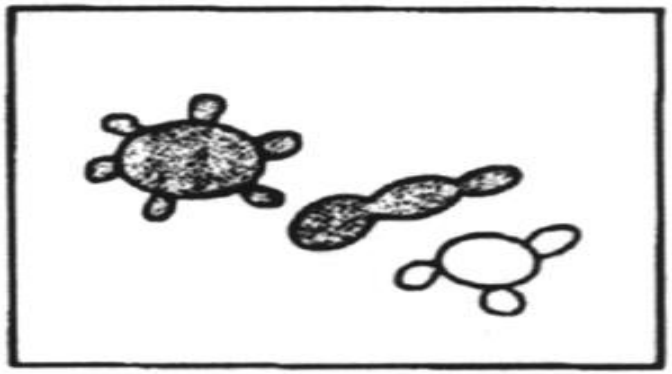


Saprobic Phase **Parasitic Phase**

Dimorphic with mold to yeast transition when infecting susceptible species. Yeast cells are medium size with thick walls.

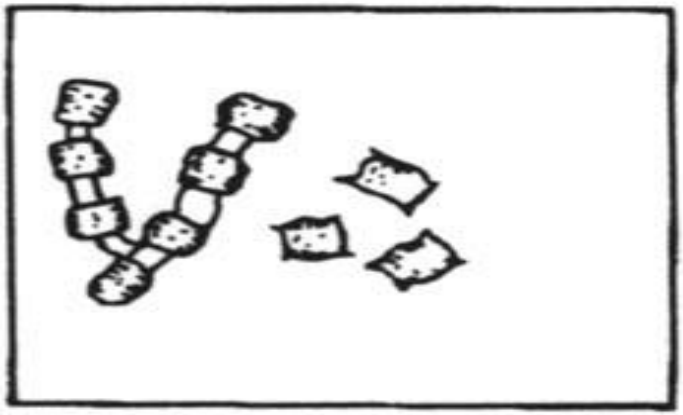


Saprobic Phase

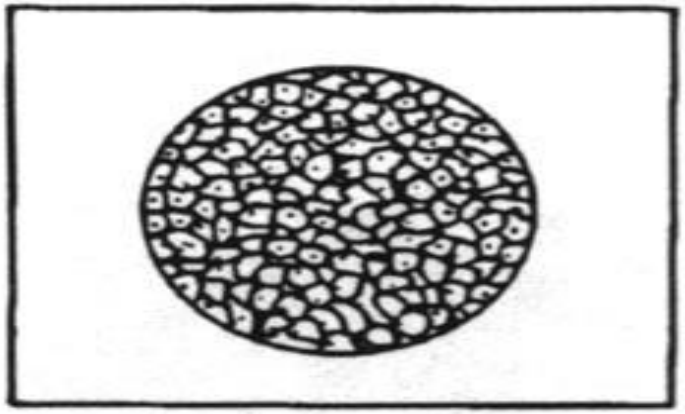


Parasitic Phase

Dimorphic with mold to yeast transition when infecting susceptible species. Yeast cells have **multiple buds**.



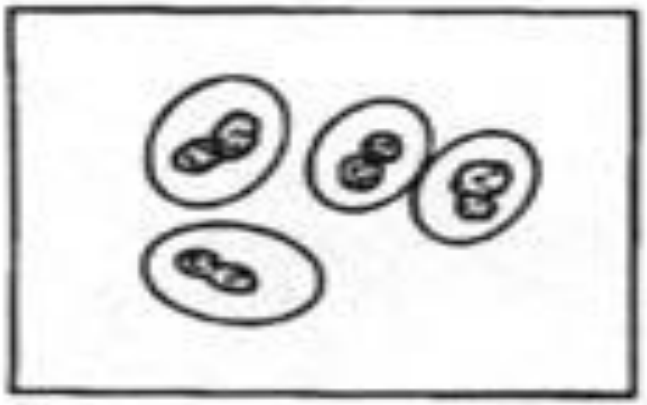
Saprobic Phase



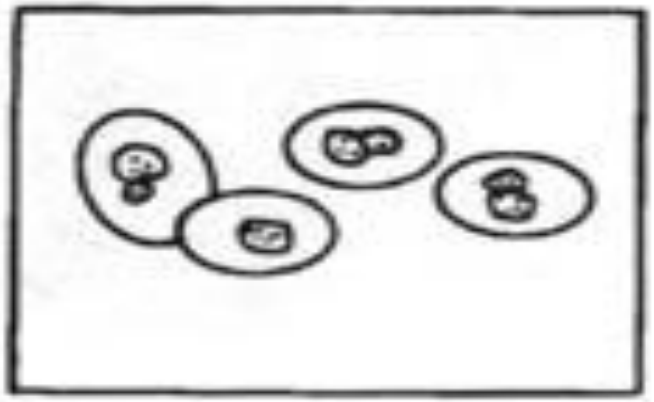
Parasitic Phase

Dimorphic with mold to **spherule** transition when infecting susceptible species. **Spherules are multinucleate**.

MONOMORPHISM



Saprobic Phase



Parasitic Phase

Monomorphic with yeast phase only. This is the only pathogenic yeast with a capsule. The capsule is extremely large eg: cryptococcus

CRYPTOCOCCOSIS

- Cryptococcus is a fungus that grows in culture as yeast. Some researchers and authorities view it as a systemic infection while others consider it opportunistic.

- In this lecture, it will be considered the **fifth systemic mycosis** since many of the clinical manifestations are similar to those of other systemic infections.
- ***Cryptococcus neoformans*** tends to be the most prominent medically important species and it is a monomorphic yeast-like organism with a perfect stage placed into the division **Basidiomycota**.

- Cryptococcus is best known for causing a severe form of meningitis and meningo-encephalitis in people with HIV infection and AIDS and currently reffered as an AIDS defining illnesses

BLASTOMYCOSIS

- This condition was first described in the United States by Gilchrist in 1894; it is also known as Gilchrist's disease or North American Blastomycosis.

- Blastomycosis refers to a chronic and granulomatous fungal infection that usually originates as a respiratory infection (95%). Blastomycosis is an extremely common infection among dogs in endemic areas.

- It has been reported in other animals, including the horse, cow, cat, bat, and lion. Dissemination can occur with both osseous and cutaneous involvement.

- **Etiologic Agent:** *Blastomyces dermatitidis* (*Ajellomyces dermatitidis*)

EPIDEMIOLOGY

- This condition occurs in the U.S. (primarily in the Mississippi and Ohio River valleys), Canada, Mexico, Central America; Old World isolates have also been reported.

- **True incidence** and **prevalence** are unknown, because there are generally no reliable markers. But based on confirmed cases, the annual incidence tends to be less than 1 case per 100,000 people in Mississippi, Kentucky, Arkansas, and Wisconsin.

- It affects all age groups with slightly higher incidence occurring in **30-50** year olds, males are affected more than females, there's no **racial** or **occupational bias** noted, and there is no apparent seasonal variation. **Person-to-person** transmission has been reported. In these situations, transmission was **sexual** with the male having the **genital tract lesions.**

MANIFESTATIONOS OF BLASTOMYCOSIS

- **Pulmonary Form** – This type usually has insidious onset and manifests initially as a mild respiratory tract infection with a dry cough that becomes productive with time.
- Pleuritic chest pain, hoarseness, low grade fever, hemoptysis, and dyspnea with night sweats are some of the symptoms. These symptoms may resolve spontaneously, but may also slowly progress over a period of several years with the development of cavitary lesions as well as dissemination.
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- **Disseminated Form** – In this type hematogenous spread that results in skin, urogenital and subcutaneous tissue lesions in addition to respiratory tract lesions occur. Central nervous system involvement can also occur; however, the first complaint is often the presence of a cutaneous lesion.

MANIFESTATION …

- **Cutaneous Form –** This type is seen in over 50% of patients. First lesions occur on the face, extremities, neck, and scalp. Initially, a well defined erythematous nodule that develops an enlarged papule and ultimately ulcerates tends to form. The lesions resemble basal cell carcinoma and the lesions may be solitary or multiple.
- **Osteoarticular Form –** This type is observed in 14-60% of studied cases. The major sites include the vertebrae, skull, ribs and extremities; the condition usually manifests as subcutaneous abscess with development of a draining sinus tract. Blastomycotic polyarthritis can be observed infrequently.
- **Genitourinary Form** – The agent is recovered from urine in approximately 25% of cases; the sources include the prostate, the epididymis or the kidney.

LASTLY;

- **Central Nervous System** – The agent is observed in 3-10% of cases manifesting as meningitis with insidious onset or brain abscess; it usually occurs late in the course of disseminated blastomycosis.
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- **Immunocompromised patients** - The incidence of blastomycosis among the immunocompromised does not appear to differ from the general population.
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- **Tissue** – In the tissue, the agent is easily diagnosed by detection of characteristic tissue phase in sputum or exudate: thick-walled spherical cells 8-20 □m are noted. These cells demonstrate solitary blastoconidia connected by a broad base.

COCCIDIOIDOMYCOSIS

- This condition is a mycosis that can range from benign to severe if left untreated.

- It has a respiratory origin and dissemination involves visceral organs, bones, joints, cutaneous and subcutaneous tissue with burrowing abscesses. Coccidioidomycosis is also referred to as valley fever, or desert rheumatism.

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- **Etiologic Agent:** ***Coccidioides immitis*** is the causative agent and it is a soil saprophyte.

Epidemiology

- **Ecology:** An arid climate, alkaline soils, hot summers, few freezings, and yearly rainfalls ranging between 5 to 20 inches characterize the endemic area. Exposure tends to be heaviest in the late summer and fall when dusty conditions prevail.

- Research indicates that **80%** of the general population has been exposed within five years of residence in an endemic area. Cases reported on other locations are due either to travel within the endemic area or from exposure to materials containing dust particles from the endemic area (fomite contamination).

- **Incidence** – There tends to be no age bias; however, there is an occupational hazard for individuals working outdoors, and the condition is more severe in dark skinned races. The two peak periods of infection are observed to be summer and late fall to early winter.

Incidence .....

- The incidence of coccidioidomycosis among AIDS patients and other immunocompromised individuals appears to be significantly higher than the general population.
- These individuals may also develop severe, often fatal disease due to reactivation of previously acquired infections.
- Symptomatic coccidioidomycosis is considered an AIDS-defining illness in an HIV positive individual.

MANIFESTATIONS;

- Sixty percent of the cases are asymptomatic and self-limiting with respiratory tract involvement or respiratory tract infections.

- Patients may also present with skin reactions known as erythema nodosum (red nodular rash, more common in females) in 10% of infected individuals; less than 1% of the patients become seriously ill.

- The incidence of symptomatic disease is greater in the population $\geq$ 65 years of age and among the immunocompromised, especially HIV-infected individuals.

- Hematogenous dissemination may be rapid and frank as well as protracted and insidious.

Manifestations….

- The symptoms include involvement of internal organs, osseous, cutaneous, arthritic and subcutaneous lesions. Meningitis tends to be observed in 30-50% of the cases.

- **Disseminated disease** generally has an overall mortality rate approaching 60%. Chronic pulmonary coccidioidomycosis tends to resemble chronic tuberculosis or histoplasmosis. Conversion of PPD skin test from positive to negative indicates a grave prognosis for disseminated cases.

Tissue – Tissue samples (sputum or exudate) demonstrate thick walled globose spherule (sporangiospore) 20-200 ·m containing numerous endospores 2-5 ·m. Endospores may also occur freely in the specimen. Immature spherules may resemble nonbudding *B. dermatitidis*.

HISTOPLASMOSIS

- This condition exists as an intracellular mycosis of the reticuloendothelial system including the lymphatic tissue (spleen, liver, nodes).

- Symptoms vary greatly, but the disease primarily affects the lungs, but can spread to other internal organs, cutaneous, mucocutaneous tissue and central nervous system.
- Most cases (95%) are asymptomatic to mild self-limiting infections.
-
- Etiologic Agent: *Histoplasma capsulatum* (*Emmonsiella capsulata*)

EPIDEMIOLOGY

- **Histoplasmosis** occurs in Central, South America, U.S. in certain areas especially Mississippi and Ohio River valleys; it has been reported from more than 60 countries worldwide. The organism is a soil saprophyte associated with chicken, pigeon, starling and bat excretment.
-
- **Incidence** - All age groups are affected and the highest incidence occurs during infancy and old age, adult males are affected greater than females, there's no racial bias, except for chronic pulmonary disease which is found predominantly among white males.

MANIFESTATIONS

- This condition exists as a respiratory tract infection; dissemination leads to hepatosplenomegaly, leukopenia, anemia, lymphadenopathy.

- This disease has a wide spectrum of manifestations. The disease may occur as a primary infection or may reactivate after several years.

- Reactivation is usually common in elderly or debilitated patients; patients with AIDS are at high risk. The main sites of reactivation are the brain, adrenal glands and mucous membranes.

- **Note:** Clinically, reactivation can resemble other mycoses, tuberculosis, or cancer.

Manifestations....

- **Acute pulmonary histoplasmosis** - fever (several days duration), malaise, headache, cough, weakness, myalgia, nausea, anorexia and weight loss are the symptoms of this type. There is usually complete spontaneous resolution occasionally requiring several weeks.

- **Mediastinitis and pericarditis** – These conditions are due to lymphatic extension of pulmonary disease; usually asymptomatic except for lymphadenitis.

- The confirmation of disease requires biopsy of mediastinal lymph nodes or pericardium since cultures of sputum, blood and bone marrow are usually negative. Symptoms include granulomatous inflammation of lymph nodes and cardiac damage including heart failure.

- **Chronic pulmonary histoplasmosis** – This type is most often seen in adults (primarily middle-aged white males) with predisposing conditions such as emphysema or chronic bronchitis. It is characterized by cavitary lesions, and it can progress to respiratory failure; the condition rarely disseminates.

- **Disseminated Histoplasmosis** – This type is a relatively rare complication of pulmonary disease with a grave prognosis; patients generally have underlying debilitation. Clinical manifestations can range from acute to severe. The clinical picture includes fever, malaise, hepatosplenomegaly, lymphadenopathy, mucosal lesions (often oral), adrenal insufficiency due to involvement of the adrenal glands.

- **Central nervous system** involvement occurs in 10-30% of cases and manifests as chronic meningitis. Fungemia can usually lead to endocarditis; routine blood cultures are generally negative.

- **AIDS –**Histoplasmosis represents the first manifestation of AIDS in many HIV positive patients living in endemic areas.

- Diagnosis is often difficult since the clinical manifestations mimic those of AIDS; weight loss, fever, generalized lymphadenopathy, leukopenia, thrombocytopenia and anemia.

- Pulmonary infiltrates resemble those associated with *Pneumocystis carinii* pneumonia. On occasion, the patients may present with disseminated intravascular coagulation and quickly die.

Tissue

- **Tissue** – Samples are usually sputum since the organism is in RE tissues; the organism can be detected in Giemsa or Wright stained smears of bone marrow or lymph node aspirates, or peripheral blood where it occurs as intracellular yeast, globose to ovoid 2-5 μm in diameter.

- The organism can also be observed in material obtained from mucosal lesions or organ biopsy.

PARACOCCIDIOIDOMYCOSIS

- **PARACOCCIDIOIDOMYCOSIS** – This condition is chronic, often a fatal mycosis characterized by primary pulmonary lesions with dissemination to many visceral organs. Also characterized by conspicuous ulcerative granulomas of buccal and nasal mucosa often accompanied by direct extension to skin and lymphatic system.
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- **Etiologic Agent:** *Paracoccidioides brasiliensis*
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- **<u>Geographic</u>** – The condition occurs in South America especially Brazil, Venezuela, and Colombia. Cases have been reported from most South American countries, Central America, and Mexico. The organism is probably a soil saprophyte in subtropical forest areas.

- **Incidence** – Condition occurs in all ages with highest frequency 30-50 years, males are affected greater than females (20/1), no reported racial biases.
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- **Manifestations** - Most cases are acquired by inhalation of infectious material, however, percutaneous inoculation is suspected in some cases with most common site being the oral mucosa. Oral lesions and lymphadenitis may be what brings patient in to the doctor initially. Although a benign self-limiting form is suspected, the disease usually progresses to fatality unless effectively treated.
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- Tissue – In the tissue, 10-25 μm globose polyblastic cells producing multiple blastoconidia (1-2 μm) connected to the mother cell by a narrow base are demonstrated.
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CRYPTOCOCCOSIS

- This condition is an acute, subacute or chronic pulmonary systemic or meningeal mycosis. Pulmonary conditions are usually transitory, mild and often unrecognized. Cutaneous, skeletal, and visceral lesions may occur during dissemination.

- However, the most familiar form usually involves CNS manifesting as acute or chronic meningitis. Prior to the appearance of AIDS, cryptococcosis had a sporadic occurrence with the most common predisposing factor being treatment with corticosteroids. Hematologic malignancies such as Hodgkin disease or lymphoma can also increase susceptibility.

- **Etiologic Agent -** *Cryptococcus neoformans* (*Filobasidiella neoformans*). There are two varieties of the anamorph; *C. neoformans* var. *neoformans* (serotypes A & D) and *C. neoformans* var. *gatti* (serotypes B & C).

EPIDEMIOLOGY

- **Geographic** – The condition occurs worldwide in soil contaminated with bird guano, especially pigeon and chickens. Evidence suggests that the teleomorph may be infectious. *Filobasidiella neoformans* may survive on trees, plants and other vegetable matter rather than avian guano.

- Guano contamination may be the result of the ingestion of fungus-contaminated foodstuff. Research has shown that the basidiospores produced by *F. neoformans* are infectious for mice. Furthermore basidiospores are smaller than yeast cells and may more readily be deposited in the alveoli.

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- **Incidence** – The condition occurs more in males than in females, higher than expected incidence with Hodgkin's disease, leukemia, lymphosarcoma, diabetes mellitus and in patients on steroid therapy.

MANIFESTATIONS

- **Pulmonary –** This type exists generally at the initial site of infection, dissemination is hematogenous. Most infections appear to be inapparent or very mild respiratory tract infections. Only half of infected patients demonstrate clinical illness with remaining cases diagnosed by routine X-ray evaluation. Severe cases have been reported in persons heavily exposed to pigeon manure.
- Rarely diagnosed except in AIDS patients who may present with severe acute respiratory distress (ARDS)
- May produce nodules or masses (usually in the upper lobes), cavities, segmental pneumonia, pleural effusion, or lymphadenopathy
- **Skin Bone and Joint** - Hematogenous spread resulting in skin lesions is observed in approximately 10% of infected individuals, usually those patients who are immunosuppressed. Skin lesions originate as painless papules that progress and ulcerate. Cryptococci may be recovered from the exudate. Subcutaneous abscesses develop adjacent to the site of bone lesions. The most frequently involved bones are the vertebrae followed by the skull and the rib.

- **Central Nervous System-** This type exists as meningoencephalitis manifested as intermittent headaches of increasing frequency and severity without clear history of pulmonary disease; this is often the first complaint bringing the patient to the doctor.

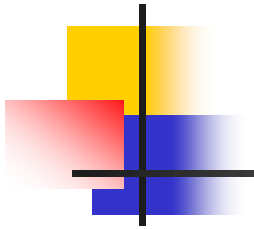
- Onset is generally insidious with a chronic course. Patients also demonstrate symptoms of low grade fever, nuchal rigidity, and tenderness.

- Other clinical symptoms of neurologic disorder occur including gait ataxia and decreased mental acuity.

- In severe and chronic cases, remission may occur intermittently. Without appropriate therapy, all CNS infections are ultimately fatal.

- **AIDS-associated Cryptococcosis -** Cryptococcosis is currently the fourth most common life-threatening infection among AIDS patients, and it occurs in 7-8% of these individuals. The diagnosis of cryptococcosis in an HIV positive patient indicates the transition to AIDS. Cryptococcosis is the presenting manifestation in approximately one third of AIDS patients. AIDS-associated cryptococcosis currently accounts for 50% of the cryptococcosis cases in the US.

- **Tissue** – In the tissue, *C. neoformans* is small encapsulated yeast. In spinal fluid the capsule may be demonstrated using a mixture of CSF or sediment plus India ink; the capsule will manifest as a clean zone around a budding cell 4-20 ·m; blastoconidia are usually solitary but multiple conidia can be observed. Connection to mother cell is narrow. India ink preparations are not performed on sputa.



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