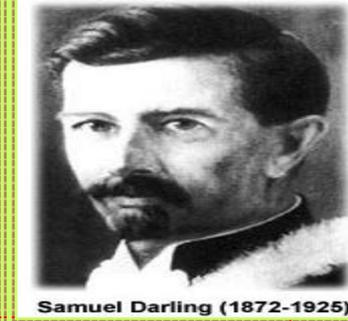




# Histoplasmosis

# INTRODUCTION

- ❖ Histoplasmosis is an endemic systemic mycosis caused by
  - Small-celled yeast form of *Histoplasma capsulatum* vari. *capsulatum* with global distribution.
  - Large celled yeast form of *H. capsulatum* var. *duboisii* with restricted to the African continent.
- ❖ Clinically and histologically distinct entities and termed as;
  - Histoplasmosis capsulati (classical or small-form histoplasmosis, Darling's disease)
  - Histoplasmosis duboisii (African or large form histoplasmosis).  
Chandler *et al.*, 1980



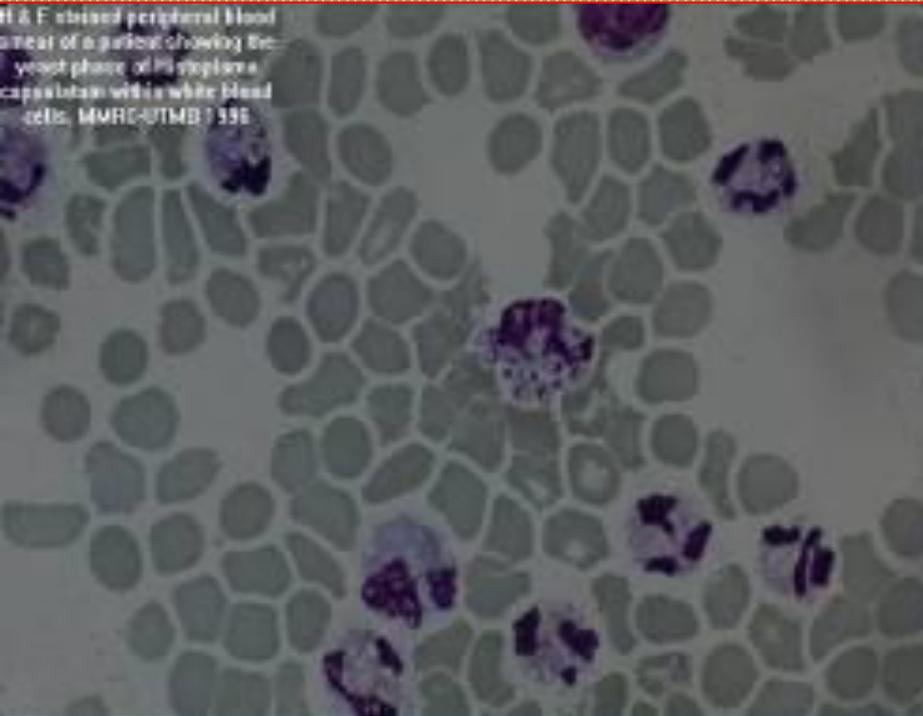
Samuel Darling (1872-1925)

**Synonyms: Caveran disease, Reticuloendothelial cytomycosis, Tingo Mario fever.**

- ◆ This disease was first seen and named by Dr. Samuel TAYLOR DARLING in 1905 from Panama Canal Zone.
- ◆ First identified in the visceral tissues and bone marrow of an adult male presumed to have died of miliary tuberculosis.
- ◆ The organism exists in the mould (mycelial) form at temperatures 25°C and switches to the yeast form at normal human body temperatures (37°C).
- ◆ The mycelial form of *H. capsulatum* has two conidia—macroconidia and microconidia.
- ◆ Microconidia are smaller infective forms, which are 2-5 micrometer in diameter and are oval & smooth.

# DIMORPHIC FUNGUS

H & E stained peripheral blood smear of a patient showing the yeast phase of *Histoplasma capsulatum* within white blood cells. MMRC-UTMB 1395



**Intracellular yeast at 37°C**

*Histoplasma capsulatum*, macroconidia and microconidia. UTMB MMRC 5/1897



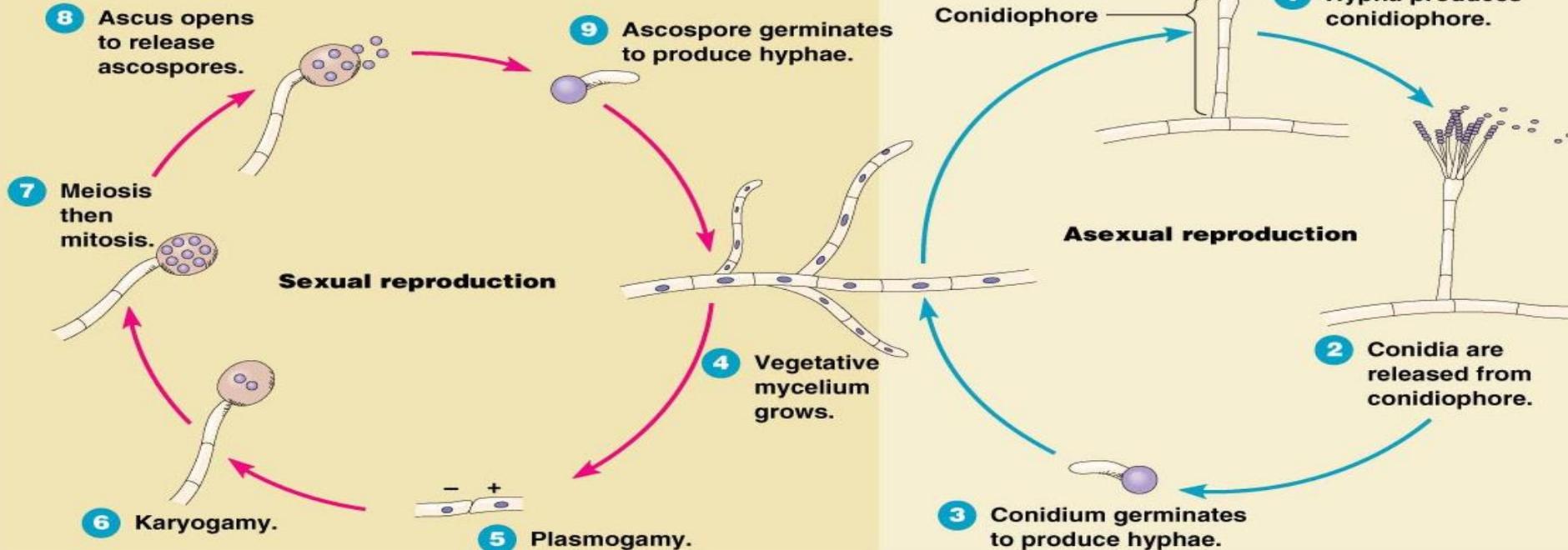
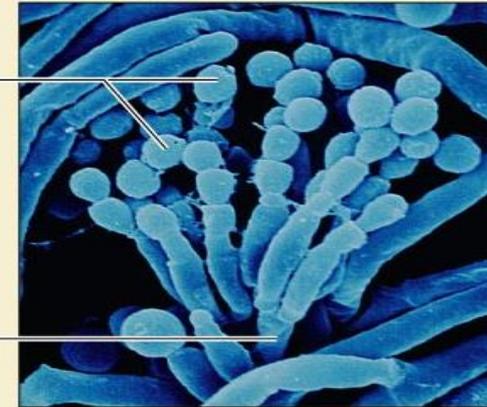
**Tuberculated macroconidia at 25°C**

# LIFE CYCLE

## ASCOMYCETE



Conidia



## PREVALENCE

### INDIA

- ◆ In 1954, Panja and Sen reported the first case of DH from Calcutta and since then individual cases have been reported from various states, mostly from West Bengal.
- ◆ In India, histoplasmosis seems to be prevalent in the Gangetic delta.
- ◆ Basu Mallick who investigated a larger population (8062) and found 6.8% prevalence of histoplasmin sensitivity.
- ◆ The prevalence of 12.3% histoplasmin sensitivity found in the riverine area was the highest ever reported from any part of India.
- ◆ Among the forms of histoplasmosis reported from India, DH is the rarest.
- ◆ Disseminated histoplasmosis (epididymis) was reported from semen of a 55- year-old male industrialist, resident of Saharanpur, Uttar Pradesh, India (Randhawa *et al.*)

# WORLD

## Asia



- ◆ In United States found along Ohio and Mississippi River valleys, mostly in central and southeastern states.
- ◆ Indigenous throughout North, Central, and South America.
- ◆ The Caribbean: parts of the Middle East (Iran and Turkey).
- ◆ Parts of Europe: Northern Italy, Bulgaria, Spain, Hungary, Austria, France, Portugal, Romania, the countries of former Soviet Union, Great Britain, Ireland & Norway.
- ◆ Parts of Africa and Australia.
- ◆ **Reported from all continents of the world except Antarctica.**



**NORTH AMERICA**

**EUROPE**

**ASIA**

**AFRICA**

**SOUTH AMERICA**

**AUSTRALIA**

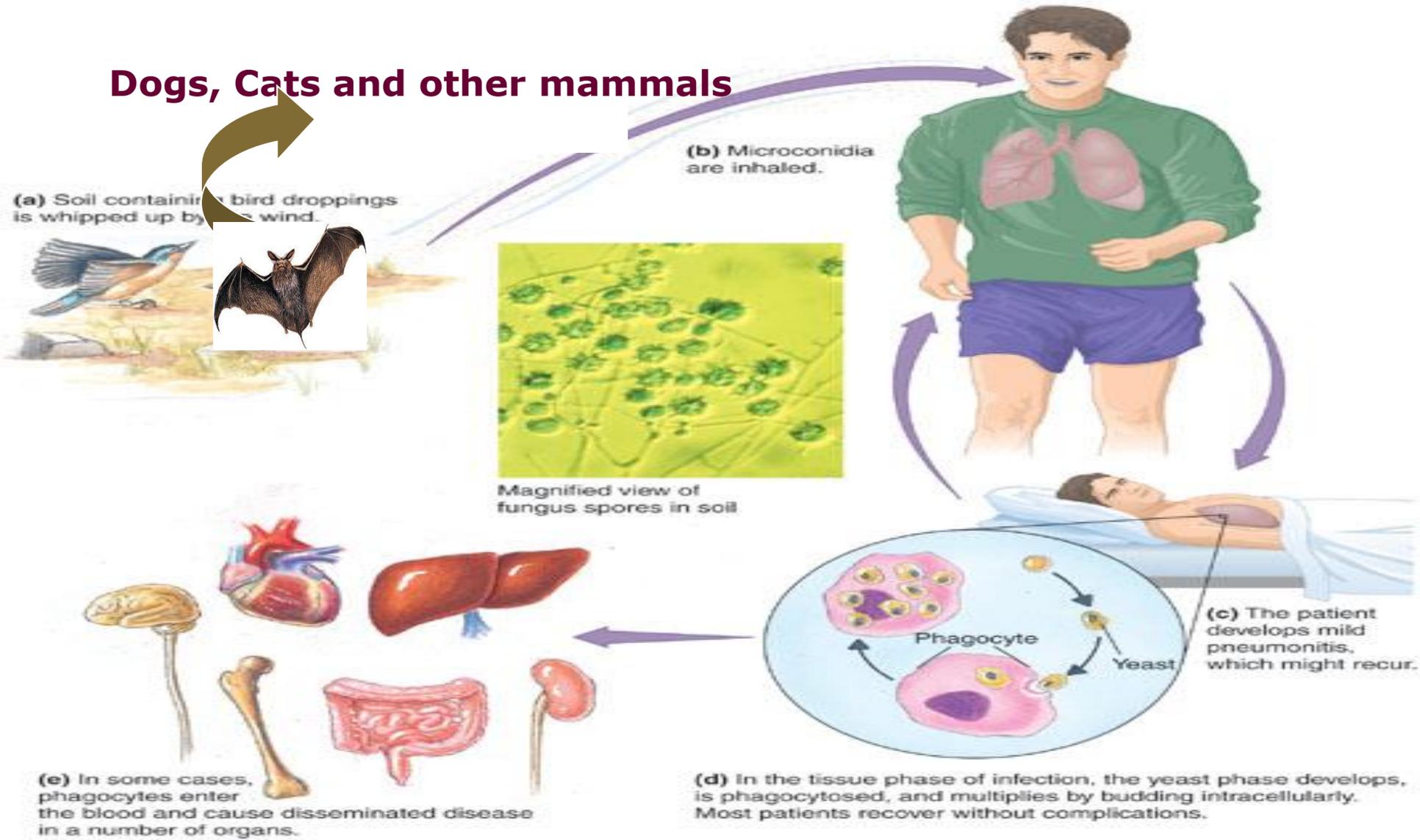
**ANTARCTICA**

# TRANSMISSION & PATHOGENESIS

❖ Histoplasmosis is not transmitted directly from person to person

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## Dogs, Cats and other mammals



- ❖ **Dimorphic fungus growing as a mold in soil and as a yeast in animal and human hosts as an intracellular pathogen.**
- ❖ **The quality of the surface soil (upper 15 cm) that supports growth of organism is usually found in the vicinities of chicken houses, roosting places of birds and bat caves (cave disease) that abound in decaying guano.**
- ❖ **During outdoor activities such as spading of soil, deconstruction of chicken coops, spelunking etc., aerosolized microconidia are inhaled.**
- ❖ **Microconidia settle in the alveoli and are then ingested by the alveolar macrophages.**
- ❖ **Convert to the yeast form (heat sensitive) and replicate within the macrophages**
- ❖ **Spread to the regional lymph nodes and throughout the reticulo-endothelial system.**

- ❖ **Intracellular growth of the pathogen in macrophages and a granulomatous reaction in tissue.**
- ❖ **The infected macrophages induce cytokines in order to enlist more macrophages and monocytes to fight the organism and these coalesce together to form granulomas.**
- ❖ **Granulomatous foci may reactivate and cause dissemination of fungi to other tissues.**
- ❖ **The activation of the T cell mediated immune response is usually complete within two weeks and failure of this result in the progressive spread of infection to other organs.**

# CLINICAL PRESENTATION

- ❖ **Histoplasmosis present clinically in different forms –**
  - **Asymptomatic infection.**
  - **Acute or chronic.**
  - **Pulmonary infection.**
  - **Mediastinal fibrosis or granulomas.**
  - **Disseminated histoplasmosis.**
- ❖ **90% of infections are asymptomatic or result in mild influenza-like illness.**
- ❖ **Incubation period is typically 3–17 days.**

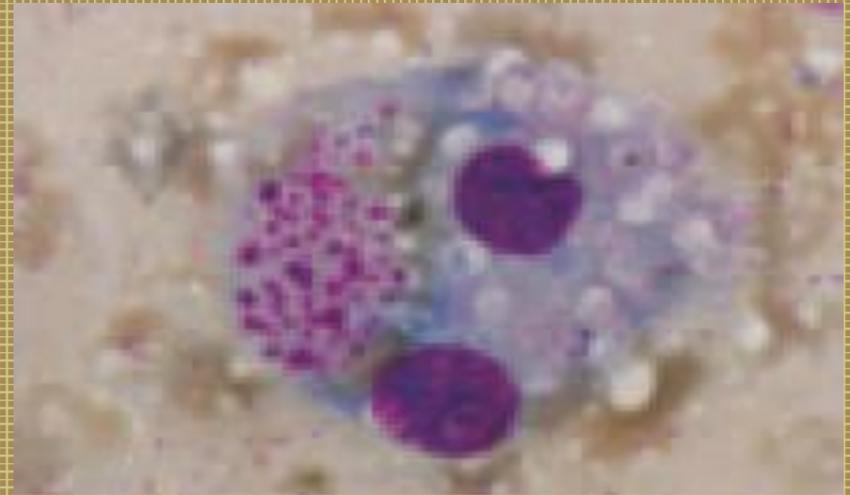
- ❖ Most persons recover spontaneously 2–3 weeks after onset of symptoms, although fatigue may persist longer.
- ❖ **Acute pulmonary histoplasmosis**, manifested by high fever, headache, nonproductive cough, chills, weakness, pleuritic chest pain and fatigue.
- ❖ Dissemination, especially to the gastrointestinal tract and central nervous system.
- ❖ Development of progressive DH indicates impaired cell mediated Immune responses
- ❖ **Acute form of DH** seen mostly in immuno-compromised host and characterized by abrupt onset of symptoms (fever, malaise, hepatosplenomegaly, lymphadenopathy, anemia, leucopenia and thrombocytopenia), lack of granulomatous inflammatory response and high case fatality rates.
- ❖ **Chronic form of DH** characterized by indolent course, focal lesions and effective cell mediated immune response.



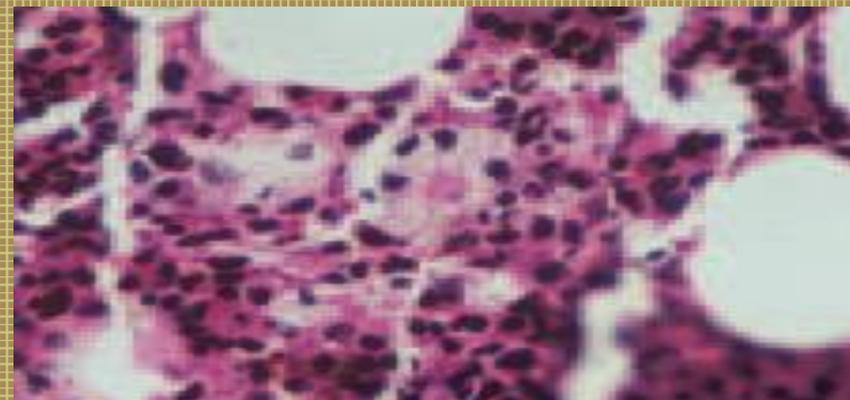
A papule on the leg is an innocent-appearing lesion that was produced by dissemination of histoplasmosis.

**Disseminated *Histoplasma capsulatum*, skin infection.  
Source: Microbiology Perspectives, 1999.**

- ◆ **Reactive haemo-phagocytic syndrome (RHPS)**  
nonmalignant syndrome characterized by expansion of monocyte-macrophage population and intense haemophagocytosis.
- ◆ It can occur de novo, but more often it occurs in the setting of another disorder, usually an infection or a malignancy.



**Bone marrow aspirate smears showing Histoplasma in histiocytes (haemophagocytosis)**



**Trephine biopsy showing Histoplasma**

- ❖ In Indian patients, skin and mucosa are the most commonly involved sites, with or without systemic involvement.



## OCCULAR HISTOPLASMOSIS

- ❖ A small fraction of individuals form scar tissue in the retina many years after the original histoplasmosis infection.
- ❖ This scarring can obscure the macula and lead to loss of central vision.
- ❖ The first signs - **small “histo spots”**.



# HISTOPLASMOSIS IN ANIMALS

- ◆ **Dogs: Chronic weight loss, cough, lethargy, pyogranulomatous lymphadenitis, diarrhoea and intermittent fever.**
- ◆ **Cat: Multicentric granulomatous nodules in lungs and involvement of spleen & heart.**
- ◆ **Horse: Abortion, chronic weight loss, fever and pulmonary symptoms.**
- ◆ **Cattle and Swine: Disseminated form.**

# DIAGNOSIS

❖ **Clinical signs and history**

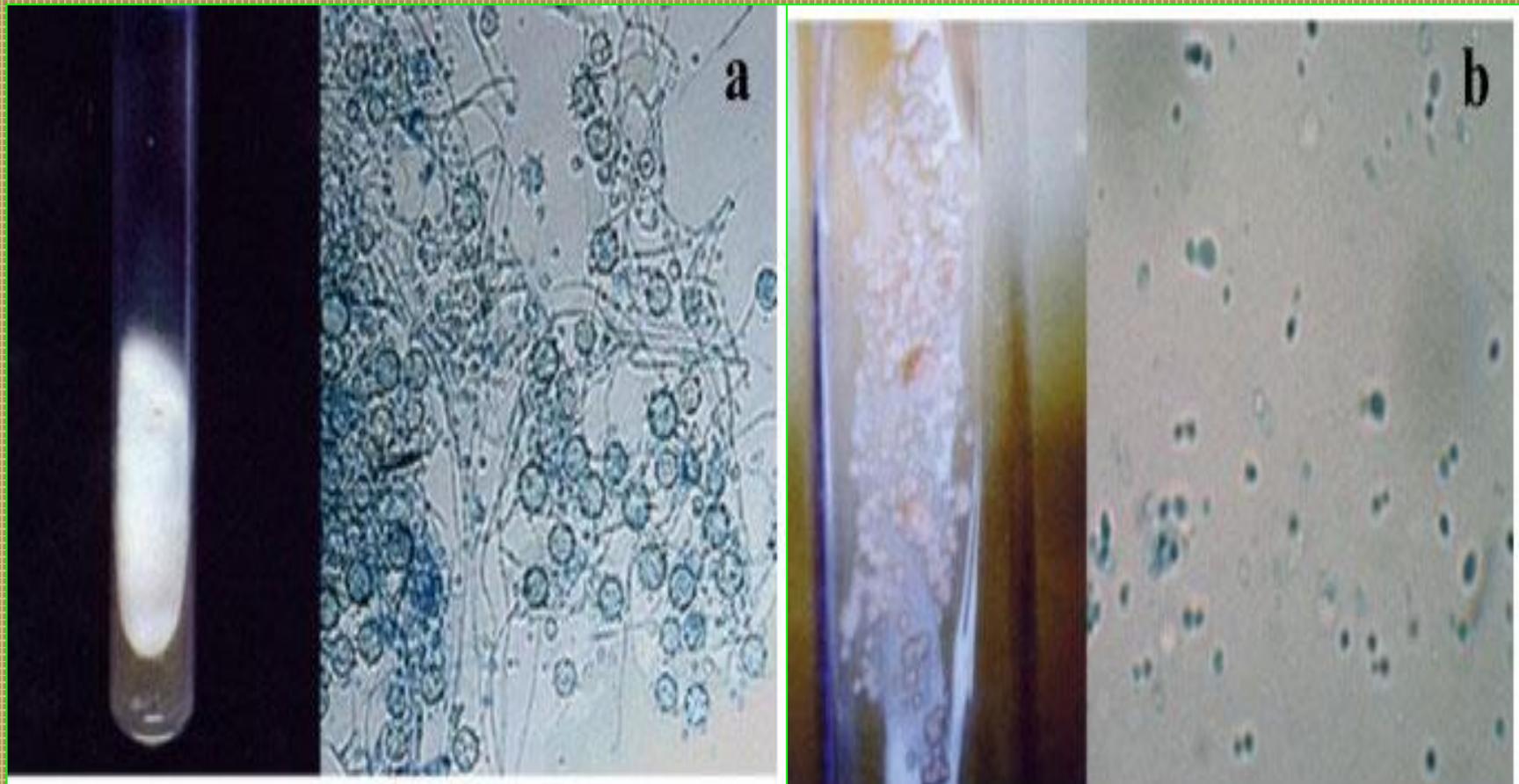
◆ **Radiography:** Active pulmonary histoplasmosis (calcified nodules in lungs)



Disseminated *Histoplasma capsulatum*, lung infection.

Source: Microbiology Perspectives, 1999.

- ◆ **Cultural examination:** From bone marrow, blood, sputum, and tissue specimens is the definitive method of diagnosis.



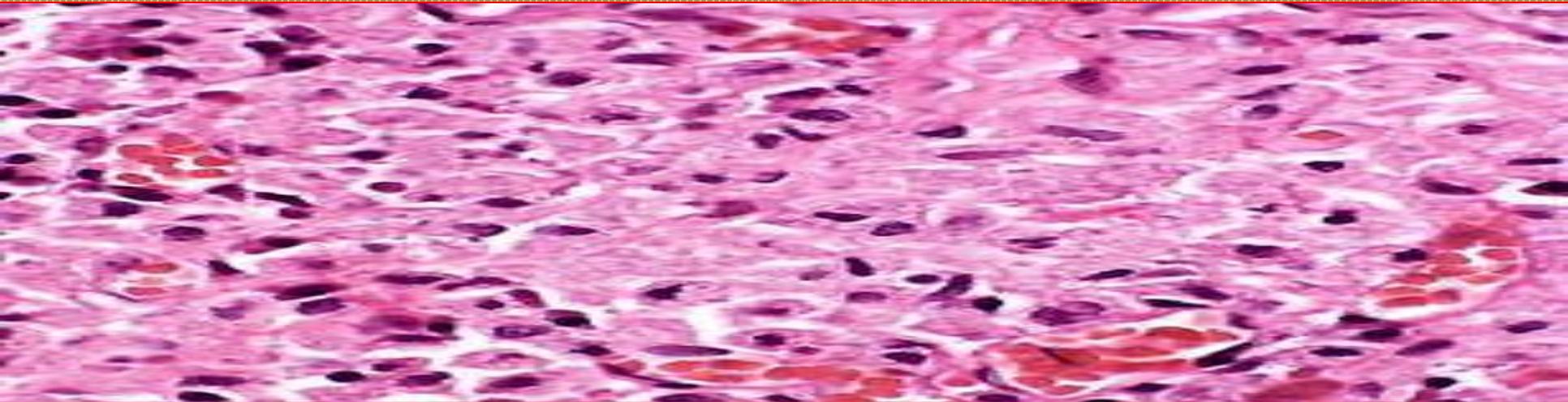
**Figure 1.** *Histoplasma capsulatum*: a) mold form (culture and microscopy); b) yeast form at 37°C (culture and microscopy respectively).

❖ **Direct detection by aspirate smear staining:**



**Geimsa stain: intracellular oval bodies surrounded by an arte-factual "capsule"**

## ◆ Histopathological:



H&E stain shows macrophages filled with organisms giving the cytoplasm a slightly vacuolated appearance



Gomori methenamine stain shows clustered organisms in cytoplasm.

- ◆ An **antigen detection test** used on urine (urine histoplasmosis antigen) and serum is a rapid, commercially available diagnostic test.
- ◆ Most sensitive for severe, acute pulmonary infections and for progressive disseminated infections.
- ◆ In HIV-infected patients with disseminated histoplasmosis, histo. antigen detection in serum and urine is 50%, and 90% sensitive, respectively.
- ◆ **Serologic testing** for antibodies (LA, CFT, AGID, RIA)
- ◆ **Histoplasmin Skin test** (0.1 ml ID) is not useful, because most people are positive in endemic area.

## TREATMENT

- ◆ Usually not indicated for healthy, immuno-competant persons with acute, localized pulmonary infection (self-limited, often resolving within 3 weeks).
- ◆ Persons with persistent symptoms beyond 1 month treated with **Itraconazole or Amphotericin B.**
- ◆ Diffuse pulmonary & disseminated histoplasmosis, treated with either Itraconazole or Amphotericin B.
- ◆ Immuno-compromised conditions and other chronic diseases require prolonged treatment.
- ◆ Ketoconazole or Itraconazole is effective as therapy for self-limited disease (used in AIDS).

## PREVENTION & CONTROL

- ◆ No vaccine is available.
- ◆ Persons at increased risk for severe disease advised to avoid high-risk areas, such as bat-inhabited caves.
- ◆ If exposure cannot be avoided, persons should be advised to decrease dust generation in infested areas by watering and masks wear and special protective equipment.
- ◆ After engaging in high-risk activities, hosing off footwear and placing clothing in airtight plastic bags to be laundered could also decrease the potential for exposure.
- ◆ Transportation of soil, guano, and other potential fomites should be avoided.

*Thank You*

