DEEP MYCOSIS or SYSTEMIC MYCOSES

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Systemic mycosis : Dimorphic fungi

Involves multiple organs, true pathogens

Saphrophytic fungi, spread by inhalation,

- Blastomycosis
- Paracoccidioidomycosis
- Coccidiodomycosis
- Histoplasmosis

0ppurtunistic mycoses

- fungi of commensals or environment ,Act as pathogen in low immunity
- Aspergillosis
- Pencillosis
- Zycomycosis
- Candidiasis
- Cryptococcosis (torulosis)
- Pnuemocystis jirovecii

Systemic mycoses
deep or disseminated fungal infection

- occur in varying severity

  Asymptomatic to fatal.

- .Soil saphrophytes . Infection is accidental

-

- thermally "DIMORPHIC FUNGI".

  (yeast forms at body temp. (37^0c)

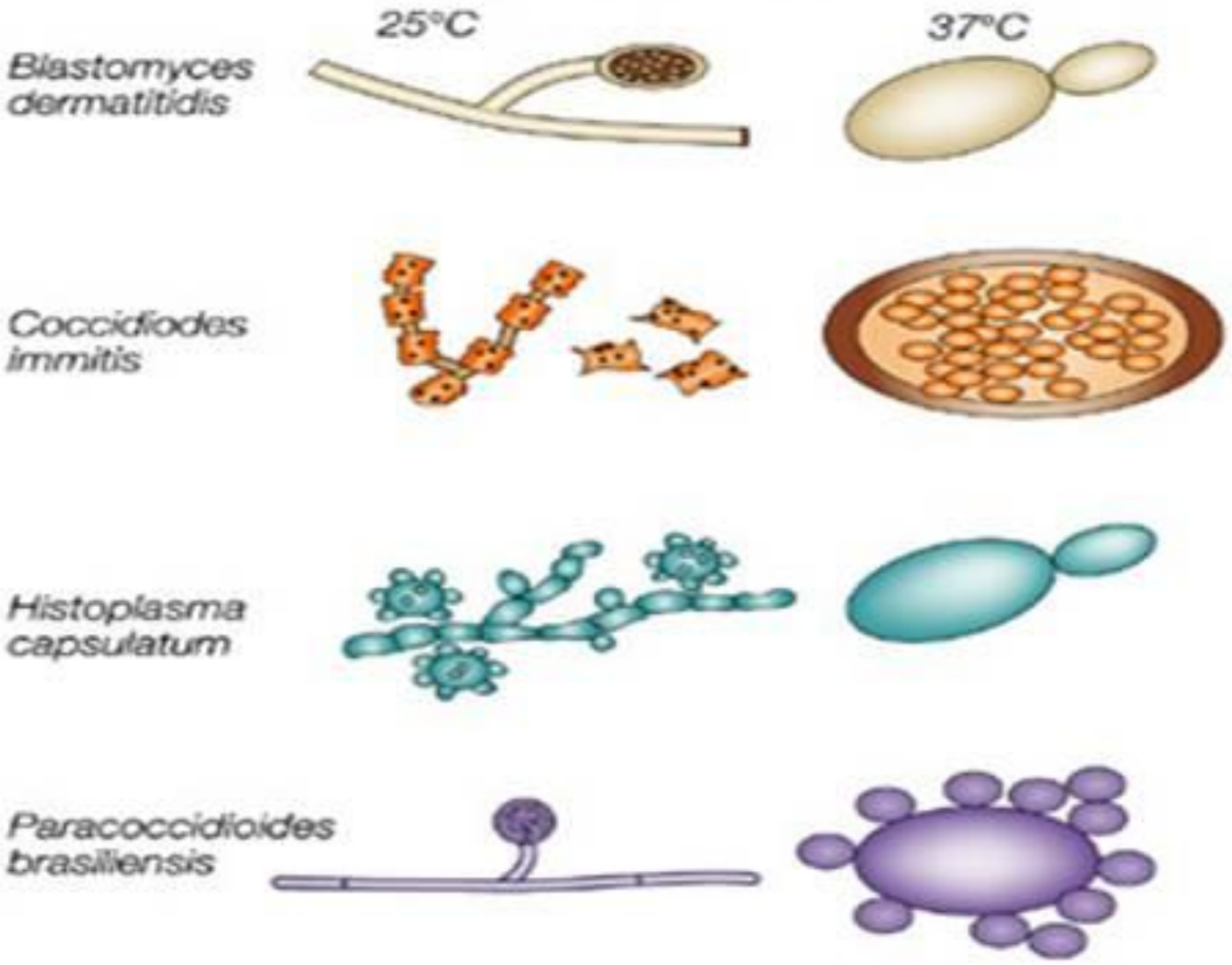
  Filamentous form at room temp. (25^0c))

Systemic mycosis :

thermally Dimorphic fungi-are

1. Blastomycosis
2. Paracoccidioidomycosis.
3. Coccidiodomycosis
4. Histoplasmosis

Dimorphic fungi



0ppurtunistic mycoses

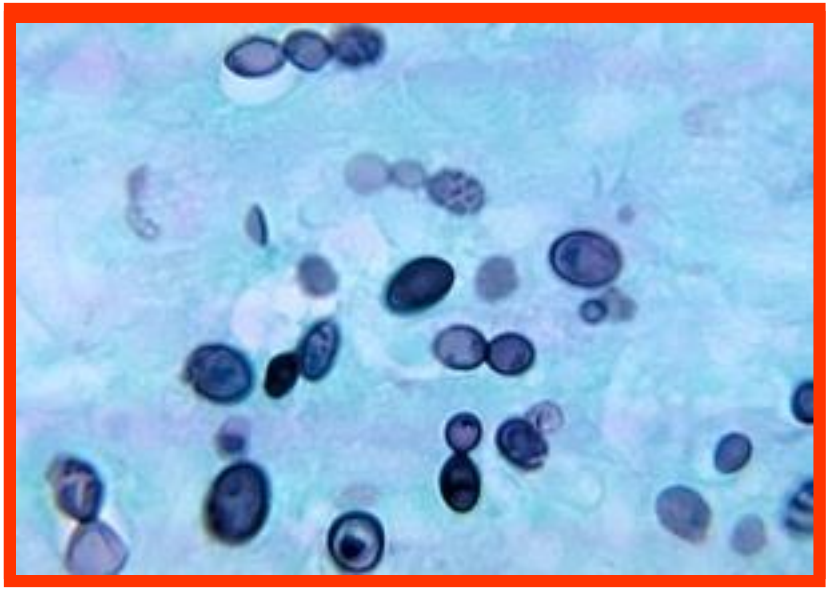
- Occur in patients
- Suffer from debilitating diseases
- Such as-cancer or diabetes
- Or physiological state is upset by
- Immunosupressive drugs,corticosteroids,x-rays,broad spectrum antibacterial antibiotics
- Useally low virulent found in environment ex penicillium,mucor and aspergillus sps

HISTOPLASMOSIS (Darling's disease)

- Histoplasmosis is an intracellular infections of RES caused by dimorphic fungus "HISTOPLASMA CAPSULATUM
- Originally described by Darling -1905
- Believed to be causative agent to be a protozoon related to Leishmania donovani

Morphology :

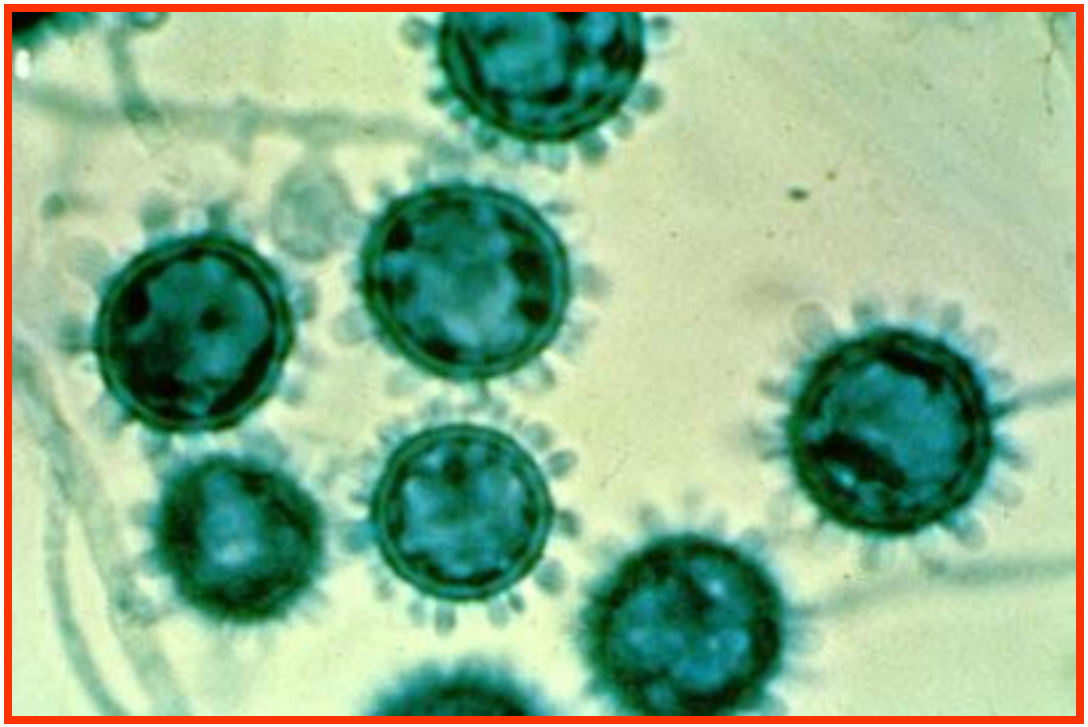
Tissues ;



37^0c → Yeast phase; Oval, budding cells of 2 – 4 μm.

25^0c → *Mycelial phase* (Thick walled, Spherical spores with tubercles (or) Finger like Projections)

"Tuberculate Spores "



DISTRIBUTION

- World wide
- Most common in USA-endemic in many central and eastern states
- Endemic areas the fungus present in the soil,
- Decaying trees
- Abundant in bird feces

Causative agent

- Two varieties
- 1) Histoplasma capsulatum var.capsulatum
- Causes classical
- Ubiquitous form of histoplasmosis

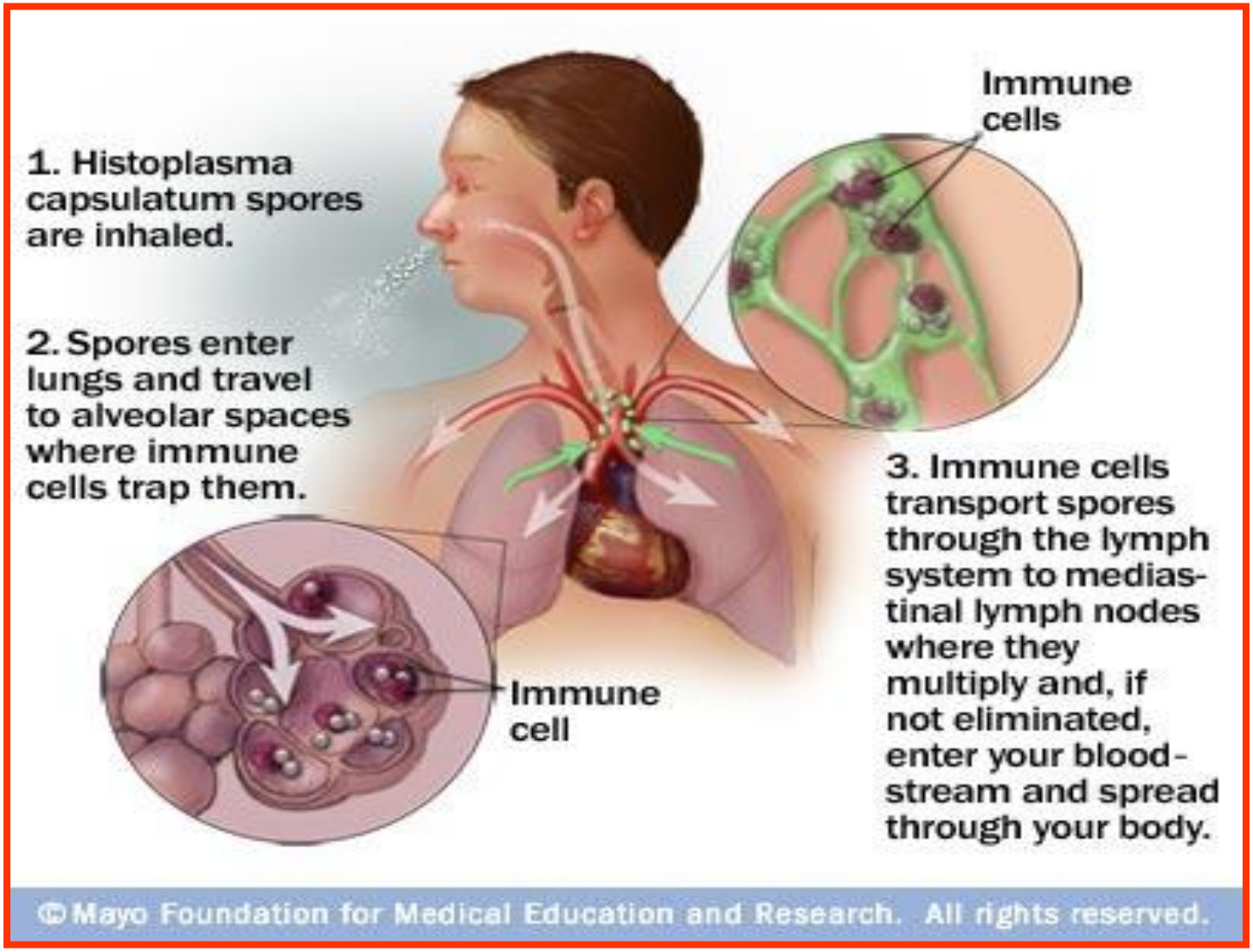
2) Hystoplasma capsulatum var.duboisii

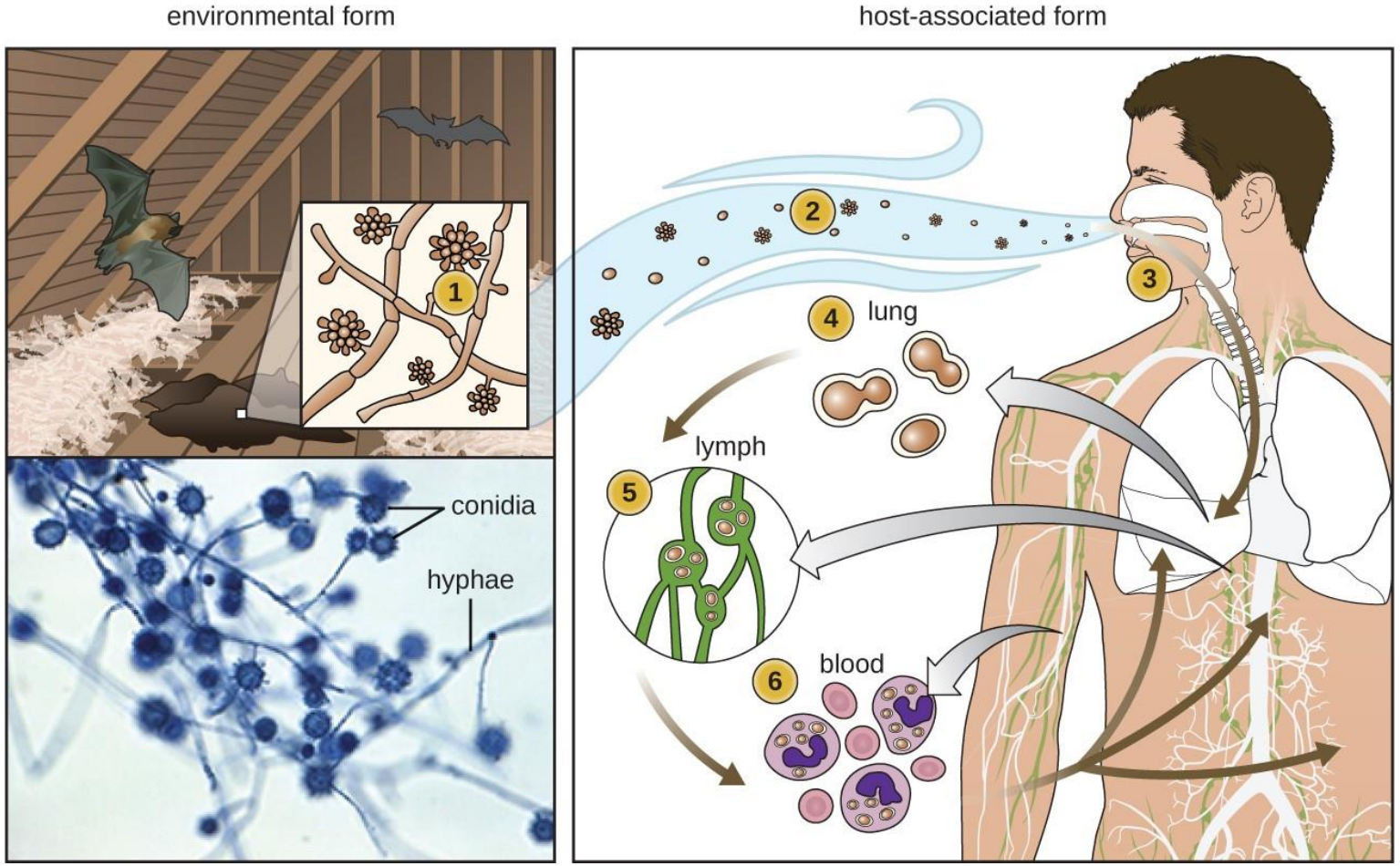
- Causes African histoplasmosis

pathogenesis

- Inhalation
- Classical 1)-most are asymptomatic
- Spontaneous healing occur
- With an area of miliary calcification
- 2)some infected individuals pulmonary disease – resembling pulmonary tuberculosis
- 3)minority develope disseminated infection

Pathogenesis:




environmental form
host-associated form
1
conidia
hyphae
2
3
4
lung
lymph
5
6
blood

Clinical fetures

- Acute pulmonary
- -asymptomatic-95%
- Few symptomatic- IP 10-16 days
- Onset influenza like(fever ,malaise,sore throat ,cough ,chest pain ,dysnea)
- Erytematous nodules
- X-ray –pul infiltration-hilar lymphadenopathy-localised nodule-calcification(mimic PT or benign malignancy)

- Chronic pulmonary-latent-same symptoms of acute -heamoptesis-epical or subepical calcification-wt loss-ulcer mouth, nose &legs
- Histoplama- central necrosis- surrounded by fibrosis-calcification-more in adult male(resemble PT or sec. malignancy)
- Cutaneous &mucocutaneous-
- -sec to primary or reactivation
- Petechial,eccymotic purpura –abdomen &thorax
- mucosal –oral cavity

- Disseminated-
- Any age(seen children and adolascence)
- Fever,anorexia,loss of wt,G.C deteriation
- Anemia lueckopenia,
- Hepatospenomealy
- Lymphadenopathy
- HIV/AIDS-more risk,common in endamic,poor prognosis,rep. failure,shock &death
- Organtrasplantation,
- infection of sinus,thyroid,prostate

- CNS –spinal cord abscess,
- GI-bloody diarrhea,(mimic ulcerative colitis or chrones disease)
- Acute intestinal obstruction,perforationand bleeding,(more in HIV) differenciated from acute abdomen
- ocular-rare POHS-pressumed ocular histoplasma syndrome-atrophy
- DD of histoplasms-mycoplsma pnuemania,PT,Maligancy,paracoccidioes

African histoplasmosis

Mainly involves

skin

Subcutaneous tissue

Bones

Lungs are not commonly effected

Disseminated disease is infrequent

Differentiating features

Classical .H	*African .H*
Yeast oval budding	*larger yeast like*
Size 2-4um	*7-15um*
May effect skin	*mainly skin*
Lungs are common	*uncommon in lungs*
USA	*AFRICA*
(ubiquitous)	

Lab. Diagnosis :

Specimen : Sputum, Bone marrow ,

Blood. Blood film.

Lymphnode biopsy.

- Microscopic examination of stained films

Classical histoplasmosis-

Giemsa or Wright-staining of infected tissue

Small intra or extra cellular yeast cells

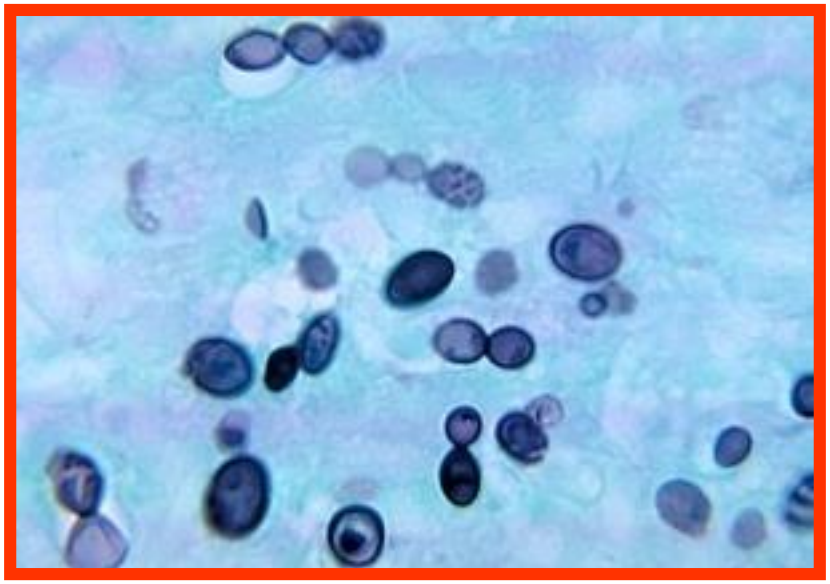
Yeast phase occure in phagocytic cells

Yeast appear as an oval,buddingcell

Size -2-4 um

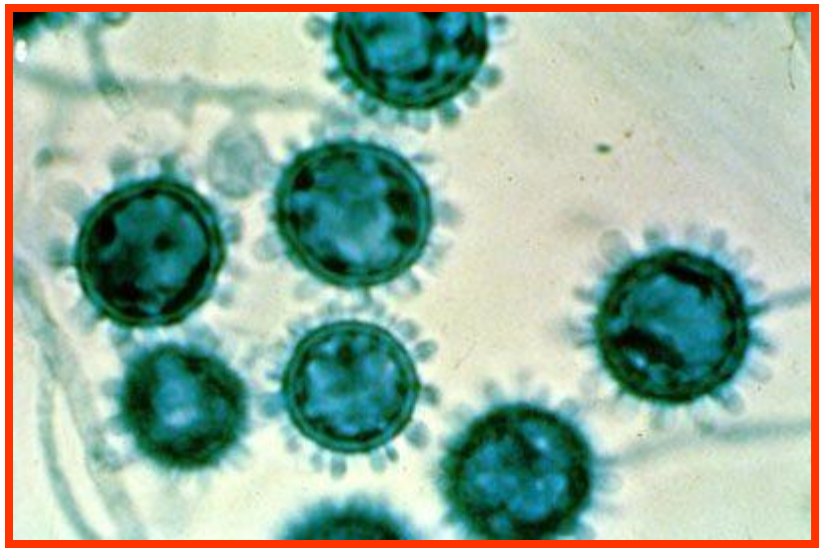
African histoplasmosis- larger yeast like cells 7-15 um

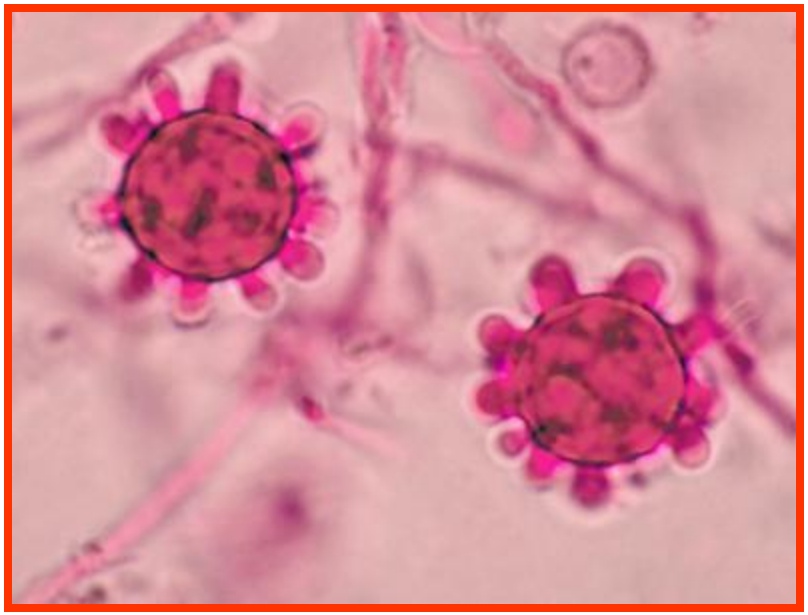
Yeast phase also grow culture on BA at 37c



Microscopy **:** → Blood film.

1. Calcofluor white stain , Giemsa stain
   Wright stain .
2. Fluroscent antibody technique .





Culture : SDA, BHI agar; BA

25^0c → white Cottony, Mycelial growth.

Larger thick walled sperical spores with

tubercles(finger like projections)

→ tuberculate spores are diagnostic

37^0c → Yeast phase.

Mycelial phases are similar

In both varieties

serodiagnosis:

1. *Antibodies develop during the cource of systemic infection*
2. *Increase in titre –progress of disease*
3. *Serological tests for diagnosis are*
4. *latex agglutination .cft ,precipitation*

Titre cosider positiveat reciprocal dilutions greater than 1:8

Active infection titre more than 1:32

- *Antigens can be detected in urine and serum*
- *These test are use ful in immunocompromised patients(antibody formation is impaired*)

Skin test

- *Delayed hypersensitivity develop after infection*
- *Demonstrated by skin test with*
- *“HISTOPLASMIN”*
- *Analogous to the tuberculin test for tuberculosis*
- *Histoplasmosis - skin tests are specific than serological methods*

Molecular test

- *PCR targeting specific ITS DI/D2 GENE (VARIABLE REGION OF 28S rRNA) is available*

- *X-ray*
- *Infiltration-hilar lymphadenopathy-calcification*

treatment

- Severe(invasive) histoplasmosis
- Drug of choice is
- Liposomal amphitercin –B

  oral ozoles
- Itraconazole
- Fluconazole
- Ketoconazole
- Corrective surgery may be used for pulmonary and cutaneous lesions

Clinical Case

- Age- 35 yr
- occupation -farm worker of chicken coops
- Present fever,cough,anorexia,lyphadenopathy
- X-ray chest-focal infiltrates &patchy opacities
- Aspiration-lymph nodes-intracellular yeast
- Culture-25c mould ,37 c yeast form
- Mycilial form –thick walled spherical spores with tubercles

Blastomycosis :

- chronic disease ,forms suppurative,granulomatous fungal leason infection lungs disseminating to extra pulmonary sites like skin, bones and genito-urinary system.
- Blastomyces dermatitidis

  (NORTH AMERICAN BLASTOMYCOSIS).

MORPHOLOGY :

- Thermally dimorphic fungus

Pathogensis :

Habitat : Soil

Mode of infection : inhalation of spores .

Hematogenous dissemination to Extra – pulmonary sites.

- *Room temperature (25^0c) :*

Mycelial phase with

septate hyphae ,

Round/ oval conidia.

- ***Tissues (37^0c) →***

yeast phase

Double – contoured,

thick walled large/

spherical (7 - 20μm)

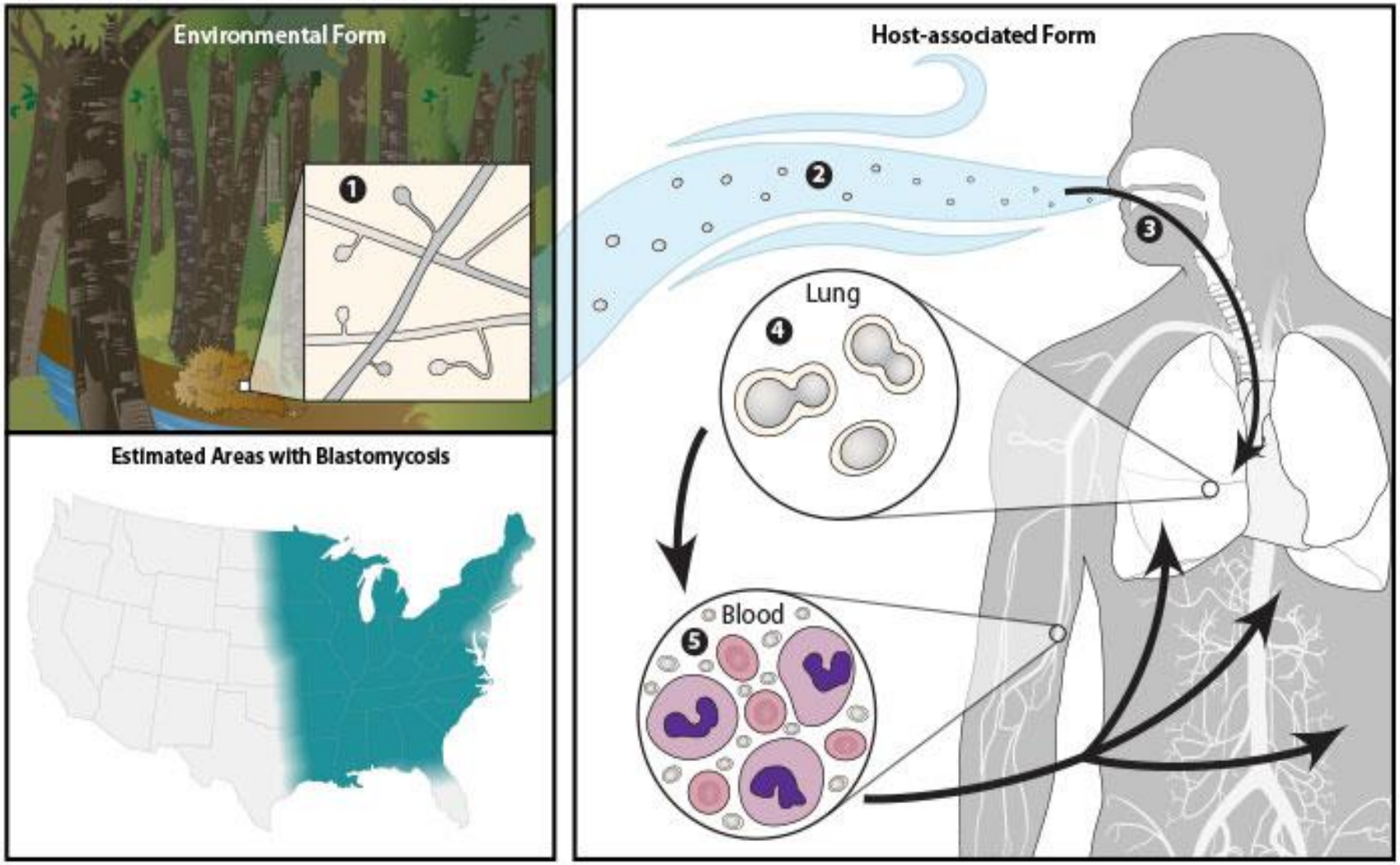
Broad – based budding

yeast cells.

pathogeneses

- Inhalation-yeast-increase in number-spread to other organs via blood-focal infection-supputative granuloma-no caseation –higly infectious
- Reactivation of pulmonary or extra pulmonary
- Diffuse infiltration(in HIV& high mortality)
- Half are symptomatic- flue like illness ,more in males
- 50% disseminated-skin .bones ,CNS,GUT
- Agressive course in immunocompromised pt

Biology of Blastomycosis



In the environment, *Blastomyces* exists as mold (1) with septate aerial hyphae. The hyphae produce spores (2). These spores are either inhaled, or inoculated into the skin (3) of a susceptible host. The warmer temperature inside the host signals a transformation (4) into a broad-based budding yeast. The yeast may continue to colonize the lungs or disseminate in the bloodstream (5) to other parts of the body, such as the skin, bones and joints, organs, and central nervous system.

313841-A https://www.cdc.gov/fungal/diseases/blastomycosis/causes.html

Clinical Spectrum :

Primary blastomycosis : Tuberculosis / Histoplasmosis .

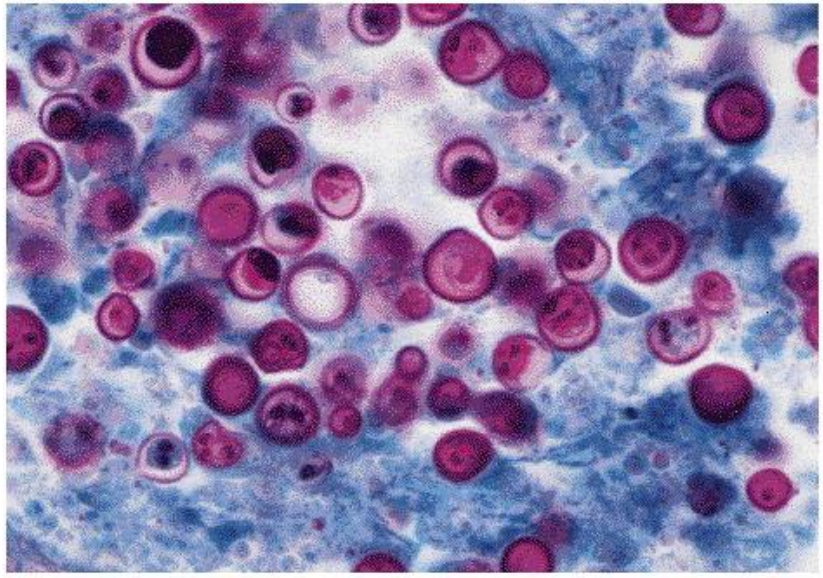
a.Pulmonary form : Asymptomatic / Self limiting.

Focal / Diffuse consolidation.

Miliary lesions / abscess formation.

b. Acute –mimic bact. pnuemonea,

c. Chronic-pulmonary tulerculosis



b.Cutaneous form: commonest- Exposed parts .

Useally face,neck and hands

IP -2 – 4 weeks

Papules → Nodules → Ulcers → Fistula

DD-Squmous cell carcinoma,NTM infection,Paracoccidiodes

- Osseus-one third
- Bones -vertebrate, pelvic,sacral ,skull ,ribs
- Vertebral is differenciated from tuberculosis by treating with antitubercular drugs
- Arthitis -kneejoint

c.Disseminated form :

Seen in Immuno compromised .

Heamatogenous route -organs.

Multiple abscess or grnuloma formation.

order of involment- lungs-skin – bones- GUT. ,

prostate in males . Fatality rate is high

Oppurtunistic infection in AIDS&transplant reci

Miscelaneous- horcenes,dysnea,CNS,retrabulbar

Lab diagnosis :

Specimens : Sputum, BAL, Biopsy, Pus, etc.

Microscopy : 1. KOH wet mount

2. Calcofluor white staining.

3. HPE : show broad – base budding, thick walled duoble – contoured yeast cells.

Culture : on SDA, BHI agar.

At 37^0c → Yeast phase

At 25^0c → Mycelial phase, septate hyphae,

round/ oval conidia

Older cultures → chlamydospores..

distribution

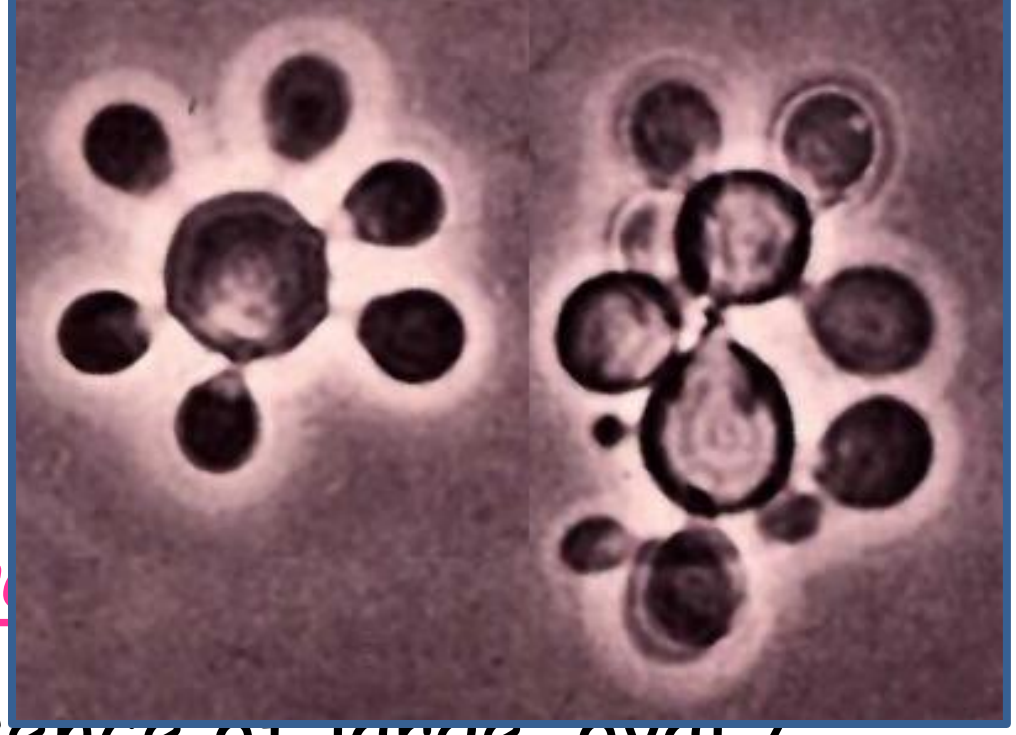
- Largely confined to NORTH AMERICA
- Known as North American blastomycosis
- Paracoccidioidomycoses is know South American blastomycoses
- Recently several cases reported from
- Africa and India
- Isolated in Delhi from bronchial aspirations

Paracoccidioidomycosis :

- "*South American blasto mycosis* "
- Chronic granulomatous endemic systemic fungal infections that involves primarily lungs and disseminates to skin, mucosa, lymph nodes and occasionally internal organs.
- Paracoccidioides brasiliensis.

Morphology :

- Dimophic Fungi



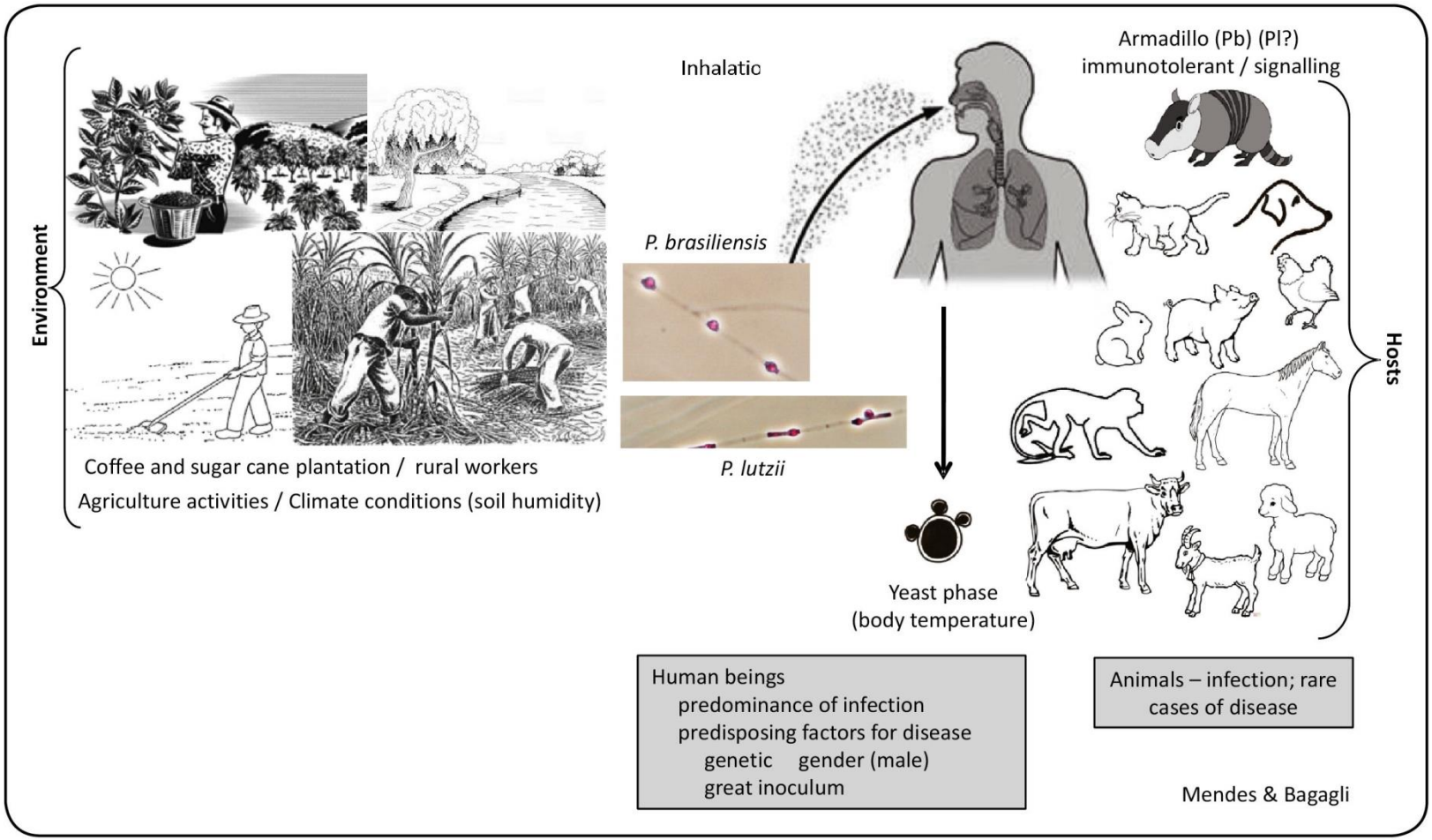
- Tissues & cultur

phase, with presence of large, oval / round cells with multiple budding. Pilotwheel or meriner"s wheel appearance

- Room temp. (25^0c) → Mycelial phase, with hyphae.

pathogeneses

- Inhalation-conversion to yeast-
- Primary establishment of infection
- Few cases disease(variability of immunity)
- phagocytosed by mononuclear cells-
- Acute form non-granualar-no CMI,only antibodies
- chronic form- granular -localised or systemic involvement .Granulomatus lesions are due to factors of host and fungus-CMI and antibodies
- --


Environment
Coffee and sugar cane plantation / rural workers
Agriculture activities / Climate conditions (soil humidity)
Inhalatio
P. brasiliensis
P. lutzii
Yeast phase
(body temperature)
Armadillo (Pb) (Pl?)
immunotolerant / signalling
Hosts
Human beings
predominance of infection
predisposing factors for disease
genetic gender (male)
great inoculum
Animals – infection; rare cases of disease
Mendes & Bagagli

- Infection-no clinical signs- only skin test +ve
- Disease –triade-pulmonary ,oral &skin
- Begin with asymptomatic pnuemonea
- spread via blood and lymphatics to mucocutaneous ,GIT, lymphnodes
- other organs, all parts of body

CLINICAL FORMS

- 1-acute/jevenile—involment of RE System
- 2-chronic/adult—pulmonary&mucocutaneous adult male ,agriculturists
- 3)Quienscet

- 1)Acute/jevenile-first 3decades,
- less common(5%,)
- Involve RES , both sexes ,
- superficial/deep lymphnodal enlargement
- grave type-progress- effects liver, spleen &bone marrow,
- moderate type-one system of lymphnodes
- Symptoms of GIT-diarrhea ,acute abdomenal syndrome
- Mucosal-infrequent, osteo-arhritis,
- pulmonary rare

- 2)Chronic/adult-long lasting,
- Unifocal –one organ or system
- Multifocal- more than one organ
- Majority males ,above 30yrs
- Restricted to lungs
- Reactivation of quienscet lung lesion
- Spread to bronchioles,
- -lymphatic, hematogenous root-
- most case with lungs inaddition to URT,GIT,oral ,skin CNS ,bone

-

- 3)Quenscent /sequele latent form
- A)mucosal lesions direct or secondary
- Pain ful ulceration-
- 0ral cavity,tongue,conjunctiva,
- less on oropharynx-cause dysnea
- Ulcers granulomatous –spread -mulbery like erotion –seen anal,genital areas-polymorphic warty,hyper keratotic,plague
- No lung involvement

- B) lymphatic lesions
- Lymphadenopathy-cervical-sub maxilary-supraclavicular,
- Massive enlarement-Bullneck
- Transform to abscess –caseation- sinus
- Look scrofuloma(cervical tuberculous lymphadenitis)
- less bones,
- CNS, spinal granuloma

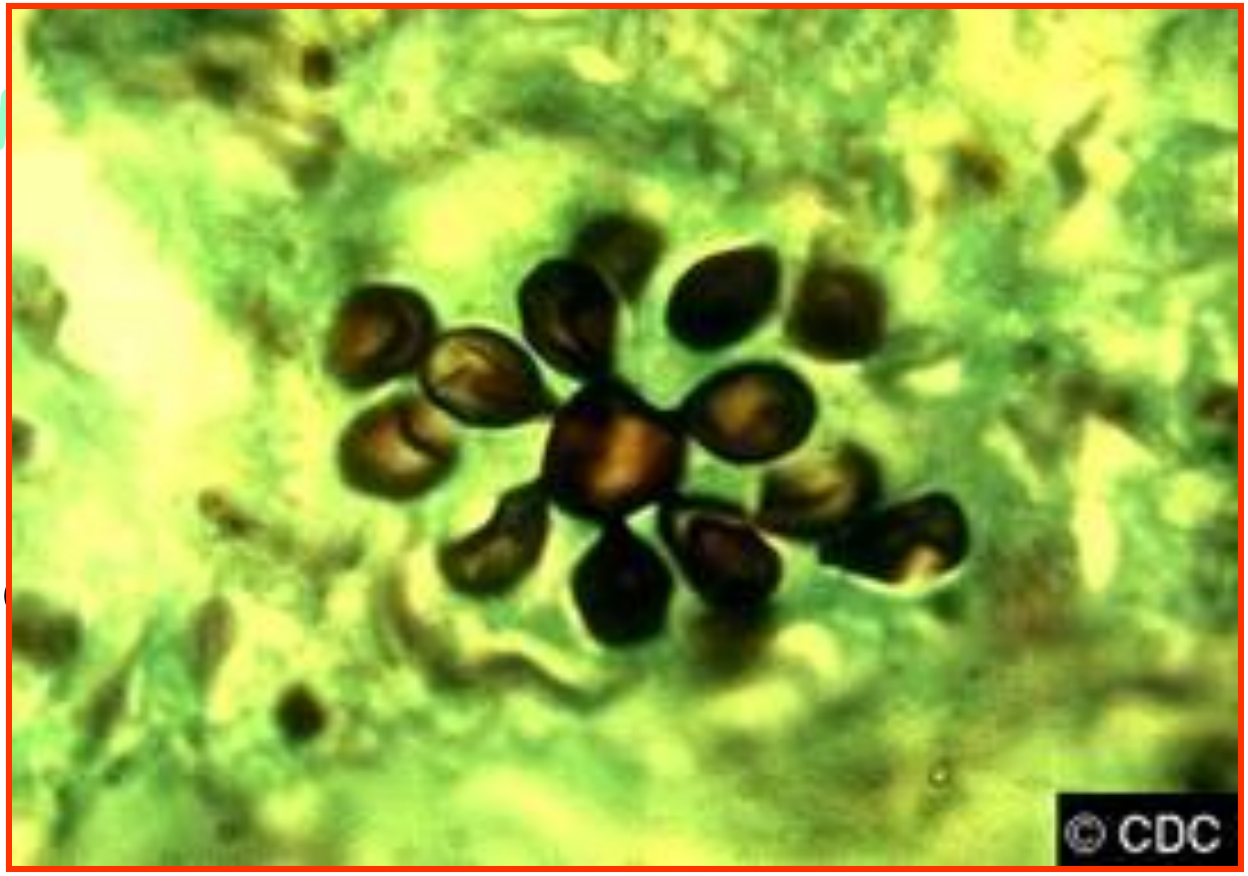
- C)veseral lesions –desseminated infection
- , fever, wt loss, anorexia
- triade of pulmonary,skin &mucosal lesions
- lung invoment 90%.
- cough ,dysnea, nodular miliary shadow/cavity,fibrotic lesion in middle&lower lung
- Lesions may be in bones, joints,eyes
- -CNS, endocrines glands
- ***Paracoccidioidomycosis in 10 – 12% cases associated with tuberculosis****

- DD- PT,
- HISTOPLASMOSIS,
- CRYPYOCOCCOSIS.
- MUCOCUTANEOUS LESMANIASIS
- ,LEPROCY

Lab. Diagnosis :

Specimen : Sputum, BAL, Pus. Etc.

Microscop



Culture :

Immuno – diagnosis :

1. ***Skin test*** → using *"paracoccidioidin".*
2. ***Serology :*** 1. Immuno – diffusion
   2. CFT
   3. ELISA
   4. DNA probes
   5. PCR.

TREATMENT

- Long term antiungal treatment-6-12 months
- Amphotericin B.itroconazole
- Ketaconazole
- fluconazole

Coccidioido mycosis :

- "Coccidioides immitis".
- "San joaquin Valley fever / Desert Rheumatism.

  Habitat : Soil, rodents.

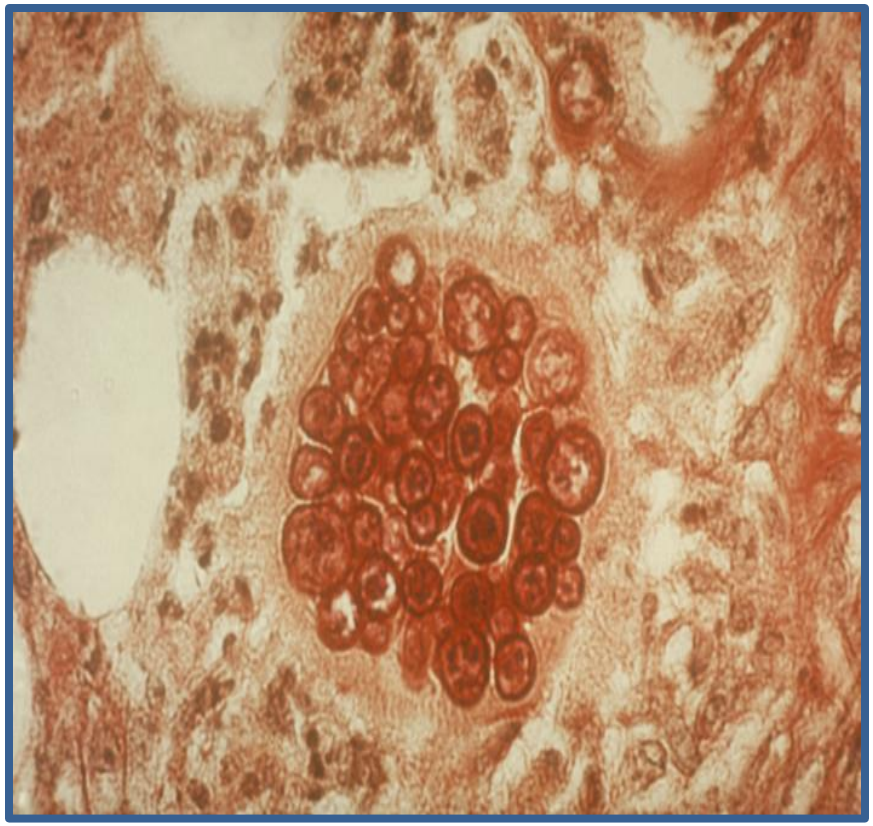
Morphology :

- Dimorphic fungus
- *Room temp.(37^0c & 25^0c)* **→
- "Mycelial phase, with thick walled septate hyphae with arthrospores. "

Tissue →

Yeast phase ,

Thick double walled refractile spherules filled with endospores .



Pathogenesis :

Mode of infection : inhalation of arthrospores .

Clinical Spectrum :

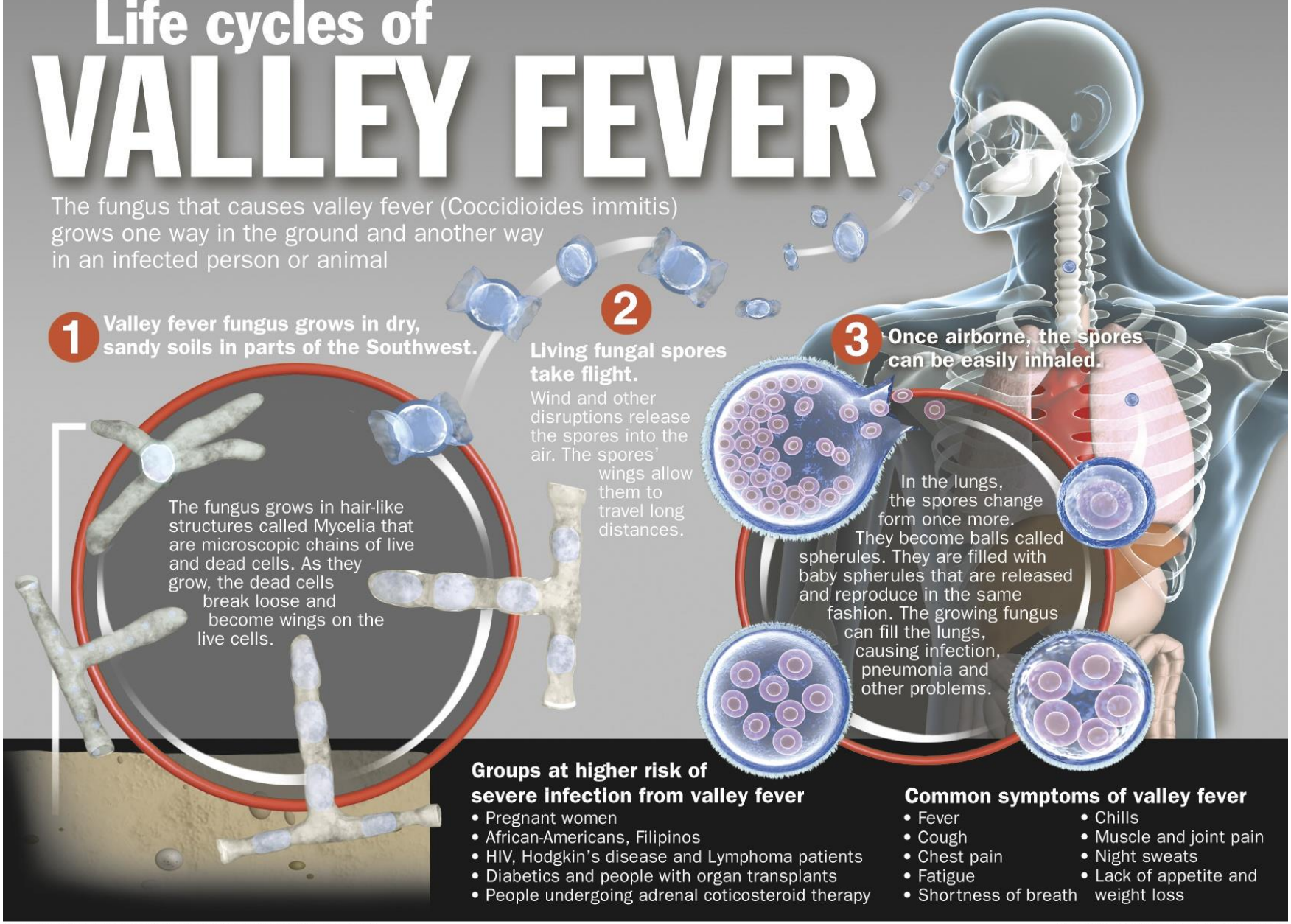
Asymptomatic (60%) .

Symptomatic but self – limited with influenza – like fever (90%) .

Chronic progressive disseminated disease .wks,month yrs.
(Coccidial granuloma) 1%.

Life cycles of VALLEY FEVER

The fungus that causes valley fever (Coccidioides immitis) grows one way in the ground and another way in an infected person or animal



Groups at higher risk of severe infection from valley fever

- Pregnant women
- African-Americans, Filipinos
- HIV, Hodgkin's disease and Lymphoma patients
- Diabetics and people with organ transplants
- People undergoing adrenal coticosteroid therapy

Common symptoms of valley fever

- Fever
- Cough
- Chest pain
- Fatigue
- Shortness of breath
- Chills
- Muscle and joint pain
- Night sweats
- Lack of appetite and weight loss

Sources: Valley Fever Center for Excellence, Californian research

MICHAEL BORJON/THE CALIFORNIAN

- PULMONARY –incubation period -2wks
- Flue like symptoms-headace, fever,malaise muscle pains,
- 20%hyper sensitivity reaction-erythemanodosum of skin.
- In endamic area pnuemonea ,arthritis or erythemanodosum .This symptom complex is known as Valley fever /dissert rheumatism-self limiting
- Progressive infiltration-fibrosis -coin like lesion on x-ray

2 Disseminated form:

Hematogenous route (<1%).

affects all organs except GIT.

Skin : →granulomas, cold abscesses

Bone → Synovitis, osteomyelitis , desrtuction &sclerosis of bones(vertebra,ribs) rarely CNS,Fatal in liver transplants, High risk in HIV &death.

other organs-eyes,larynx,

Chronic meningitis – hydrocephalus

Laboratory diagnosis :

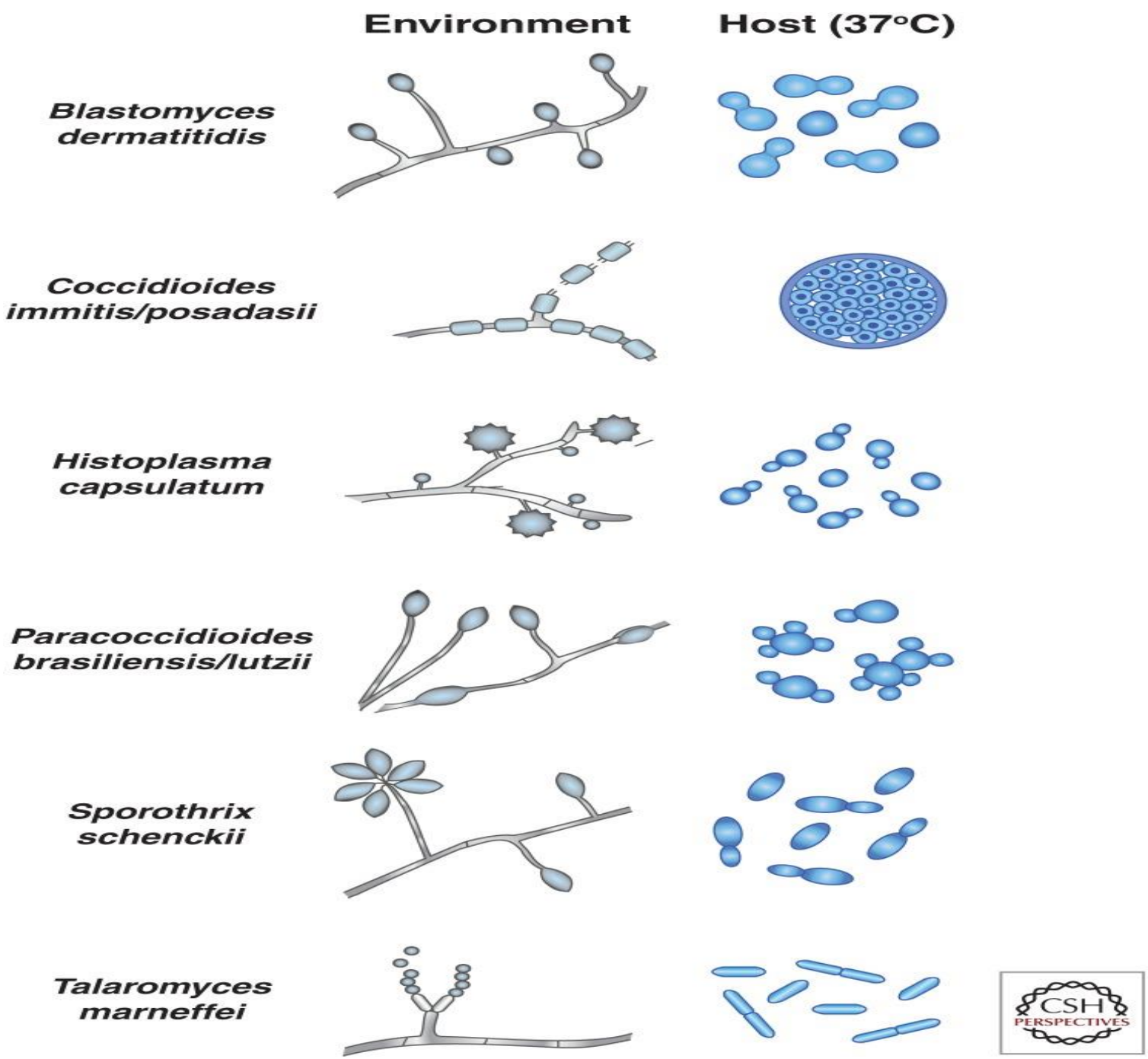
Specimen : Sputum, CSF, Pus, Biopsy.

Microscopy :- 1. Wet mount: Double – walled, globular spherules.

2. H & E stain : with / without Endospores.

3. PAS .

Culture : on SDA, BA, BHI agar - 4 -5 days growth.


Environment
Host (37°C)
Blastomyces dermatitidis
Coccidioides immitis/posadasii
Histoplasma capsulatum
Paracoccidioides brasiliensis/lutzii
Sporothrix schenckii
Talaromyces marneffei
CSH PERSPECTIVES

Cryptococcosis (Torulosis) (European blastomycosis)

- Acute, sub-acute, chronic fungal disease caused by on encapsulated yeast, belonging to genus "Cryptococcus"
- Cr. neoformans. (MC)
- 4 serological types A, B, C, D
- 1970 " Ajello" → "Sleeping gaint"
- "Awakening gaint" .

Habitat : World – wide

Avian sources : Pigeon droppings, Soil.

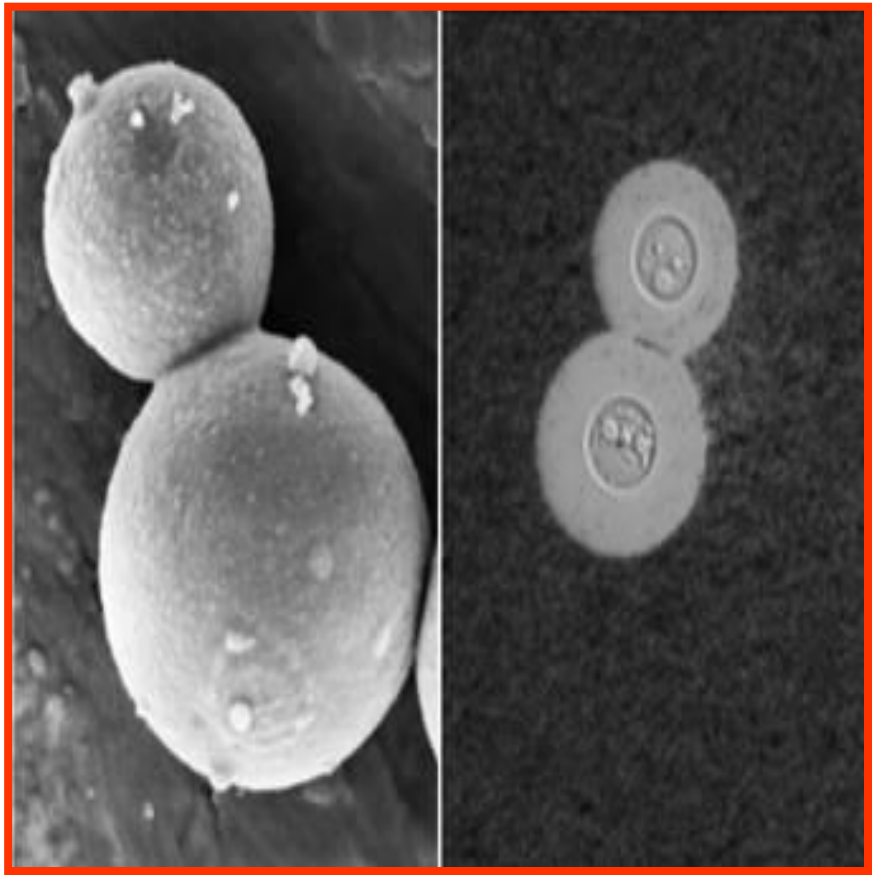
Morphology :

Round (or) ovoid budding Yeast cell, 4 – 20μm .

Polysaccharide capsule :

twice as thick as

diameter of yeast cell.

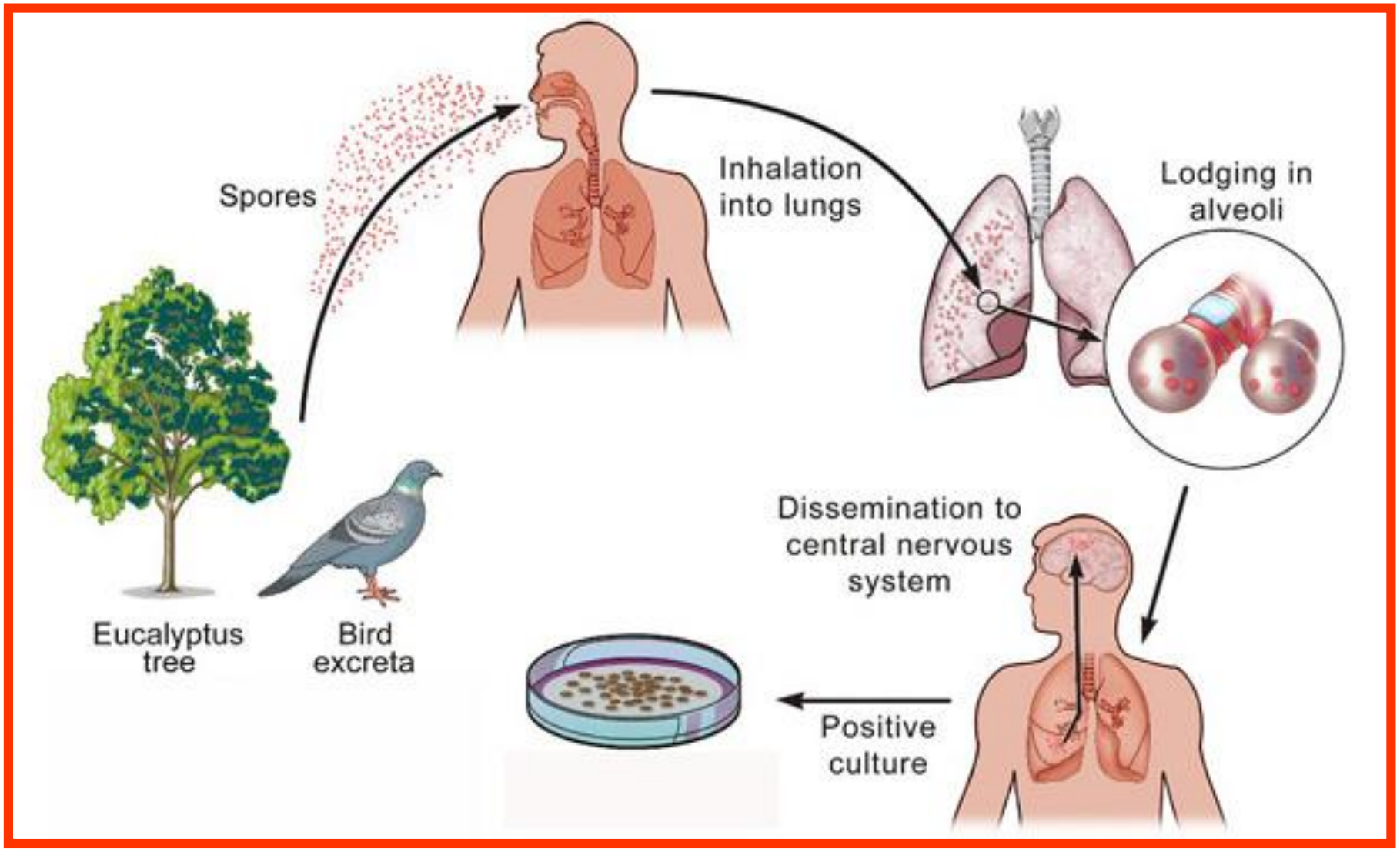


Virulence Factors :-

- Capsular polysaccharide.
- Sialic acids.
- Melanin production,
- urease production.

Pathogenisis :

Incubation period → 2 – 4 weeks.



Clinical Features :

1. *Pulmonary cryptococcosis* : → Mild pneumonitis

   (Self – limiting).

   Asymptomatic.

2. *Visceral Cryptococcosis* :

   Lungs represent Mc site.

   Simulate TB & malignancy.

3. *Cutaneous cryptococcosis :* 10 – 20%.

Papules, Nodules, abscesses, ulcers, granulomas.

4. *CNS cryptococcosis :*

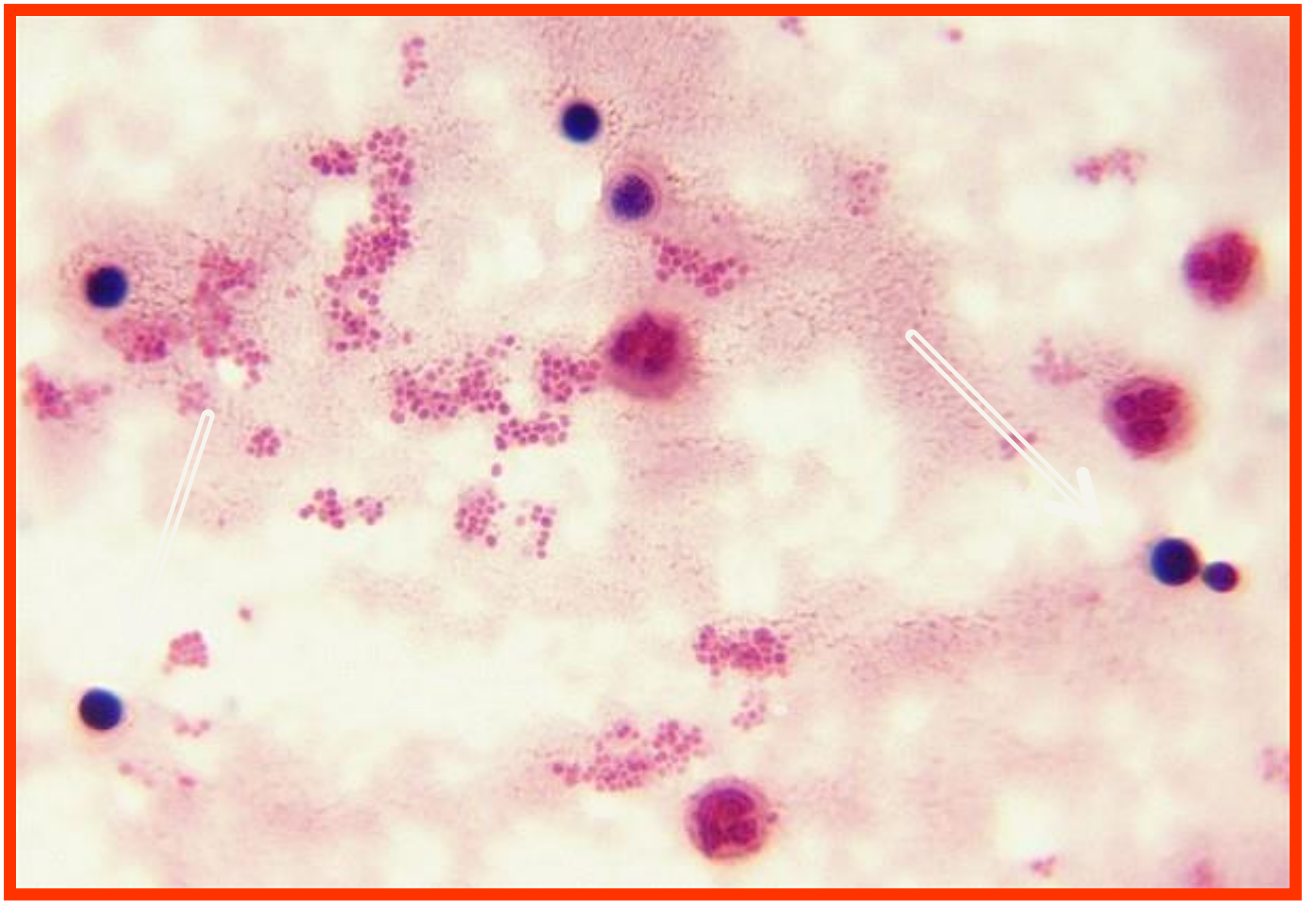
Meningo – Encephalitis ..Meningitis (HIV)

Lab. Diagnosis :

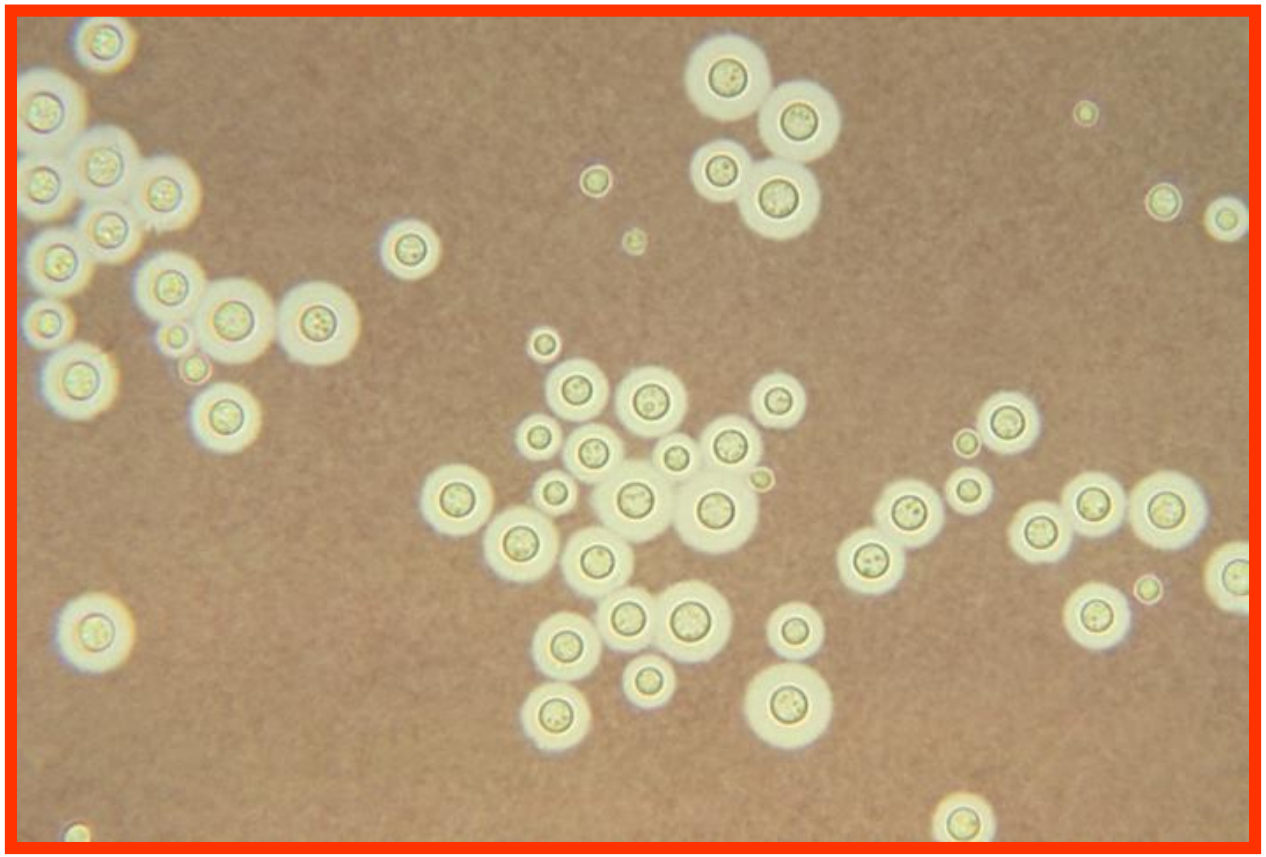
Specimen : CSF, Serum, Body fluids.

Microscopy :

Gram stain : Gram positive budding yeast cells.

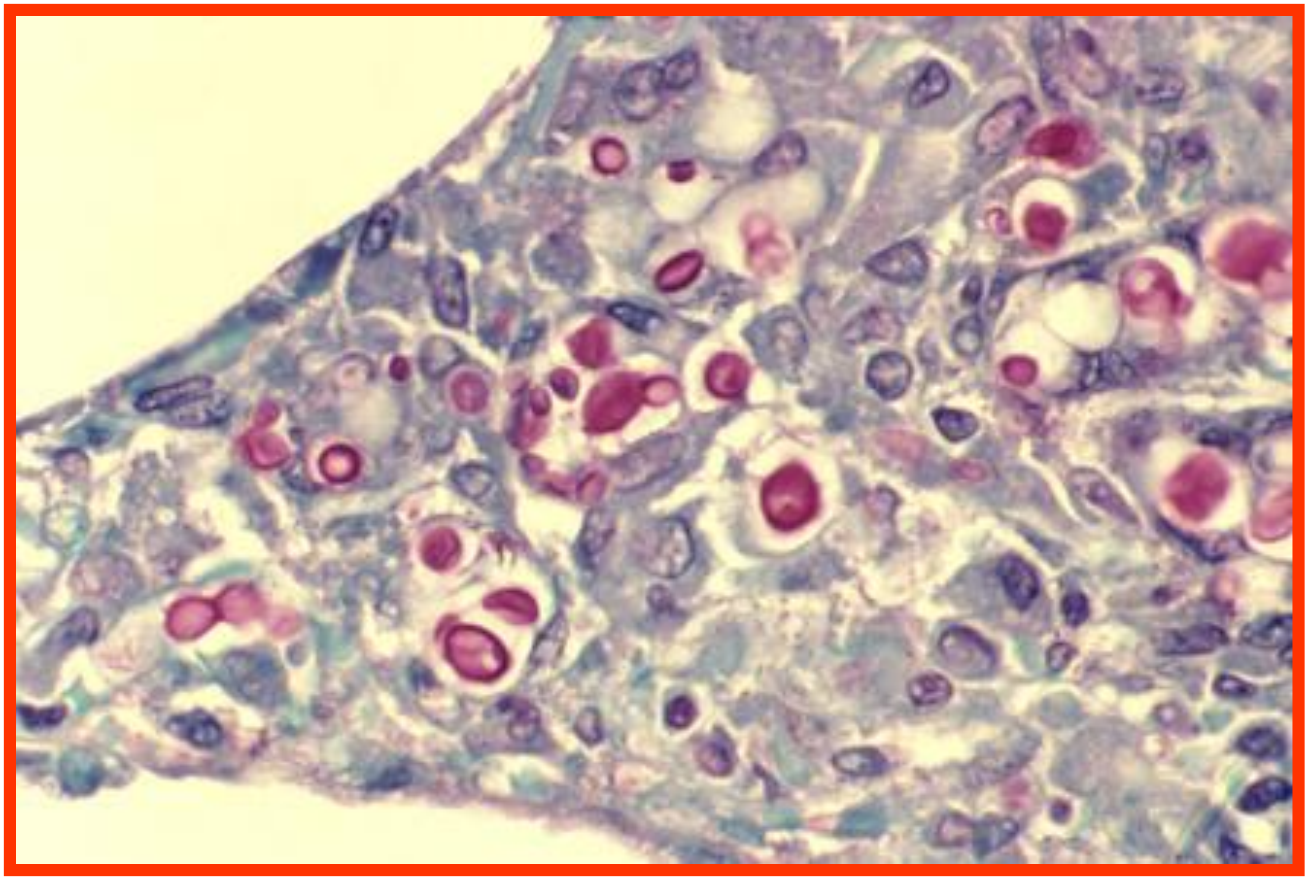


Indian ink preparation : → Capsulated round budding yeast cell of 4 - 20μm.



HPE of Biopsy →

Periodic Acid – schiff stain.



Culture :-

- On sabourads dextrose agar :

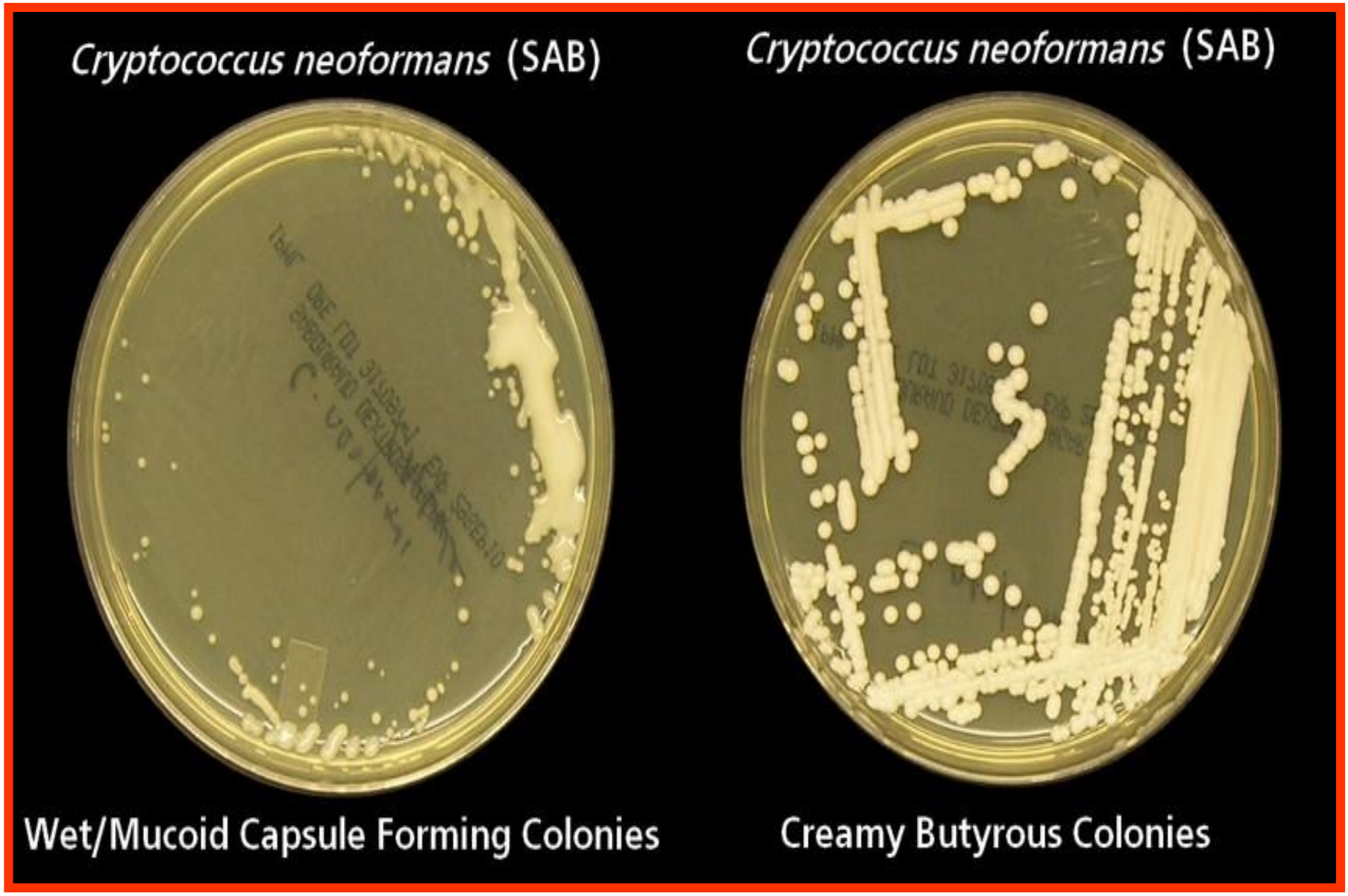
  Smooth, Mucoid, Cream Coloured

  colonies at 37^0c

- Bird – seed agar :

  Brown – colored colonies .

- Urease positive


Cryptococcus neoformans (SAB)
Cryptococcus neoformans (SAB)
Wet/Mucoid Capsule Forming Colonies
Creamy Butyrous Colonies

Immuno – diagnosis :

- Urine, Serum, CSF.
- Antigen detection → Crypto LA – test, Precipitation.
- Antibody detection→ CFT, IFAT, ELISA

→ less specific.

Treatment :

- Amphotericin B, Flucytosine,

  Miconazole, Clotrimazole.

- Immunotherapy with Mono – clonal antibodies.


Thank you

- **MYCOLOGY**
- **SHORT ANSWERS: 4 marks**
- What is Onychomycosis? List the fungi causing it and write about its laboratory diagnosis.
- Dermatophytosis; Clinical presentation ,Lab.diagnosis
- Mycetoma
- Chromoblastomycosis
- Sporotrichosis
- Rhinosporidiosis

- Histoplasmosis
- Clinical features and laboratory diagnosis of Aspergillosis
- Penicillosis
- Mucormycosis/Zygomycoses
- Candidiasis
- Cryptococcal meningitis
- Fungal meningitis

- Name the fungi causing otomycosis and describe their laboratory diagnosis
- Oculomycosis
- Mycotoxicosis
- Antifungal agents; Classification, mechanism of action

- **BRIEF ANSWERS : 2 Marks**
- 1. Identification of candida
- 2. Difference of fungi from bacteria
- 3. Dimorphic fungi
- 4. Classification of dermatophytes
- 5. Aspergilloma
- 6. Rhinosporidiosis
- 7. Slide culture for fungi
- 8. Penicillosis

- 9. Germ tube test
- 10. Mycotoxins
- 11. Ectothrix
- 12. Morphology of Rhizopus . 13.SDA
- 14. Blastomycosis
- 15. T.rubrum
- 16. Keratomycosis

- 17. Identification of C.neoformas
- 18. Fungal infections in AIDS
- 19. Morphology of Aspergillus
- 20. Four examples for Deep fungal infections

- 17. Identification of C.neoformas
- 18. Fungal infections in AIDS
- 19. Morphology of Aspergillus
- 20. Four examples for Deep fungal infections
- 21. Examples for thermophilic fungi
- 22. White fields ointment
- 23. Id reaction
- 24. Mycetism

- 25. Name 4 anti fungal agents
- 26. Sandal ring worm
- 27. Woods lamp
- 28. Hair perforation test
- 29. Otomycosis
- 30. Pneumocystic Jerovici
- 31. Allergic broncho pulmonary aspergillosis
- 32. Sclerotic bodies
- 33. Asteroid bodies