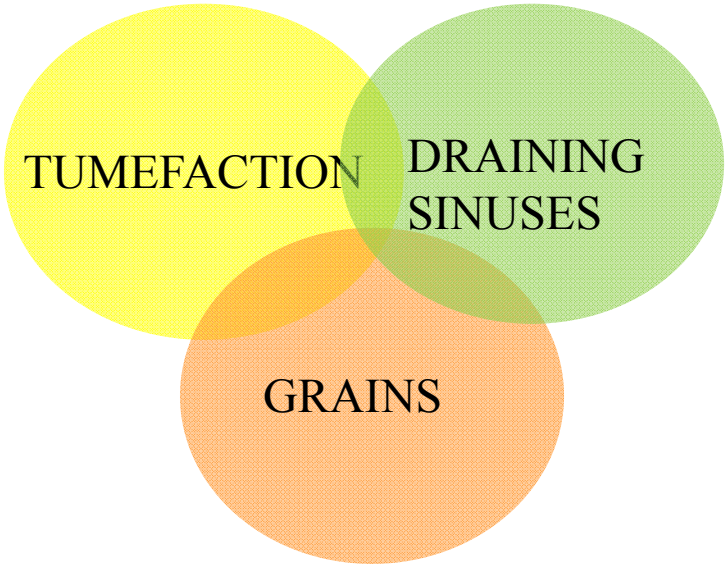

MYCETOMA
(worse than the thorn itself!!)
(c) Scott Bilotta

INTRODUCTION

- Mycetoma is a chronic progressive granulomatous exogenous infection of subcutaneous tissue characterized by swelling & presence of granules of the etiological agent which may spread contiguously to involve adjoining skin with formation of multiple sinuses discharging pus, granules, fragments of degenerated muscles, tendons & bones



HISTORY

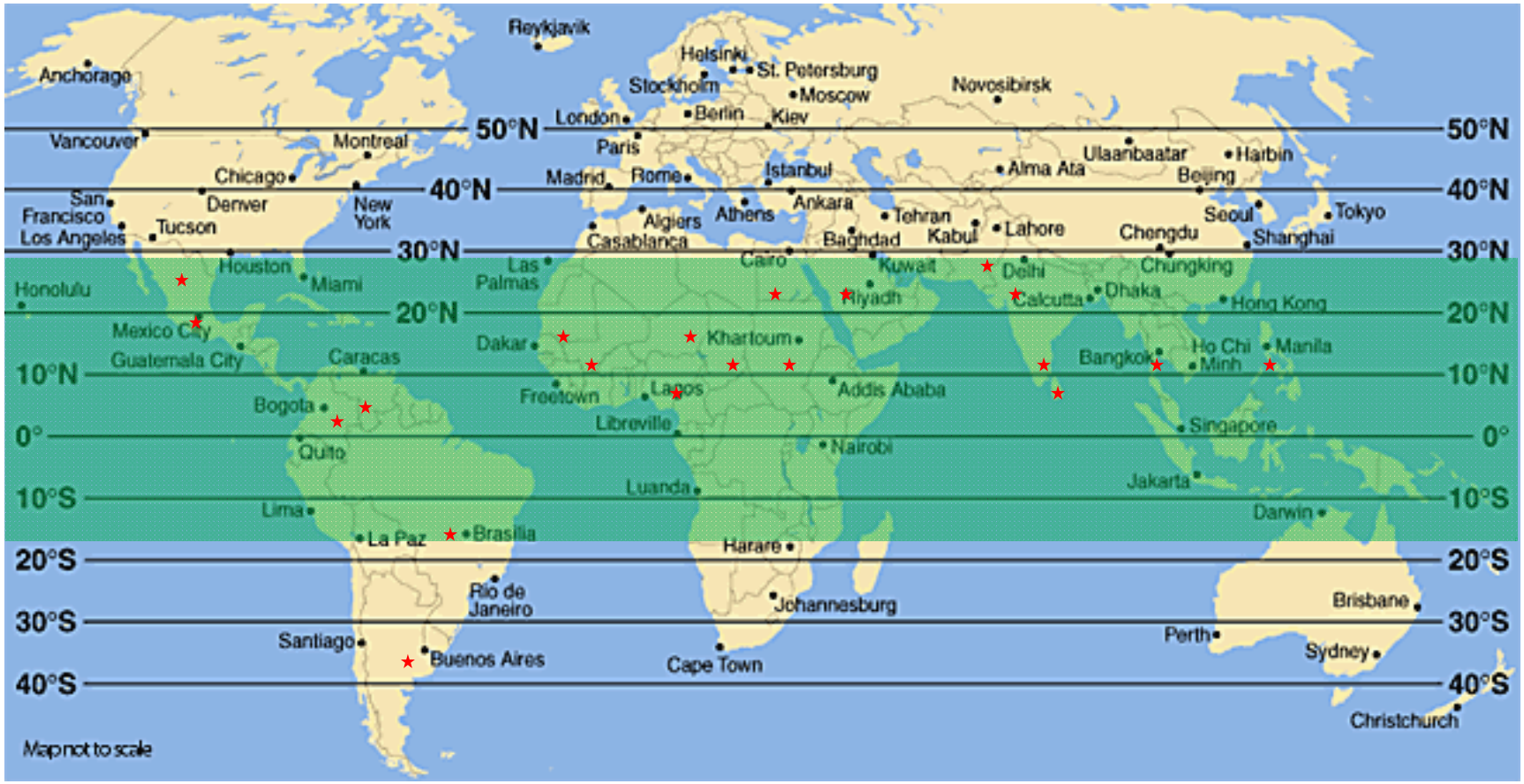
- "Padavalmika" (foot anthill): Atharva-veda
- Dr. John Gill, 1842: "Madura foot"
  - "when the leg has been amputated, the foot has been found to be one mass of disease of fibrocartilaginous nature, with entire destruction of joints, cartilages & ligaments; it has neither shape nor feature & is covered with large fungoid excrescences discharging an offensive ichorous fluid."
- Vandyke Carter, 1860: "Mycetoma"
- Kanthack, 1892 & Vincent 1894
- Brumpt, 1905: genus *Madurella* and described multiple fungal etiologies
- Pinoy, 1913: divided into "actinomycosis" & "true mycetoma"

- Chalmers , Archibald & Christopherson (1913-16):
  - “maduramycosis” (true mycetoma)
  - Included all body sites
- Currently:
  - Actinomycotic mycetoma
  - Eumycetoma

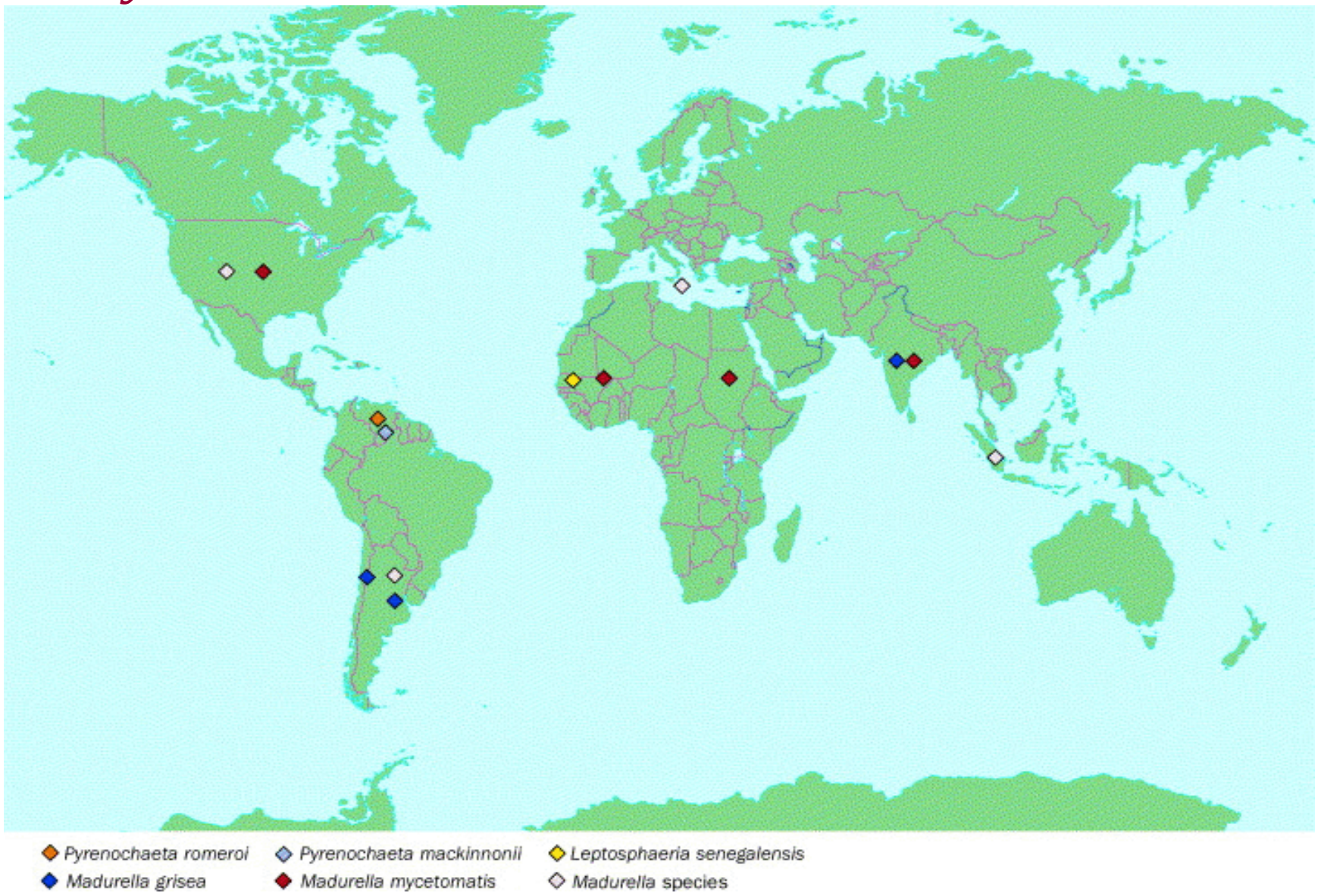
EPIDEMIOLOGY & ECOLOGY

- Tropics & sub tropics, but sporadic in temperate zones
- Latitude 15° S and 30° N: “Mycetoma belt”
- Arid regions, short rainy season, little temperature fluctuations
- Extremely rare to have infection by more than one species in the same individual
- Endemic countries
  - India, Sudan *(M. mycetomatis)*
  - Mexico (*N. braziliensis*) & Senegal
  - Somalia, Egypt, Uganda, Nigeria, Chad, Algeria, Mauritania, Mexico, Venezuela
  - USA, Japan, S. Arabia, Rumania
- *M. mycetomatis*(19%) & *Nocardia* spp.(32%)

MYCETOMA BELT



Eumycetoma


Pyrenochaeta romeroi
Pyrenochaeta mackinnonii
Leptosphaeria senegalensis
Madurella grisea
Madurella mycetomatis
Madurella species

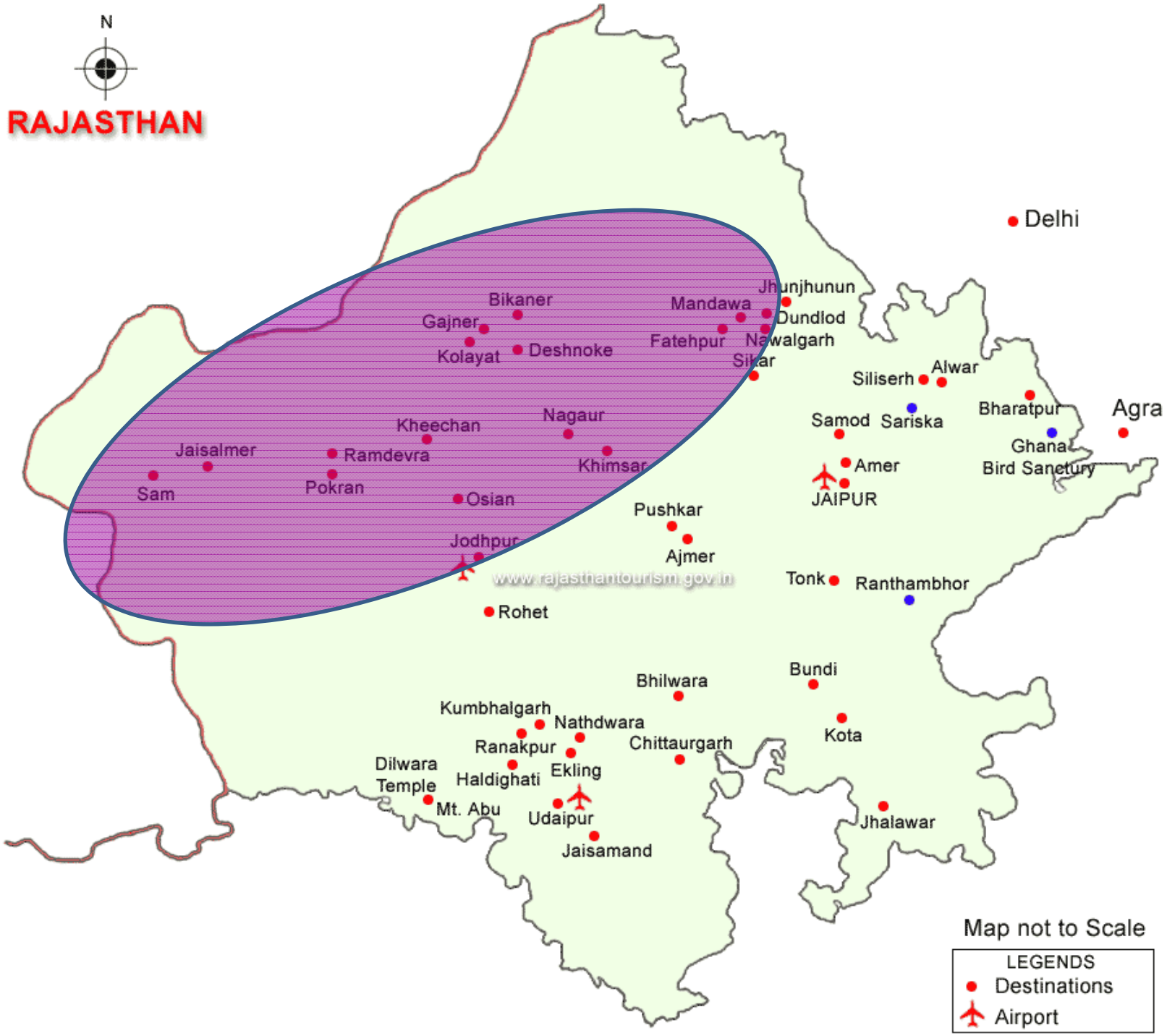
- Nigeria: *S. somaliensis*
- S. Arabia: *S. somaliensis*
- Mexico: *N. brasiliensis(86.6%), A. madurae (10.2%)*
- Brazil: actinomycetes (68%), commonest *N. brasiliensis*
  - True fungi 32% cases
    - *M. mycetomatis*
    - *M. grisea*
    - *Scedosporium apiospermum*

India

- Vanbreuseghen stated that mycetoma occurs in
  - Rainfall: 50-500 mm/yr
  - Temperature: 15-25°C
- But, in India conditions vary amongst different geographic locations
  - Actinomycotic: S. India, N. India
  - Eumycetoma: NW India
- Maximum cases
  - Rajasthan
  - Tamil Nadu

Rajasthan

- 3 arbitrary regions (rainfall, soil)
  - NW desert region (rainfall < 350mm/yr)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Map not to Scale
LEGENDS
Destinations
Airport

- 3 arbitrary regions (rainfall, soil)
  - NW desert region (rainfall < 350mm/yr)
    - Most prevalent region: 2/3rd cases
    - Eumycetoma:actinomycetoma; 3.2:1

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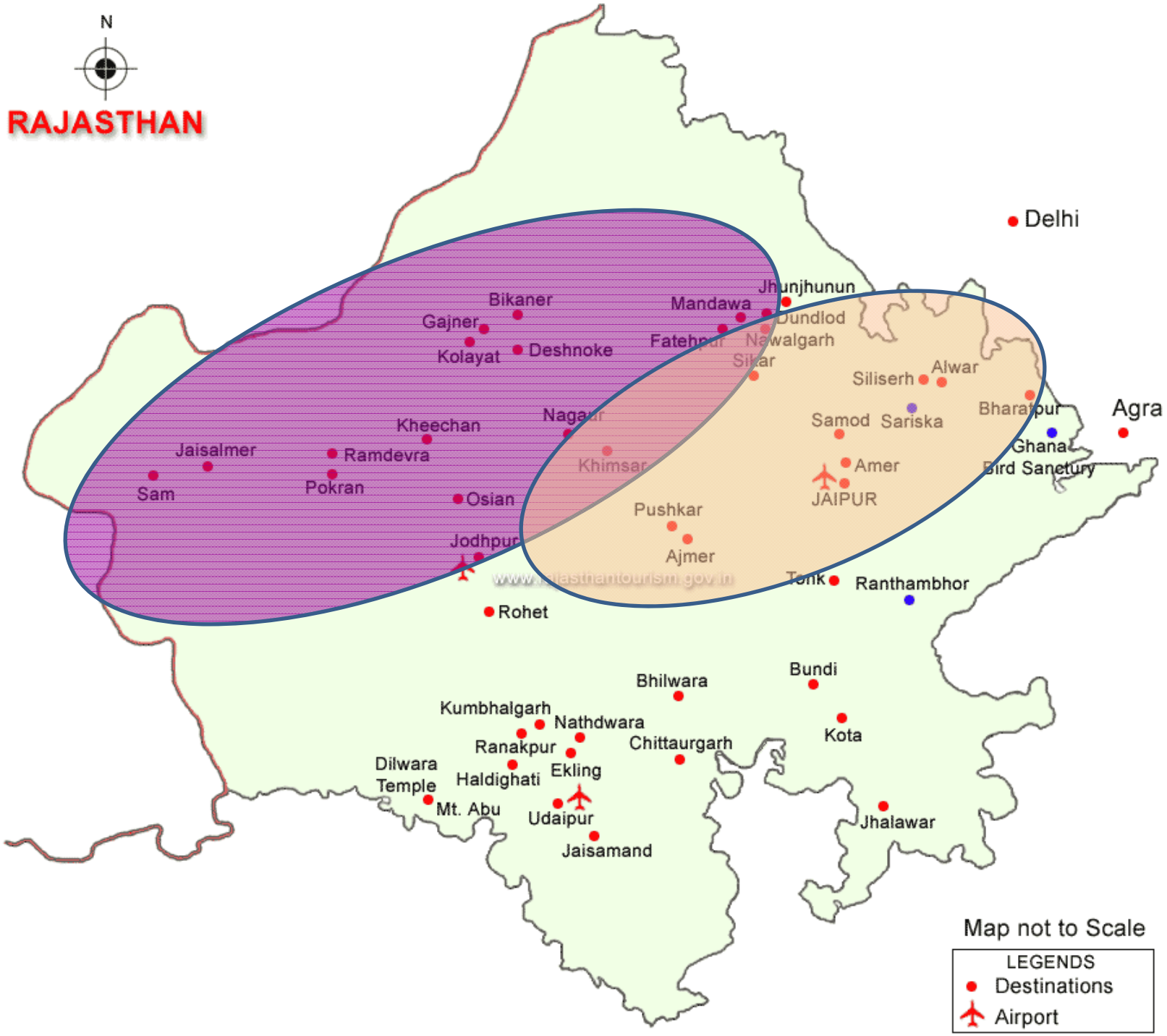
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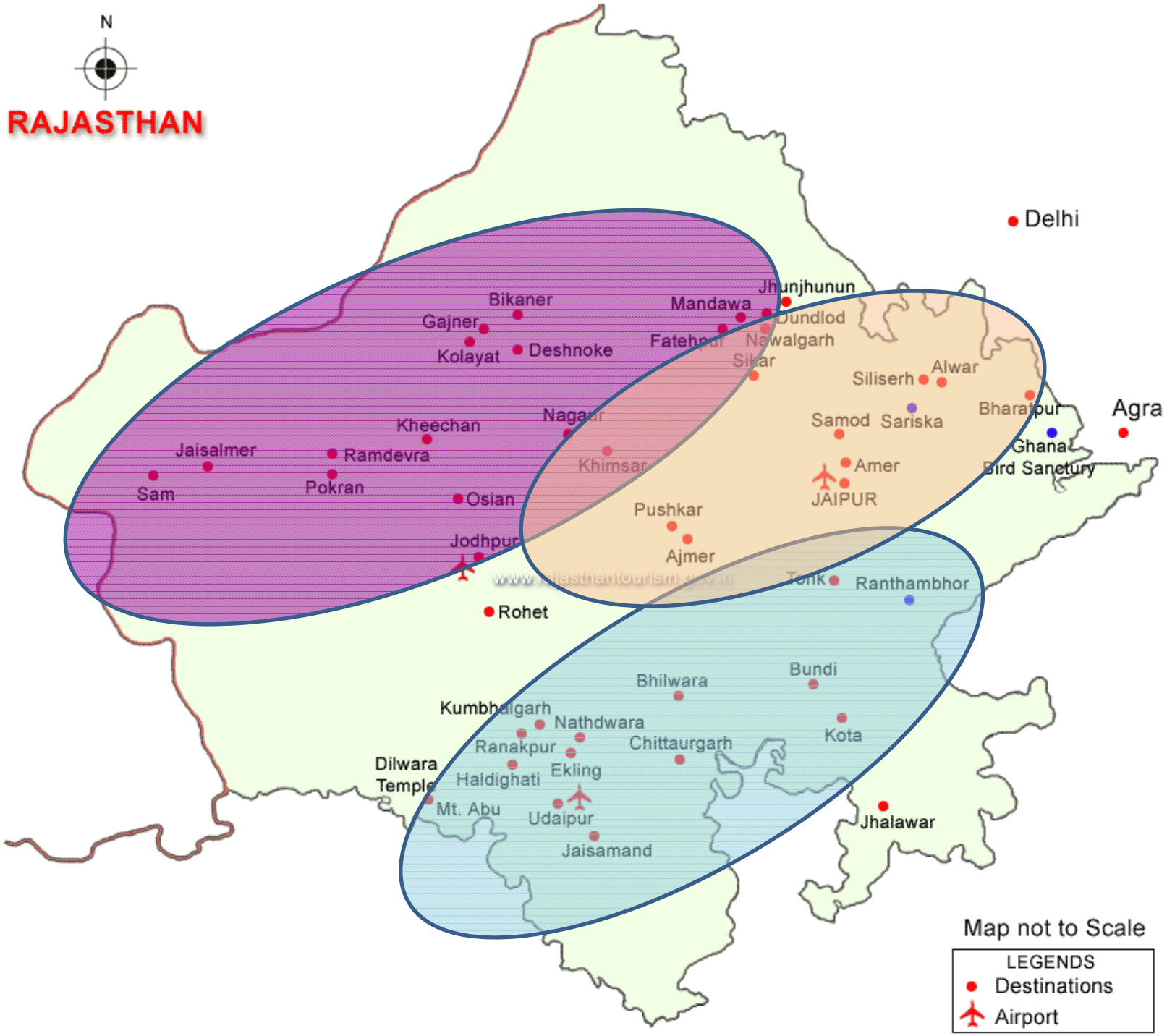
  - SE Aravali hill region (rainfall > 600 mm/yr)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  - SE Aravali hill region (rainfall > 600 mm/yr)
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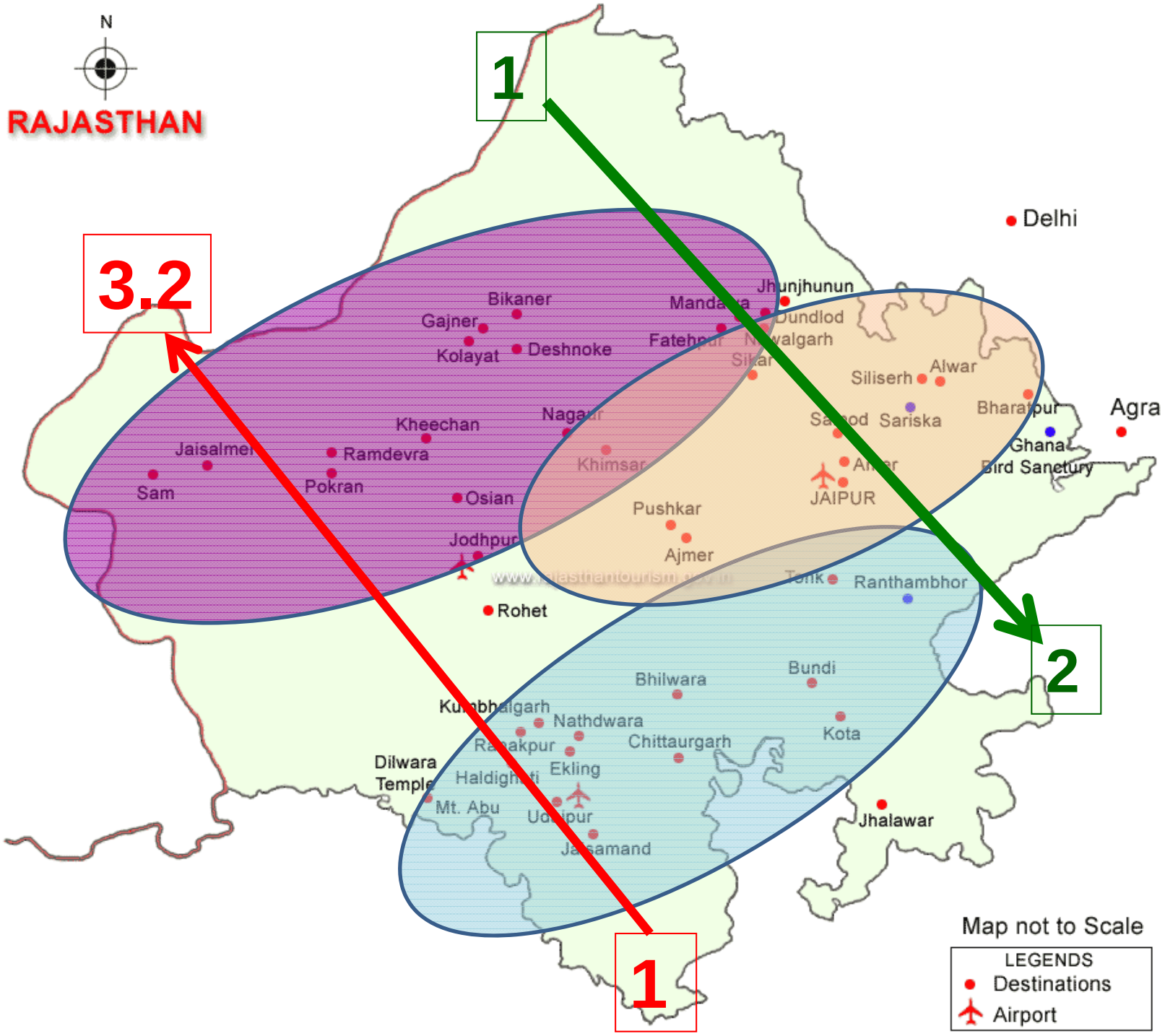
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- Singhvi et al, 1995 (Jodhpur, Rajasthan): higher prevalence of actinomycetoma from extra pedal sites
- Overall, Actinomycetoma >Eumycetoma
- Tamil Nadu, Actinomycetoma = Eumycetoma
- Rajasthan,
  - *M. mycetomatis* > *S. somaliensis*, *A. madurae*, *Nocardia* spp.
  - Least common, *M. grisea*, *Leptosphaeria senegalensis*, *Phialophphora* spp., *P. boydii*, *A. pelletieri*
  - *Nocardia* spp. was more common in SE rajasthan

- South India
  - *M. mycetomatis*
  - *A. madurae*
  - *A. pelletieri*
  - *Nocardia* spp.
  - *Leptosphaeria senegalensis*
  - *Leptosphaeria tompkinsii*
  - *Pseudoallescheria boydii*
  - *Acremonium kiliense*
  - *Acremonium falciforme*

From soil samples
- *M. mycetomatis*
- *P. boydii*
- *S. somaliensis*
- *N. asteroides*
- *N. braziliensis*
- *N. caviae*

- Prevalent throughout India
  - Tamil Nadu, Pondicherry, A.P.
  - Rajasthan, Gujarat, Maharashtra
  - Punjab, Delhi, Haryana, Chandigarh
  - Bengal

- *Nocardia* spp. infections more common in SE India
  - *N. brasiliensis*
  - *N. asteroides*
  - *N. caviae*
  - *N. transvalensis*

Chandigarh

- Infrequent
- 1967-1977: 20 cases
- 1980-96: 23 cases
  - Actinomycotic agents: 56.5%
  - Eumycotic agents: 43.5%
  - *Madurella mycetomatis*, most frequently isolated
  - Other agents isolated were *N. asteroides*, *A. madurae*, and *Streptomyces* spp. and *M. grisea* was least common
  - Foot was the commonest site of infection
  - Males and females were found to be equally affected

- Vegetations: acacia tree
- *S. somaliensis* in hot & dry climates, with rainfall <250mm/yr, whereas *Pyrenochaeta romeroi* in areas with higher ranfall
- Male:female ratio; 4:1
  - Mendez-Tovar et al have shown that progesterone can inhibit the growth of *M. mycetomatis* and *Pyrenochaeta romeroi*, which might contribute to the sex bias in the incidence of mycetoma
- Rural workers16-45 yrs old, rarely in non-manual workers
  - Occupation predisposes to trauma

EUMYCOTIC MYCETOMA AGENTS

White granules

- *Acremonium falciforme* (soft,<1)
- *Acremonium kiliense* (soft,irregular,>1.5)
- *Acremonium recifei*(soft,<1.5)
- *Cylindrocarpon cyanescens*
- *Cylindrocarpon destructans*(oval,0.5)
- *Pseudallescheria boydii*(lobulated, oval,>1)
- *Fusarium oxysporum*
- *Fusarium moniliforme*(soft,<1)
- *Fusarium solani*(oval,<1.5)
- *Aspergillus nidulans*(soft,ovo-lobular,<0.6)
- *Polycytella hominis*(soft,0.5-1)
- *Neotestudina rosatii*(soft,<1)

Black granules

- *Curvularia geniculata* (irregular)
- *Curvularia lunata* (ovo-lobular,<1)
- *Leptosphaeria senegalensis* (tubular,hollow,<1.2)
- *Leptosphaeria tompkinsii* (irregular,1)
- *Madurella grisea* (soft,oval to lobulated,<1)
- *Pseudochaetosphaeronema larense*
- *Pyrenochaeta mackinnonii* (firm,ovolobular,0.5-1)
- *Pyrenochaeta romeroi* (soft,oval to lobulated,<1)
- *Madurella mycetomatis* (hard,brittle,oval to lobulated,<2)
- *Exophiala jeanselmei* (soft,0.2-0.3)
- *Phialophora verrucosa*
- *Plenodomus avramii*
- *Corynespora cassiicola*

Green granules

- *Aspergillus flavus*

ACTINOMYCOTIC MYCETOMA

- *Nocardia asteroides* (soft,irregular,1)
- *Nocardia brasiliensis*(lobular,soft,0.5-1) } *White*
- *Nocardia transvalensis*(lobed,2)
- *Nocardia caviae*(soft,loblar,<1) - *White to yellow*
- *Nocardia dassonvillei*(<0.5) - *Cream*
- *Actinomadura madurae*(soft,oval,1) - *White to yellow or pink*
- *Streptomyces* somaliensis(hard,spherical,0.5-2)- *Yellow to brown*
- *Actinomadura pellitieri*(hard,oval,0.3-0.5) - *Red*

SOURCE & MODE OF INFECTION

- Exogenous
- Thorn pricks
- Minor abrasions & trauma to skin
- Perineal mycetoma:
  - Due to inadequate clothes over groin & working in squatting position in the fields
  - Cleaning of perianal region with soil after defecation

- Use of straw wicks for cleaning the external ear
- Carrying bags/ wood on the back/ shoulders/ head
- H/O guinea worm extraction by using thorns
- Domestic fencing using thorny shrubs or tree branches

- Recovery rate of fungi from soil: 25% & from thorns: 16%

(Singhvi et al, 1995)

- Occupational hazard to farmers, herdsman, field workers
- Walk barefooted
- Also to carpenters, builders and land workers

MYCETOMA SITES

- Foot – 80%, left>right
- Hand , right>left
- Knee, arm, leg, head and neck, thigh, perineum
- Rarely, chest, abdominal wall, mandible, paranasal sinuses, eyelid, vulva, orbit, scrotum, surgical incisions

MYCETOMA SPREAD

- May spread along the fascial planes involving – skin, subcutaneous tissue & underlying structures
- Spares nerves and tendons
- Spread is rapid and extensive in case of involvement of trunk and buttocks

- Bone involvement early in mycetoma of scalp

- 1-3% lymphatic spread to the regional lymph nodes – may suppurate & discharge
  - More common with actinomycetoma
  - Incidence augmented – repeated incomplete surgical excision attempts
- Blood borne spread – reported only in case of infection by Nocardia and Streptomyces

CLINICAL PRESENTATION

- Clinical presentation in both the conditions is almost similar
- Presents as slowly progressive, painless, subcutaneous swelling, usually firm & rounded but may be soft, lobulated, rarely cystic & mobile on palpation
- Multiple secondary nodules – may suppurate – multiple sinus tracts
- Sinus tracts keep healing & developing at the same time
- Discharge – serous/ serosanguinous/ purulent
- Grains discharged during the active phase
- Usually painless (?anaesthetic substances, ? Nerve damage)
- Skin changes
- Local hyper-hydrosis

CLINICAL PRESENTATION

- Triad of Symptoms
- Tumefaction i.e tumor like swelling
- Multiple draining sinuses
- Presence of granules

- Actinomycetoma
  - Rapidly progressive
  - Lesion is more inflammatory, destructive & invades the bone early
- Eumycetoma
  - Slowly progressive
  - Clear defined margins of the lesion
  - Remain well encapsulated for a long time


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cm

Botryomycosis: "a close mimic"

- A rare, chronic, persistent bacterial infection also characterized by formation of draining sinuses & grains
- Clinically & histologically resembles actinomycosis
- May metastasize
- Skin, head, pinna, hands, feet
- Etiology
  - *S. aureus, S. epidermidis*
  - *E. coli*
  - *P. aeruginosa*
  - *Proteus* spp.
  - Non hemolytic *streptococci*
  - *Bacteroides* spp.
  - *Rhodococcus* spp.

- Two types:
- Cutaneous: simple inflammatory nodules to discharging sinuses and ulcers/ fistulae
- Usually localised
- more on hands, feet and head

- Visceral type: in chronically ill
- Lungs mostly involved

- Treatment depends on organism sensitivity

PATHOLOGY of Mycetoma

- In tissues, *M. mycetomatis* forms numerous black sclerotia (grains)
  - Grains are vegetative aggregates of the fungal mycelia embedded in a hard brown matrix

- This matrix consists of extra-cellular cement (1,8-dihydroxynaphthalene melanin) in combination with host tissue debris
  - Rigid matrix might act as a barrier protecting the fungus from the natural immunity of the host and antifungal agents
  - Melanins are thought to be protective in circumstances of host-induced oxidative stress

- Grains
  - Different shapes and sizes
    - Mostly rounded, oval, or lobulated
  - Two types of grains have been identified
    - Filamentous
      - Consists of brown, septate and branched hyphae that might be slightly more swollen and thick towards the periphery of the colony
    - Vesicular
      - Less common, has a cement-like matrix in the cortex and a central area filled with numerous vesicles (6–14 μm in diameter) and light-coloured hyphae

Histological differences

ACTINOMYCETOMA	EUMYCETOMA
Late stages: acute suppurative pyogenic reaction persists	Foreign body granuloma with epithelioid hyperplasia & giant cell formation
More extensive & obliterative involvement of bone with lytic & hypertrophic changes	Late bone involvement with lytic but no hypertrophic involvement
Invades muscle more readily	Not so
Produce cellular proliferation around the sinus opening-raised border	No cellular proliferation around the sinus opening

DIAGNOSIS

Radiology

- Calcification & obliteration of fascial planes
- Cortex may be compressed from outside – bone scalloping & periosteal reaction
- “Sun-ray appearance” & “codman triangle”
- Multiple bony cavities may be seen
  - Despite this pathological fractures are rare (? Filled with solid mass of grains & fibrous tissue)
- Skull: purely sclerotic, with loss of trabeculations
- Useful for follow up

Ultrasonography

- Can differentiate between eumycetoma/ actinomycetoma/ non-mycetomatous lesions
- Grain cement substance gives sharp bright hyper-reflective echoes
- Ultrasonographic diagnosis is more precise & accurate when no discharging sinuses are there: planning surgical excision

MICROBIOLOGICAL DIAGNOSIS

- Specimens
  - Pus
  - Exudate
  - FNAC
  - Excised tissue/Biopsy
  - Grains from soiled bandage

- Lesions are cleaned with antiseptics
- Press the sinus from periphery to express exudate
- Granules collected on a sterile gauze

- Alternatively, collected with the help of a loop

- If more granules needed, lift the flap of the lesion with the help of a loop and collect granules in a petri dish

Direct examination

- Granules are first washed in normal saline a number of times

- Size, shape, colour, consistency of granules
- 10% NaOH mount
  - Size of hyphae
  - Septation
  - Pigment formation in hyphal walls

- Morphology

- EUMYCOTIC GRAINS
  - 2-6 μm wide hyphae, often have large, globose swollen cells (upto 15μm) at margins

- ACTINOMYCOTIC GRAINS
  - Filaments with diameter of 0.5 – 1 μm, as well as coccoid to bacillary elements
  - Usually gram positive filaments

- GRAM STAIN PREPARATION
  - Crush the grain between two slides, heat fix & stain
- KINYOUN'S MODIFIED ACID FAST STAINING (1%)
- LPCB PREPARATION
- HISTOLOPATHOLOGY
  - GMS
  - PAS
  - H & E

Culture

- Grains washed in N/Saline & crushed before inoculation
- SDA with antibiotics
  - Media should not contain cycloheximide
- For actinomycetes
  - SDA with 0.5% yeast extract but without antibiotics
  - BHI
  - LJ media
  - Blood agar
- Incubation at 25 & 37° C

Serodiagnosis

- Immunodiffusion
- CIE
  - Not very useful
  - Suffer from poor specificity & sensitivity due to cross reactivity

PCR

- Targeting ribosomal gene complex
- Have been detected from biopsy as well as soil samples

TREATMENT

Eumycetoma

- Surgery is most acceptable
- Reports of successful chemotherapy: few
  - Ketoconazole
  - Itraconazole
- Prolonged chemotherapy (upto many years)
- Chemotherapy before & after surgery

Actinomycetoma

- Amenable to medical treatment
  - Streptomycin + dapsone
  - If no response: replace dapsone with cotrimoxazole — **FIRST LINE**
  - Amikacin with/ without cotrimoxazole (Welsh regimen)
  - Rifampicin
  - Sufadoxine + pyrimethamine — **SECOND LINE**
  - Sulphonamides
- Mean duration: 1 year
- Cure rate: 60-90%

EXPERIMENTAL MODELS

- Balb/c mice
  - *M. mycetomatis* mycelia in sterilized soil (adjuvant) given subcutaneously & intra-abdominal
  - Infection was inoculum dependant
    - ? Immune system may not be the culprit

	Eumycetoma	Actinomycetoma
Causative agents	Fungi	Bacteria
Lesion characteristics	Well-encapsulated with a clear margin	Diffuse with no clear margin
Sinuses	Few	Many
Colour of grains	Different colours, but mostly white or black	Different colours, but not black
Course of infection	Slowly progressive	Inflammatory and rapid progression
Bone invasion	After a long time	Rapid
Cavities in radiograph	Small in number, but large in size with clear margins	Numerous, small in size (except in case of Actinomadura madurae) with unclear margins
Drug of choice	Ketoconazole, Itraconazole	Dapsone+streptomycin Rifampicin or sulfadoxine pyrimethamine Amikacin+co-trimoxazole
Medical treatment only	Partial cure or improvement	Useful in most cases

…… could dramatically reduce the incidence!!