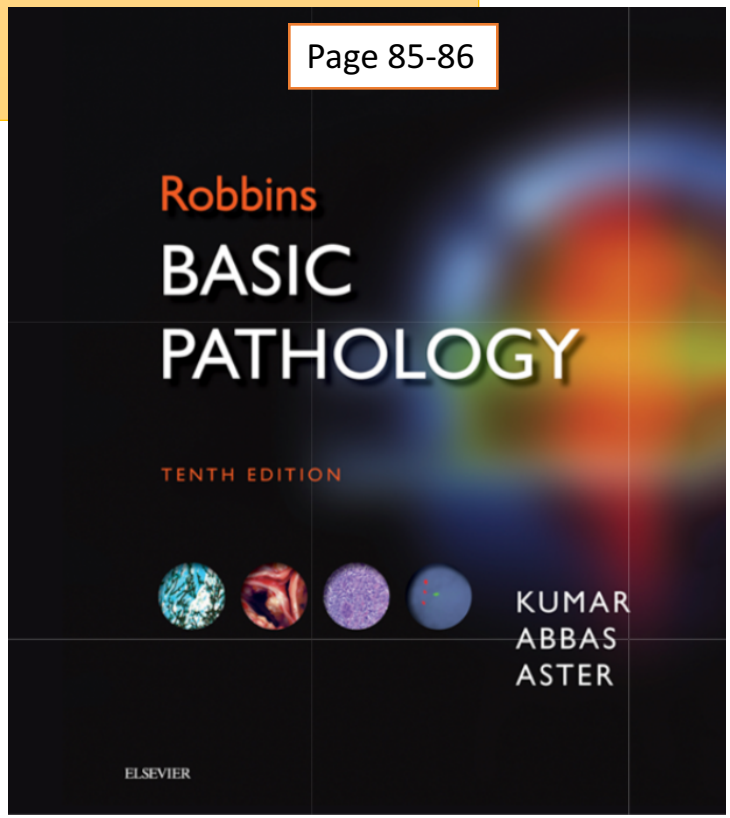
Foundation Block, Pathology
Oct, 2019

# GRANULOMATOUS INFLAMMATION

**Dr. Maha Arafah**
**Associate Professor**
**Department of Pathology**
**King Saud University**
Email: marafah@ksu.edu.sa
marafah@hotmail.com



# OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT:

**Upon completion of this lecture, the student should:**

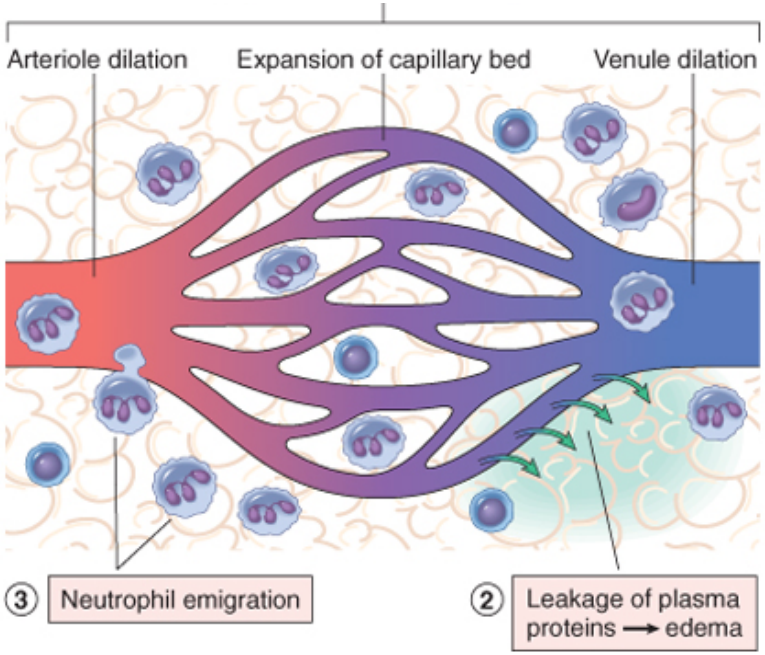
- **Define Granulomatous inflammation.**
- **Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance.**
- **Understands the pathogenesis of granuloma formation.**
- **Identify the two types of granulomas, which differ in their pathogenesis.**
  - **Foreign body granulomas**
  - **Immune granulomas**
- **List the common causes of Granulomatous Inflammation.**

## ⦿ Define Granulomatous inflammation

# Inflammation

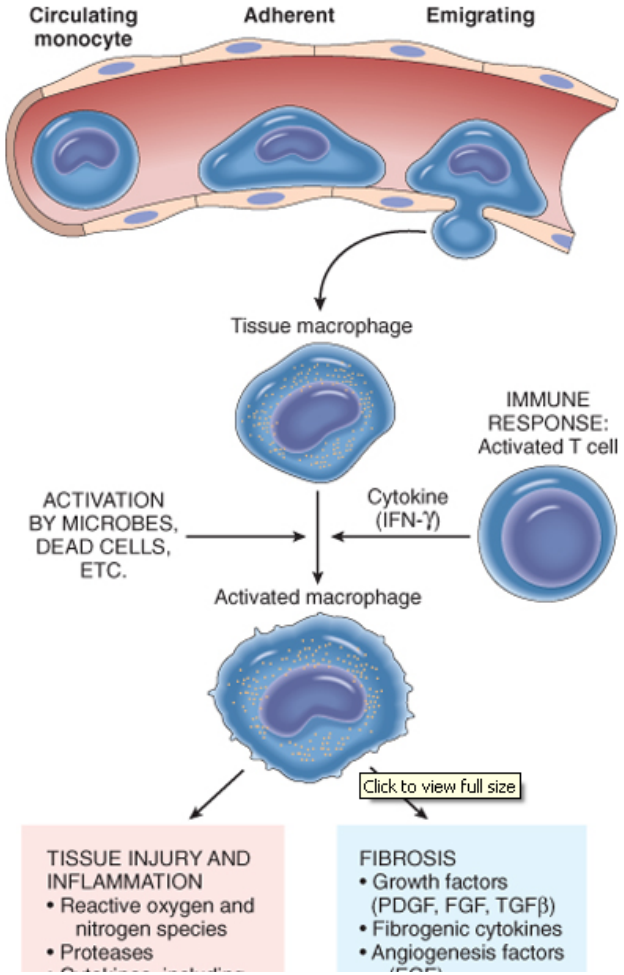
**Acute *inflammation***

Neutrophils




**Chronic *inflammation***

Macrophage, Lymphocytes & Plasma cells



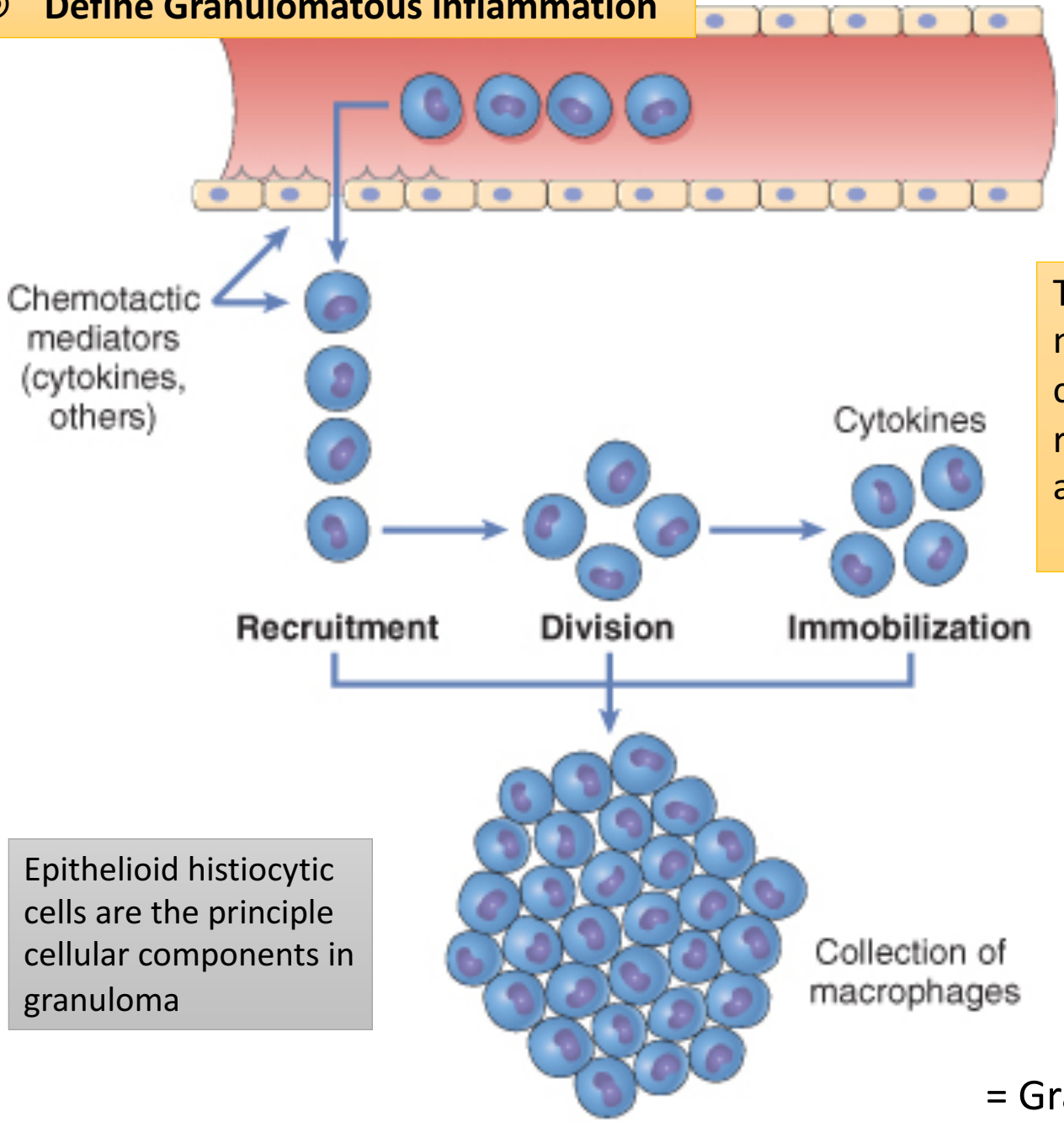
⦿ **Define Granulomatous inflammation.**

# Granulomatous inflammation

A form of chronic inflammation characterized by the formation of granulomas

**Collections of activated macrophages, often with T lymphocytes, and sometimes associated with central necrosis**

## ⦿ Define Granulomatous inflammation




The activated macrophages may develop abundant cytoplasm and begin to resemble epithelial cells, and are called *epithelioid cells*.

Epithelioid histiocytic cells are the principle cellular components in granuloma

= Granuloma

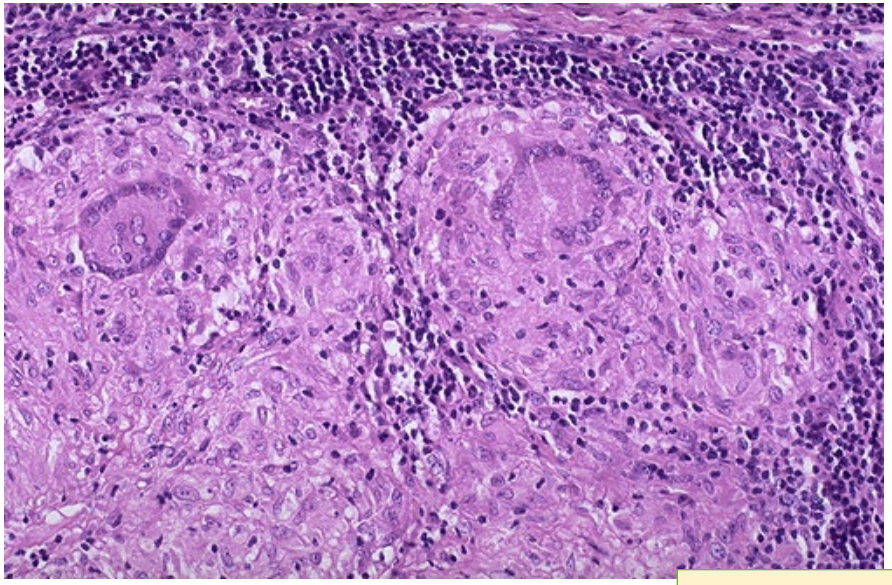
**Define Granulomatous inflammation.**

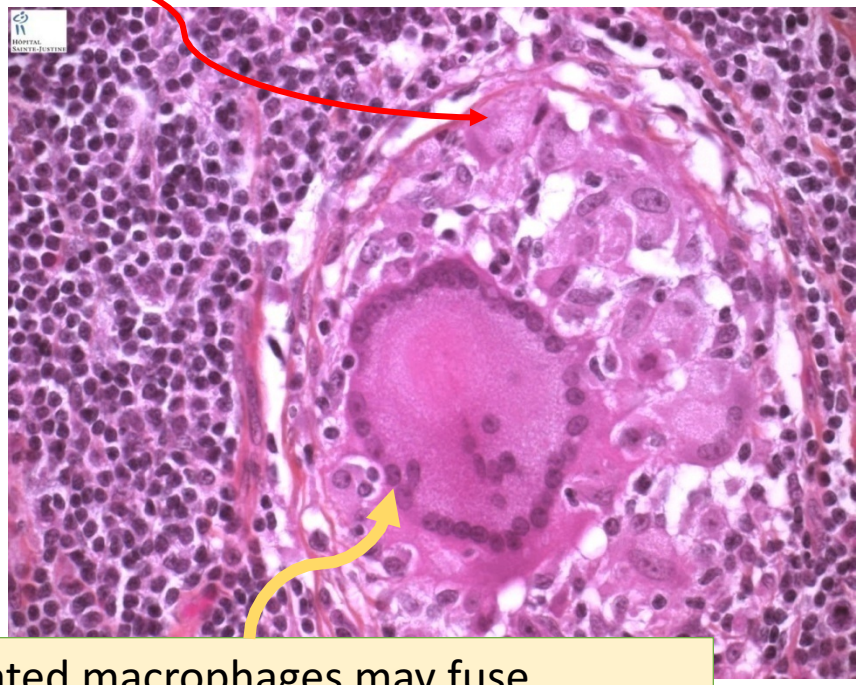
# Why is it important?

- Granulomas are encountered in certain specific pathologic states.
- Recognition of the granulomatous pattern is important because of the limited number of conditions (some life-threatening) that cause it

# Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance

- Granuloma = Nodular collection of *epithelioid macrophages* surrounded by a rim of lymphocytes
- *Epithelioid macrophages*: squamous cell-like appearance

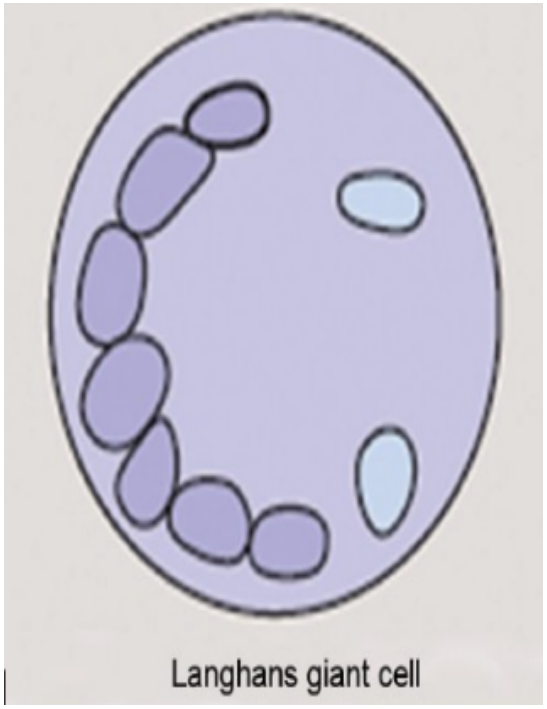


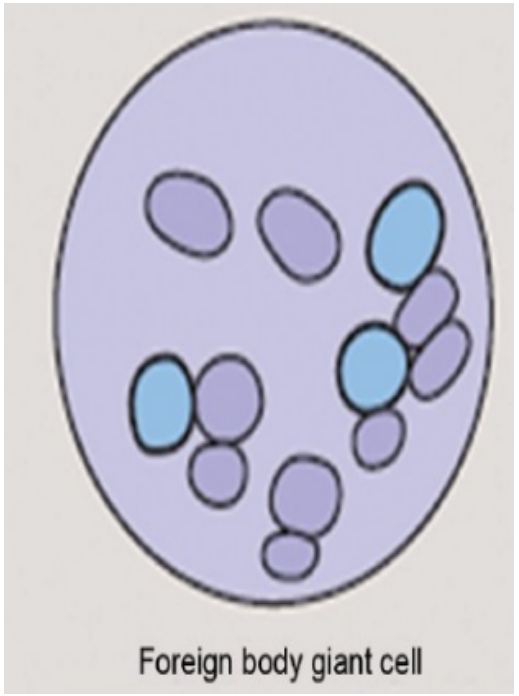


Some activated macrophages may fuse, forming multinucleate *giant cells*

**Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance**

- The nuclei arranged either peripherally (**Langhans-type giant cell**) or haphazardly (**foreign body-type giant cell).**

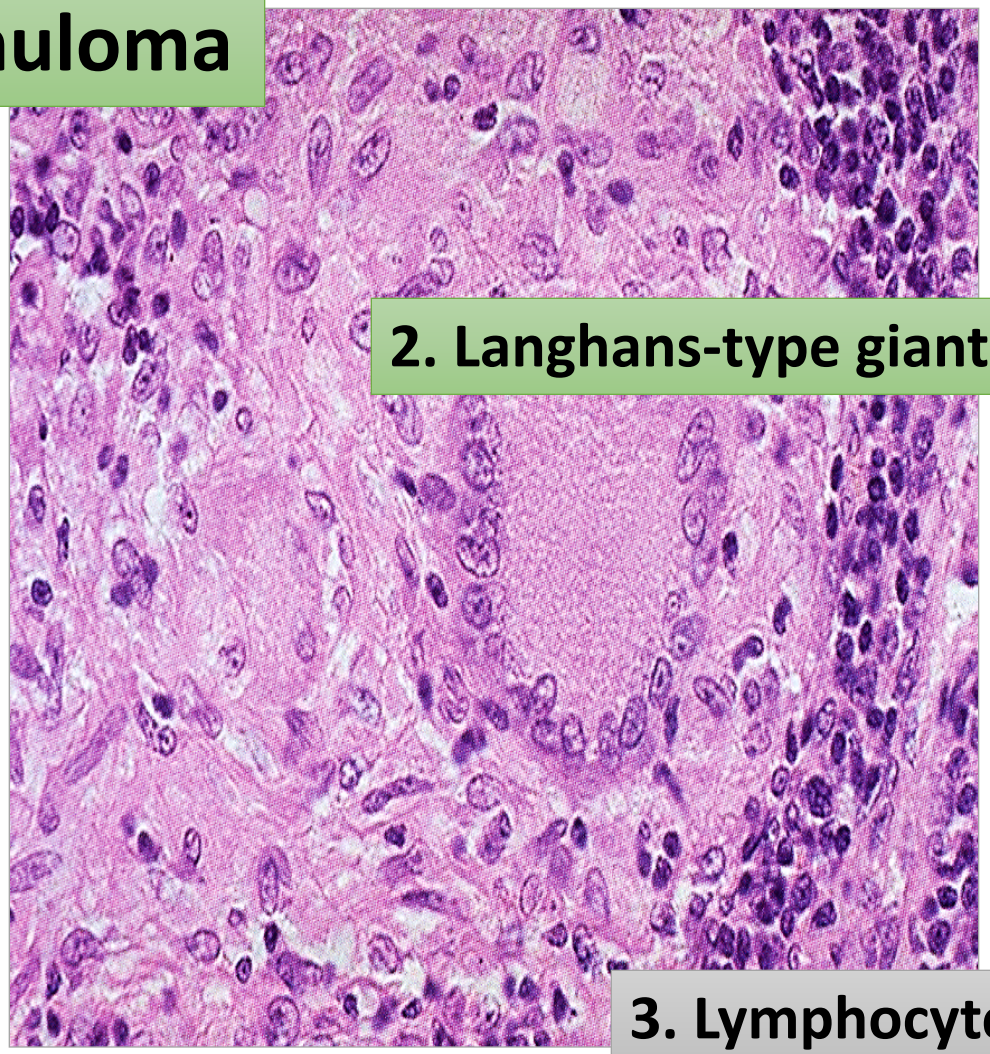


# Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance

## Granuloma

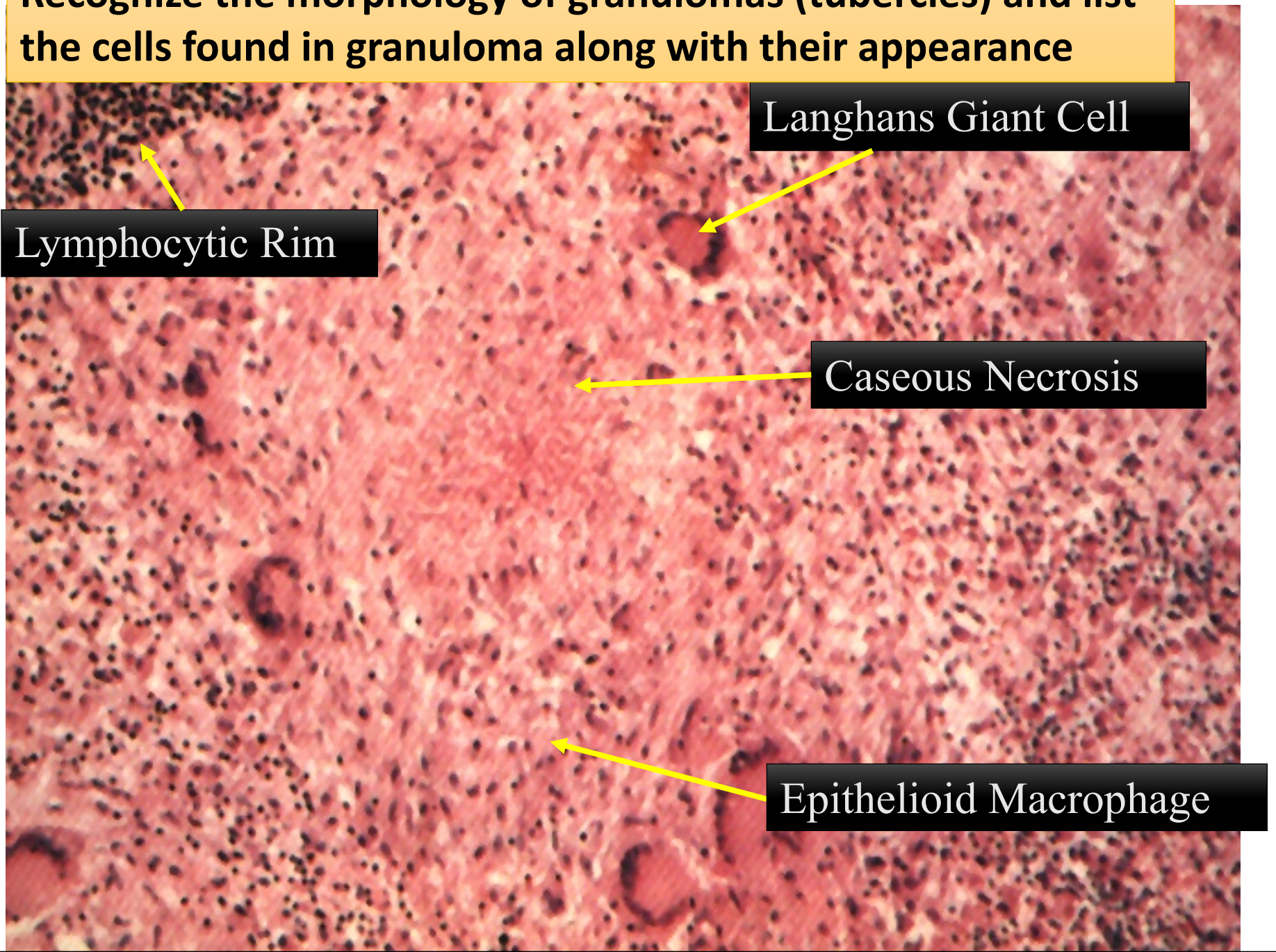
1. microscopic aggregation of activated macrophages

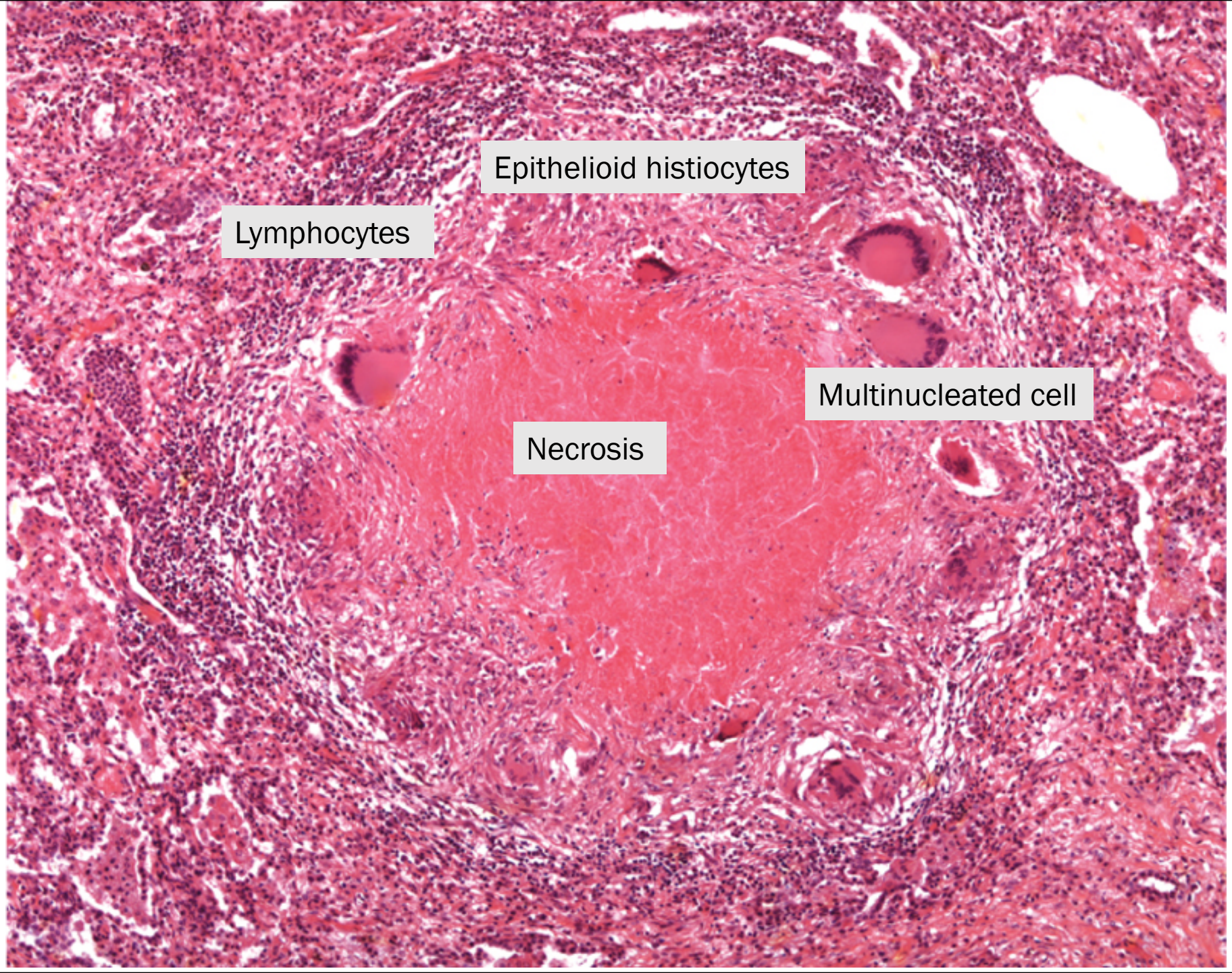


2. Langhans-type giant cell

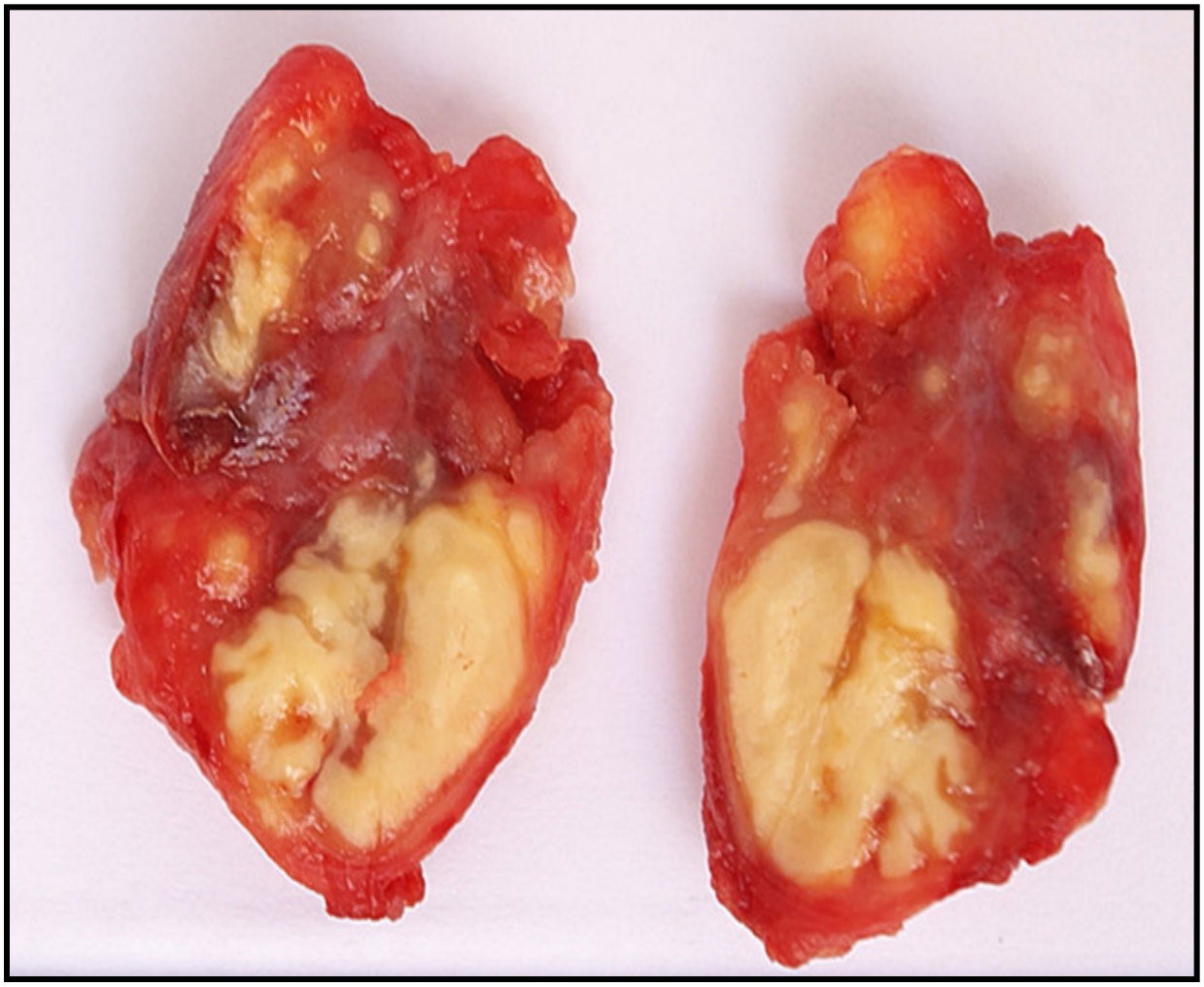
3. Lymphocytes

**Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance**




Epithelioid histiocytes
Lymphocytes
Multinucleated cell
Necrosis

## Recognize the morphology of granulomas



*Section of a lymph node with caseation necrosis*

## ◉ Understands the pathogenesis of granuloma formation

# Granulomatous Inflammation

## Pathogenesis

- Neutrophils ordinarily remove agents that incite an acute inflammatory response. However, there are circumstances in which reactive neutrophils ***cannot*** digest the substances that provoke acute inflammation.

## ◉ Understands the pathogenesis of granuloma formation

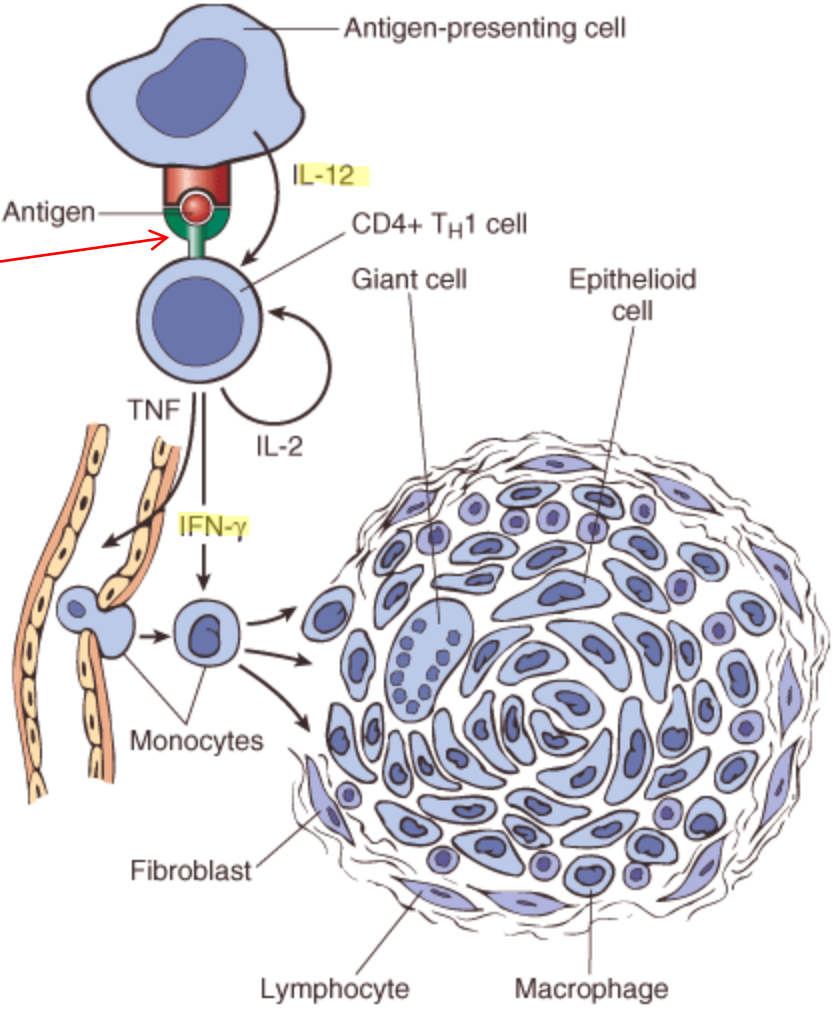
# Granulomatous Inflammation Mechanism

- **What is the initiating event in granuloma formation?**

➢ **deposition of a *indigestible* antigenic material**

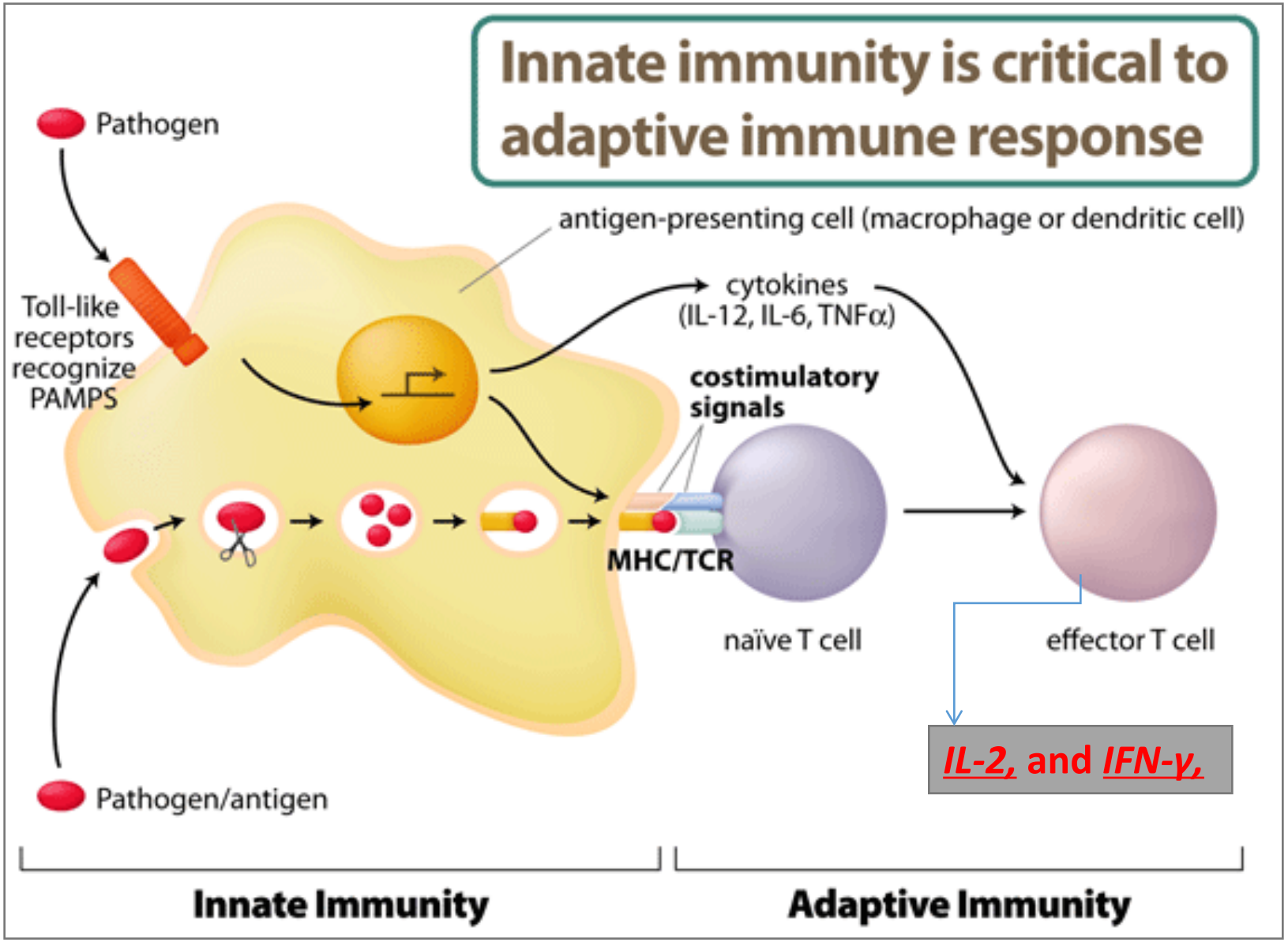
***IFN-γ released by the CD4+ T cells of the $T_H1$ subset.***

***IFN-γ*** **helps to activate and convert macrophages into epithelioid cells during the process of granuloma formation**




Type IV hypersensitvity

# ⦿ Understands the pathogenesis of granuloma formation



## ◉ Identify the two types of granulomas, which differ in their pathogenesis

There are two types of granulomas

### Foreign body granuloma

are incited by relatively inert foreign bodies e.g. talc (associated with intravenous drug abuse) or sutures

Typically, foreign body granulomas form when material are large enough to preclude phagocytosis by a single macrophage

These material **do not incite any specific inflammatory immune response.**

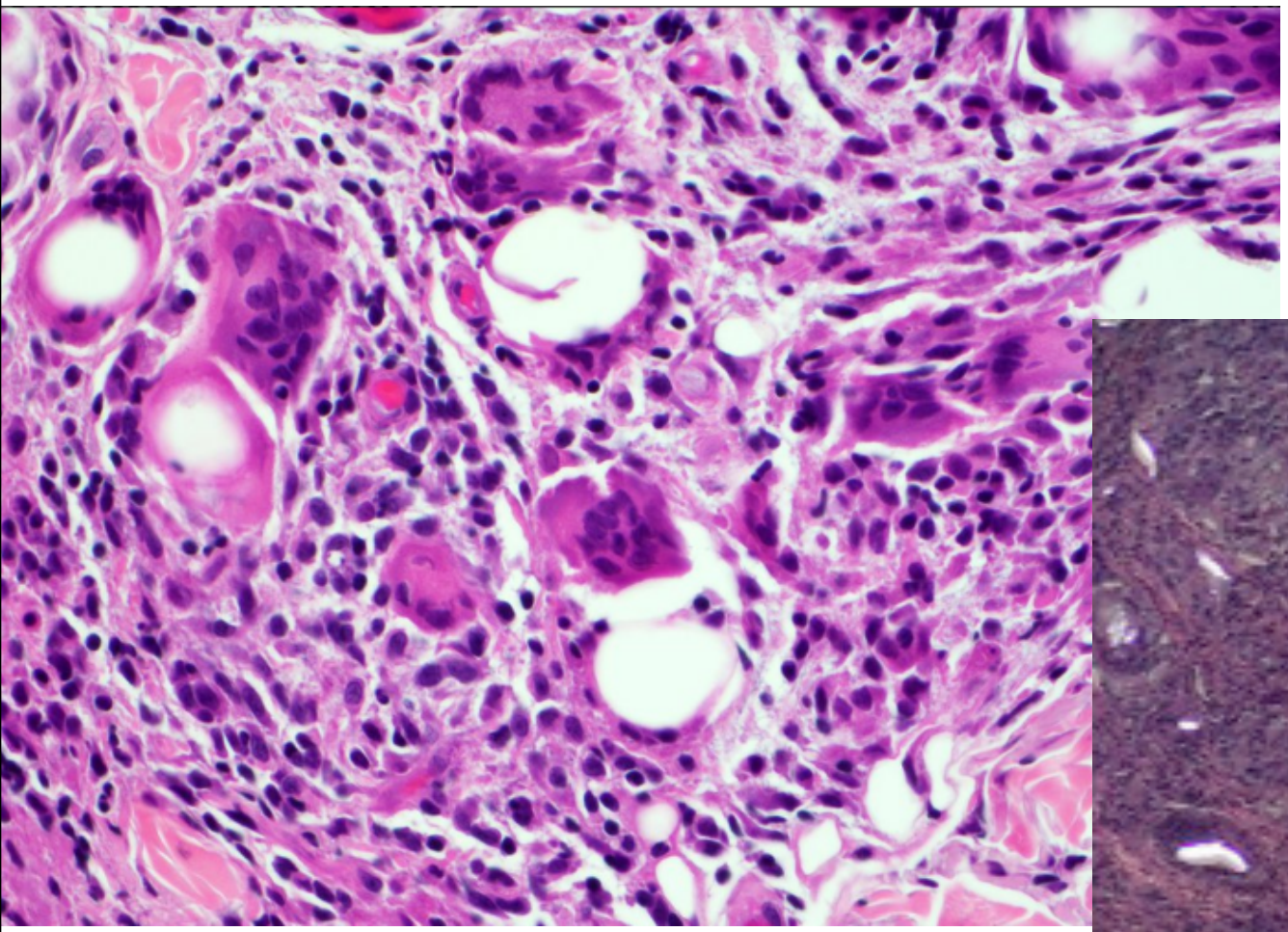
The foreign material can usually be identified in the center of the granuloma, by polarized light (appears refractile).

### Immune granuloma

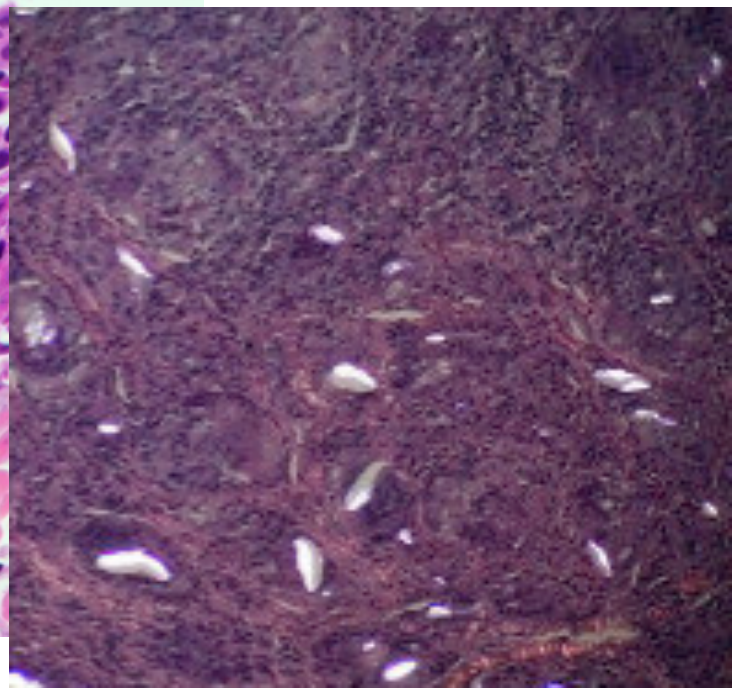
are caused by a variety of agents that are capable of inducing a persistent T cell–mediated immune response, typically persistent microbes, that are capable of inducing a **cell-mediated immune response**.

- **Identify the two types of granulomas, which differ in their pathogenesis**

## Foreign body granuloma



polarized light



# ◉ List the common causes of Granulomatous Inflammation

## Causes

**Non-immune granuloma**

◉ **Foreign body**
- **Suture**
- **Graft material**
- **talc (associated with intravenous drug abuse)**

**Immune granuloma:**

◉ **Bacteria**
- **Tuberculosis**
- **Leprosy**
- **Actinomycosis**
- **Cat-scratch disease**

◉ **Parasites**
- **Schistosomiasis**
- **Leishmaniasis**

◉ **Fungi**
- **Histoplasmosis**
- **Blastomycosis**

◉ **Metal/Dust**
- **Berylliosis**

**unknown**

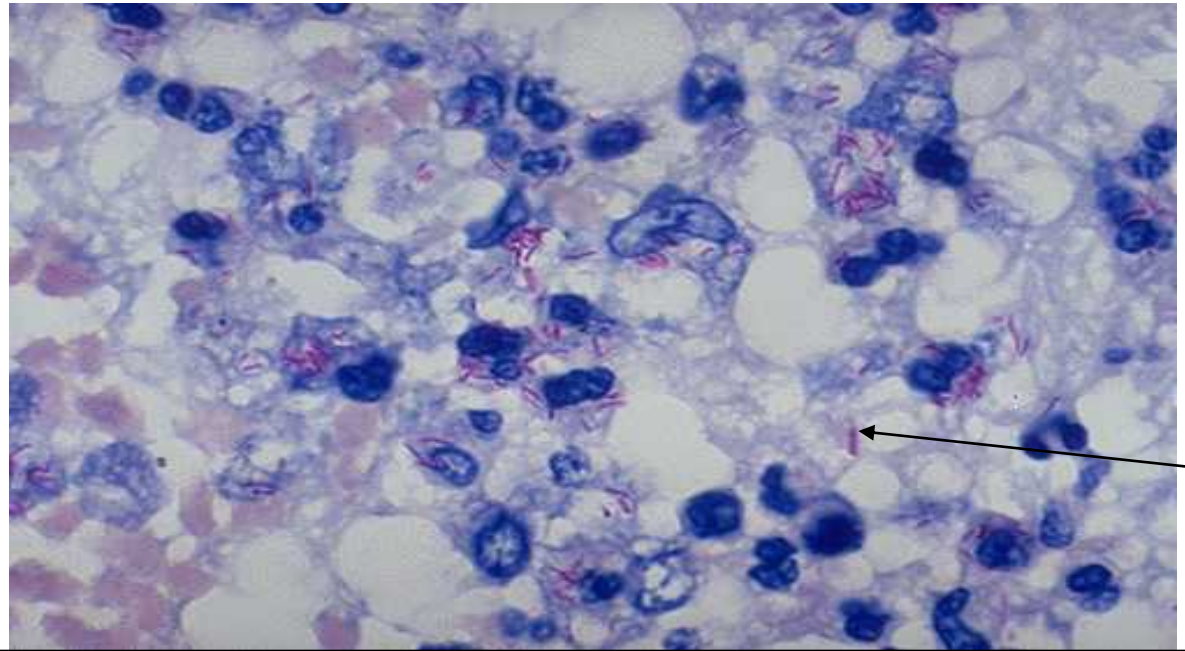
**Sarcoidosis**

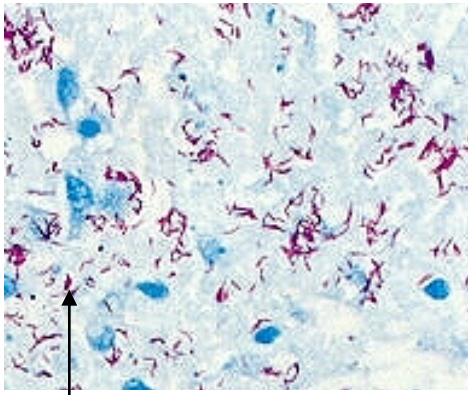
**Crohn's disease**

# ◉ List the common causes of Granulomatous Inflammation

## Tuberculosis: *Mycobacterum tuberculo*


- Mycobacteria – 'fungus like..
- slender rods
- acid fast bacilli [AFB] (i.e., they have a high content of complex lipids that readily bind the Ziehl-Neelsen [carbol fuchsin] stain and subsequently resist decolorization).



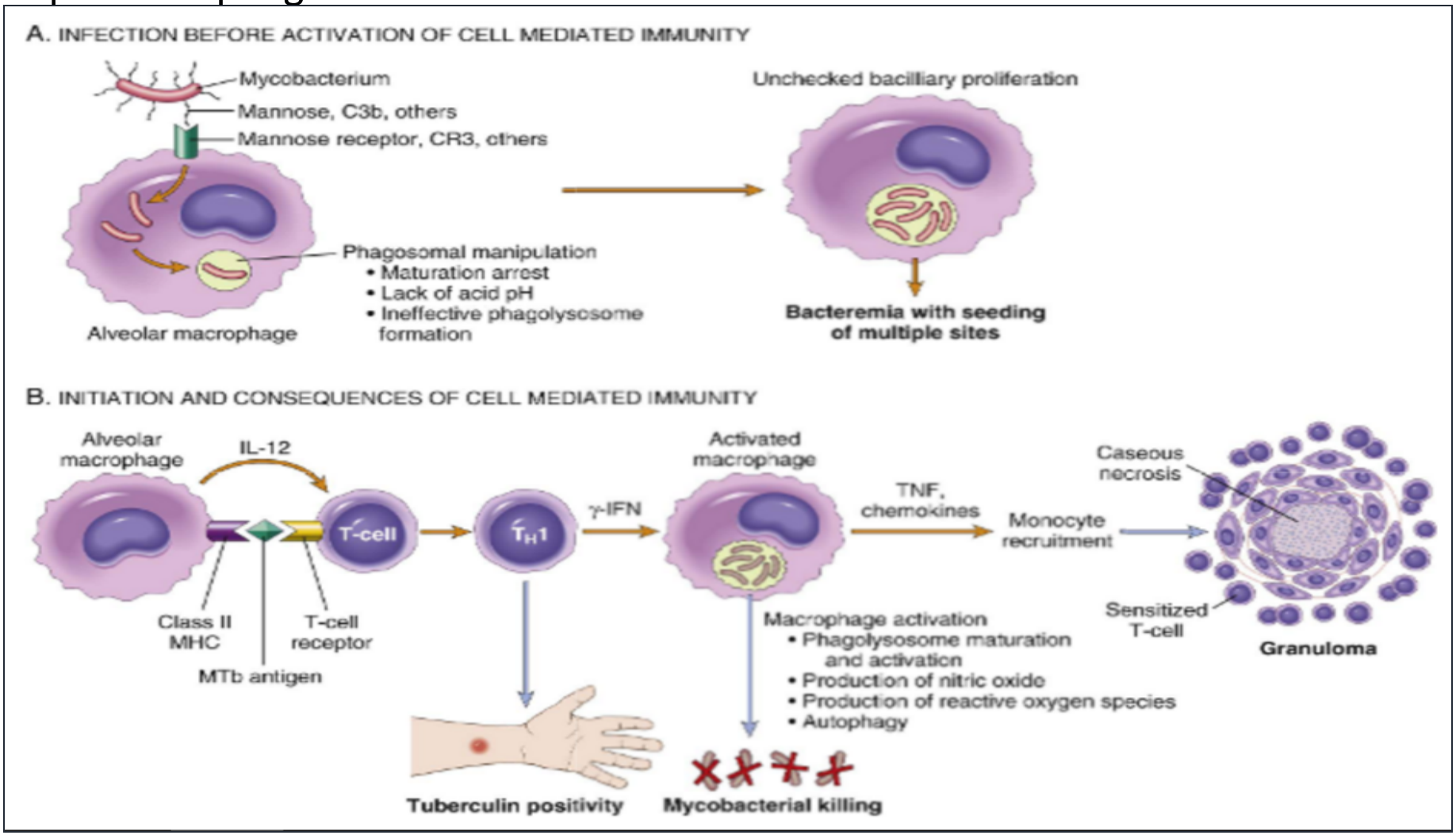


acid fast bacilli

# ⦿ List the common causes of Granulomatous Inflammation

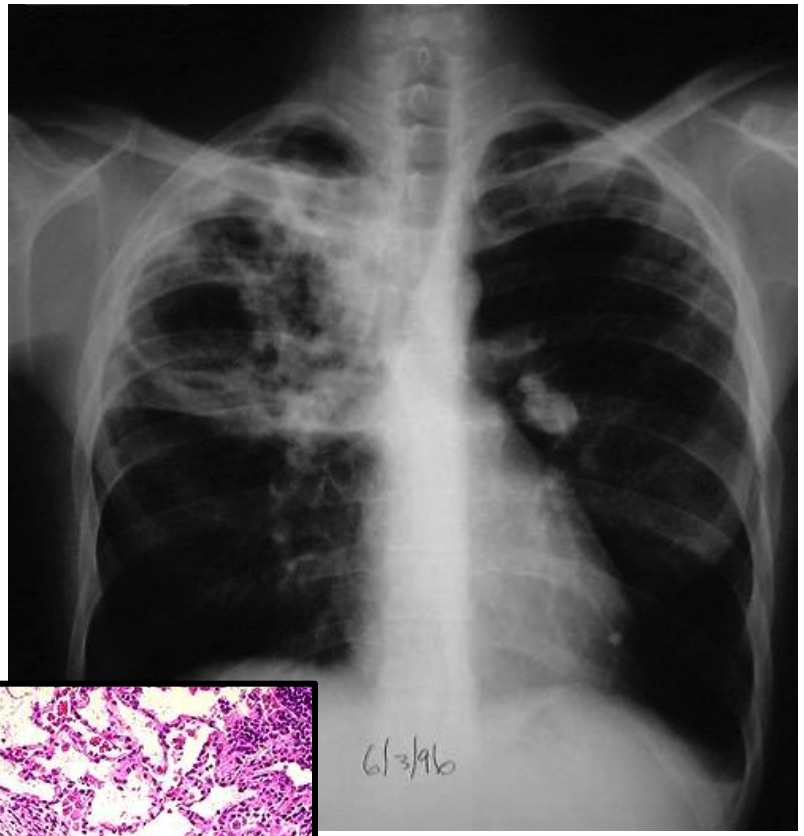
Pathogenesis of TB

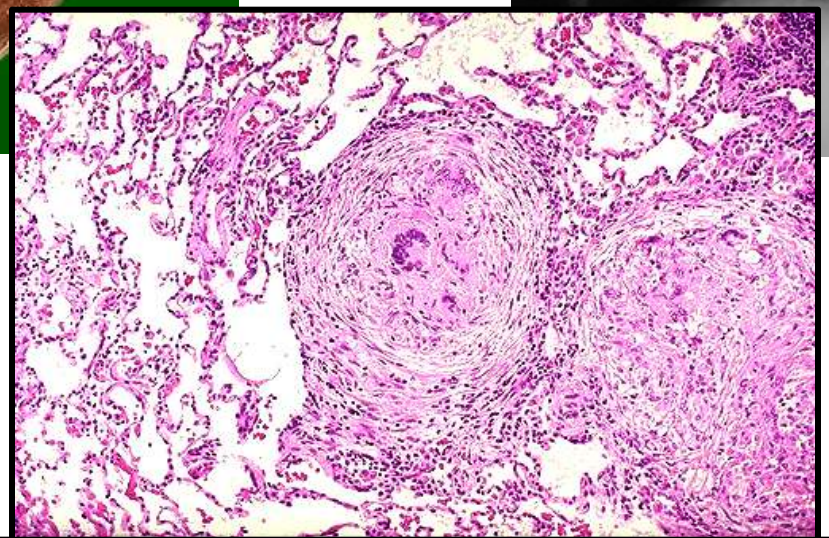
- Cord factor is a glycolipid molecule found in the cell wall of TB bacilli. It prevents phagosomal function

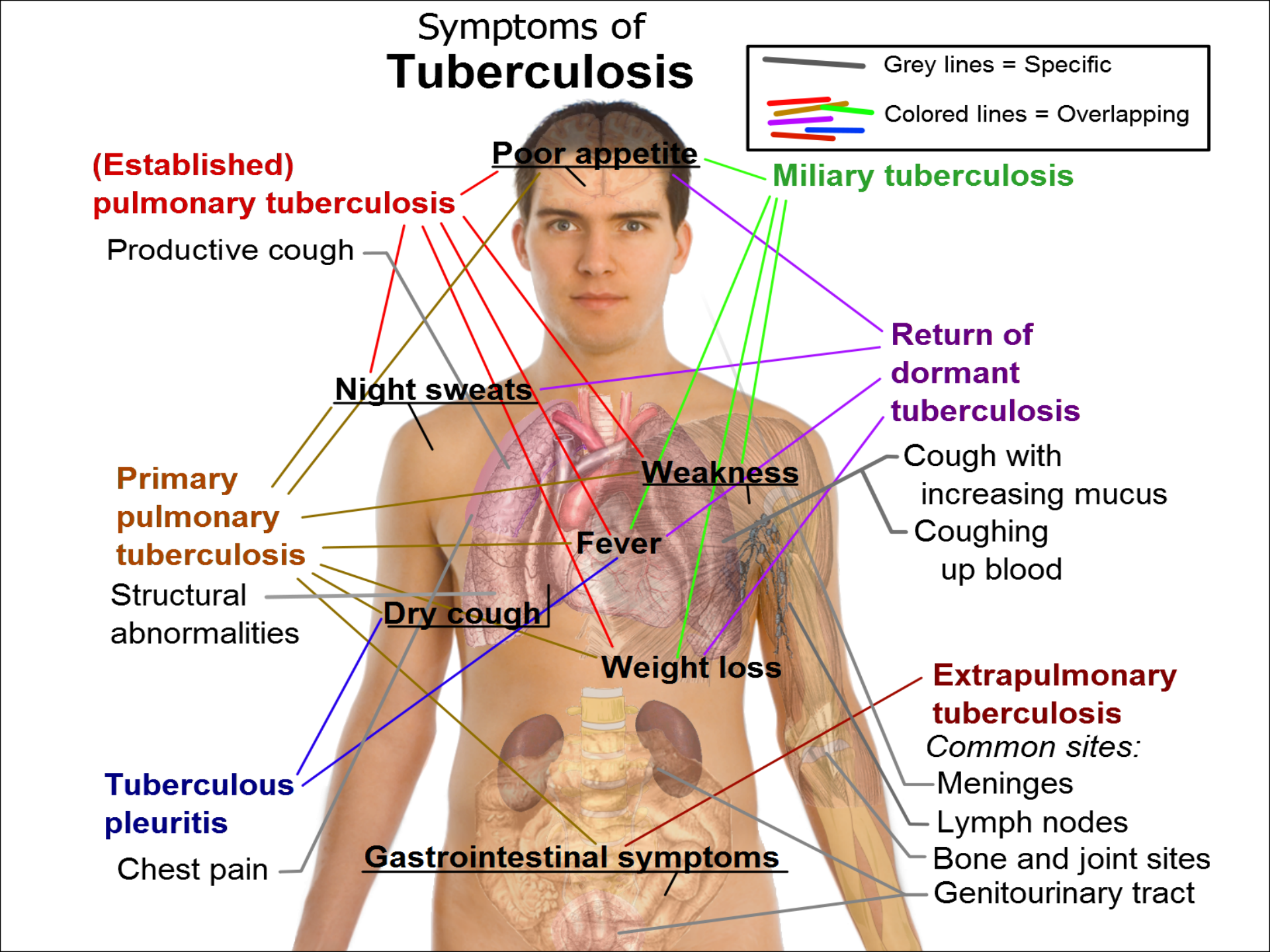


## ◉ List the common causes of Granulomatous Inflammation

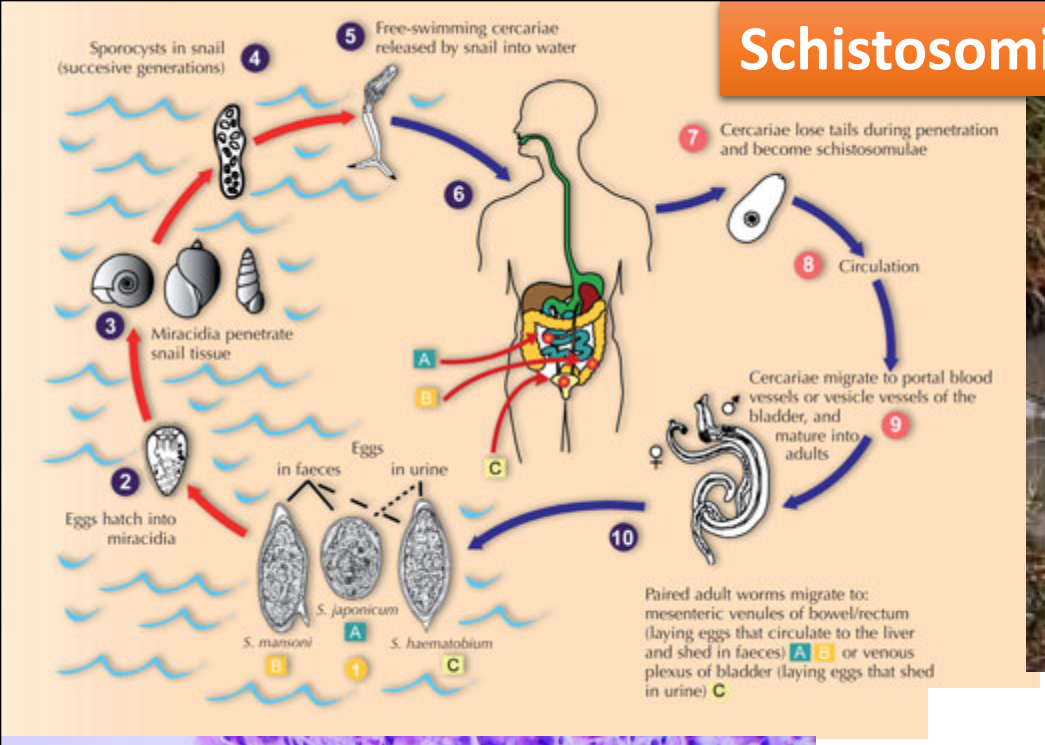
# Tuberculosis

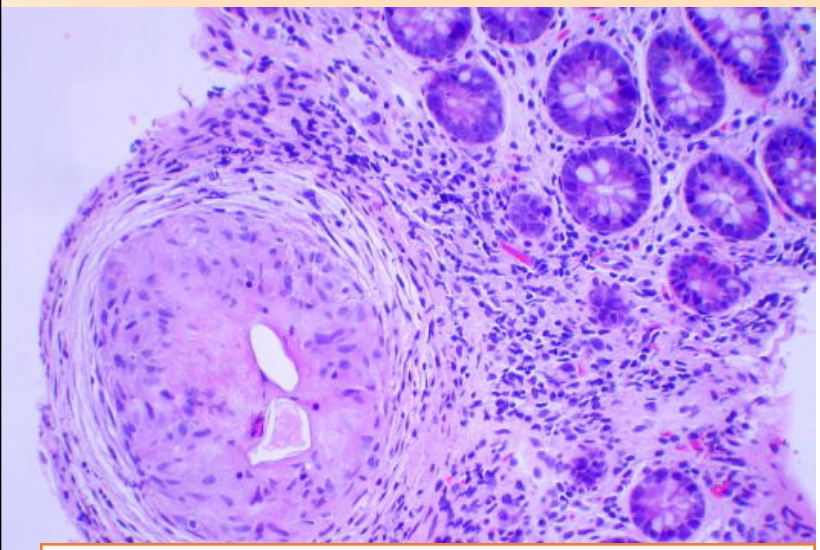





Symptoms of
Tuberculosis
Grey lines = Specific
Colored lines = Overlapping
(Established) pulmonary tuberculosis
Productive cough
Poor appetite
Miliary tuberculosis
Return of dormant tuberculosis
Night sweats
Cough with increasing mucus
Coughing up blood
Primary pulmonary tuberculosis
Weakness
Fever
Structural abnormalities
Dry cough
Weight loss
Extrapulmonary tuberculosis
Common sites:
Meninges
Lymph nodes
Bone and joint sites
Genitourinary tract
Tuberculous pleuritis
Chest pain
Gastrointestinal symptoms

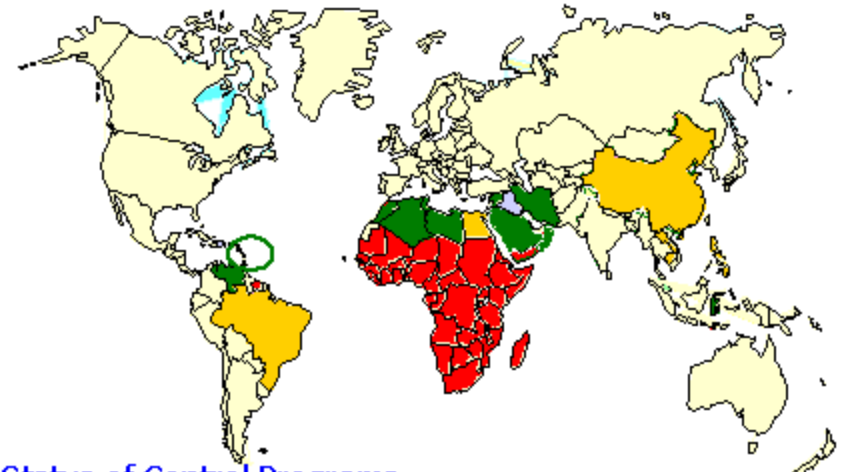
# Schistosomiasis



In parasitic infection, the granuloma is associated with eosinophils

## Global Distribution of Schistosomaisis

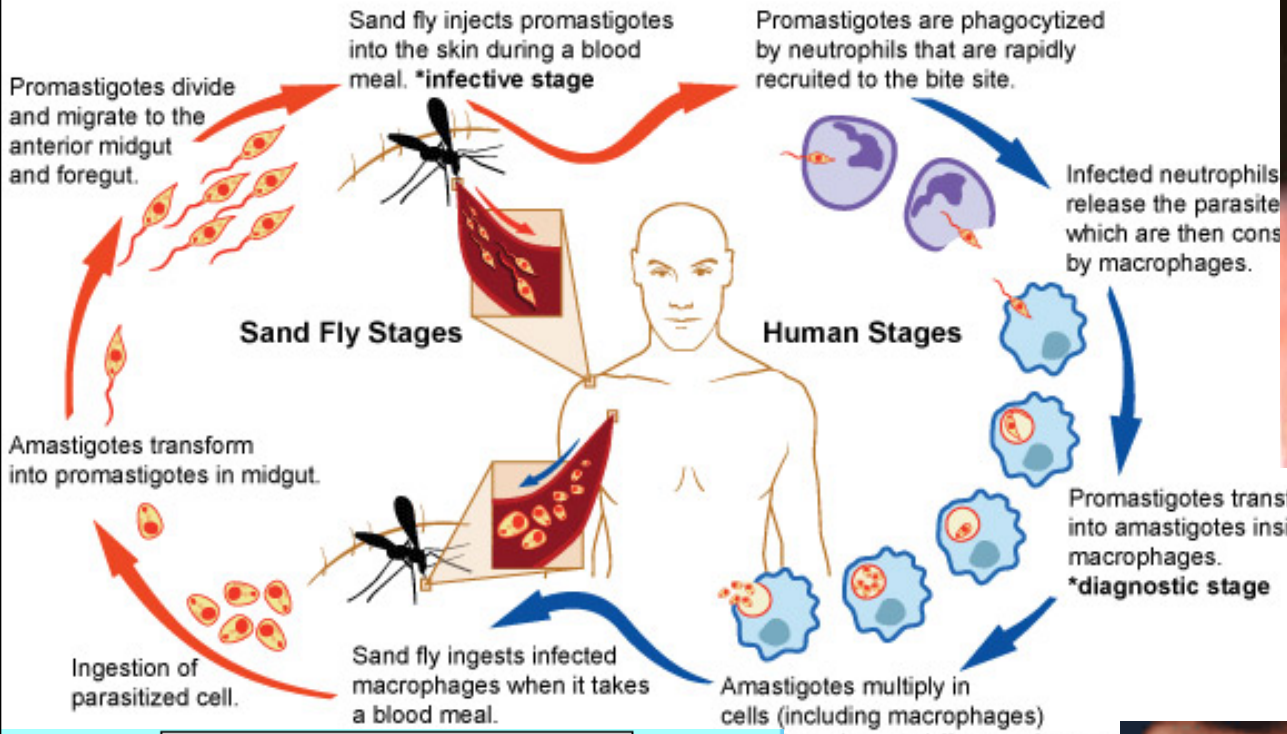


### Status of Control Programs

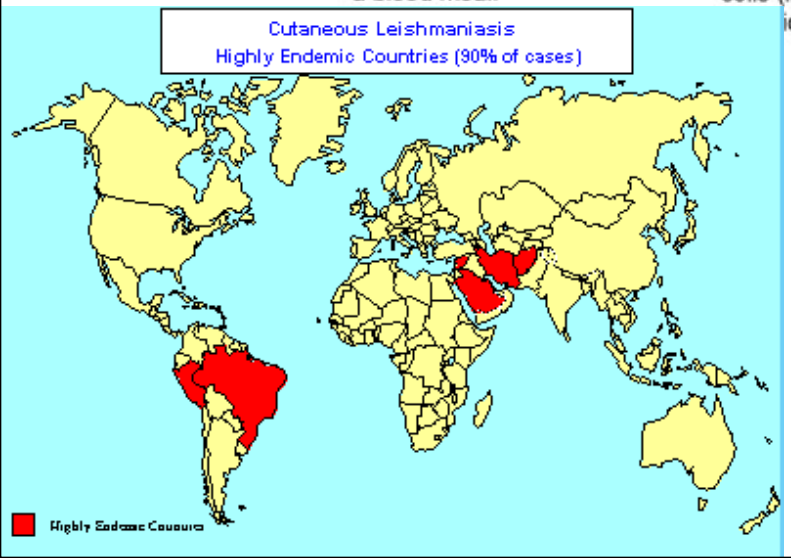
almost eradicated
ongoing large-scale control programmes
limited or no control

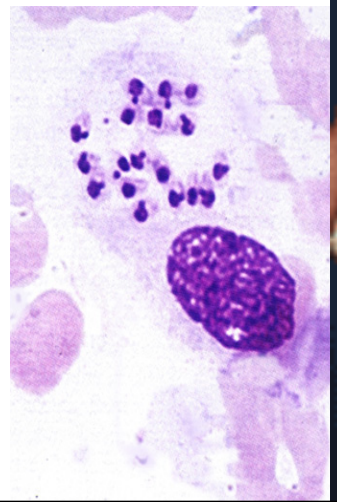
Source: WHO

# Leishmaniasis

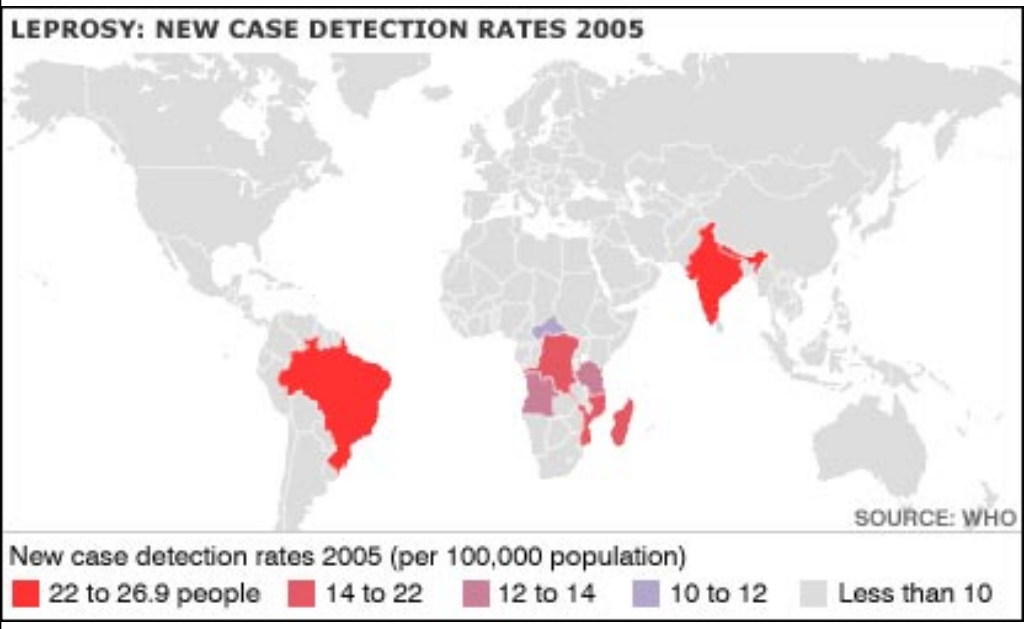


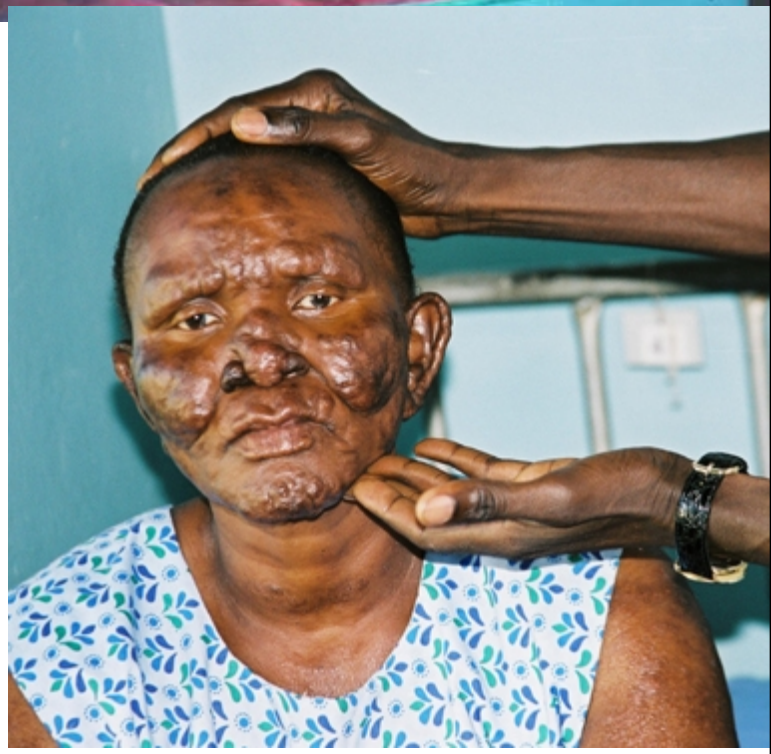




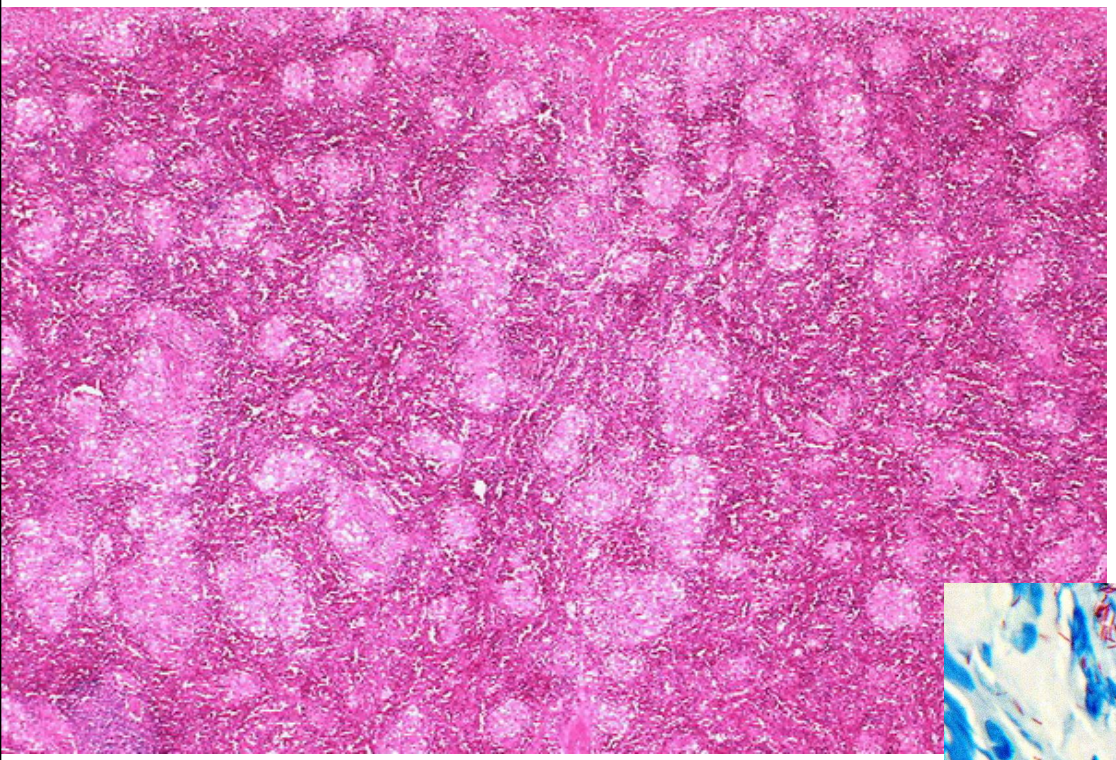



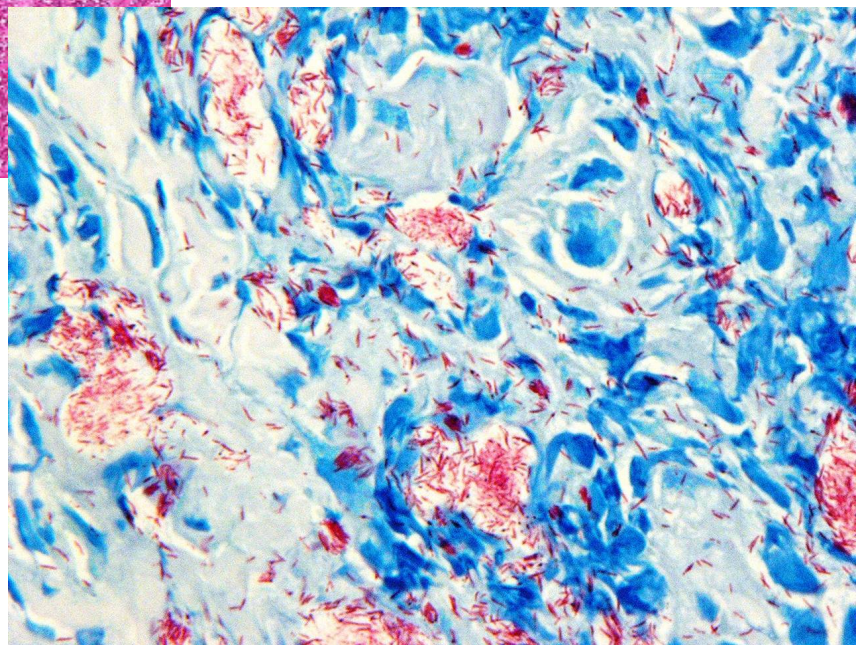
# Leprosy


LEPROSY: NEW CASE DETECTION RATES 2005
SOURCE: WHO
New case detection rates 2005 (per 100,000 population)
22 to 26.9 people
14 to 22
12 to 14
10 to 12
Less than 10



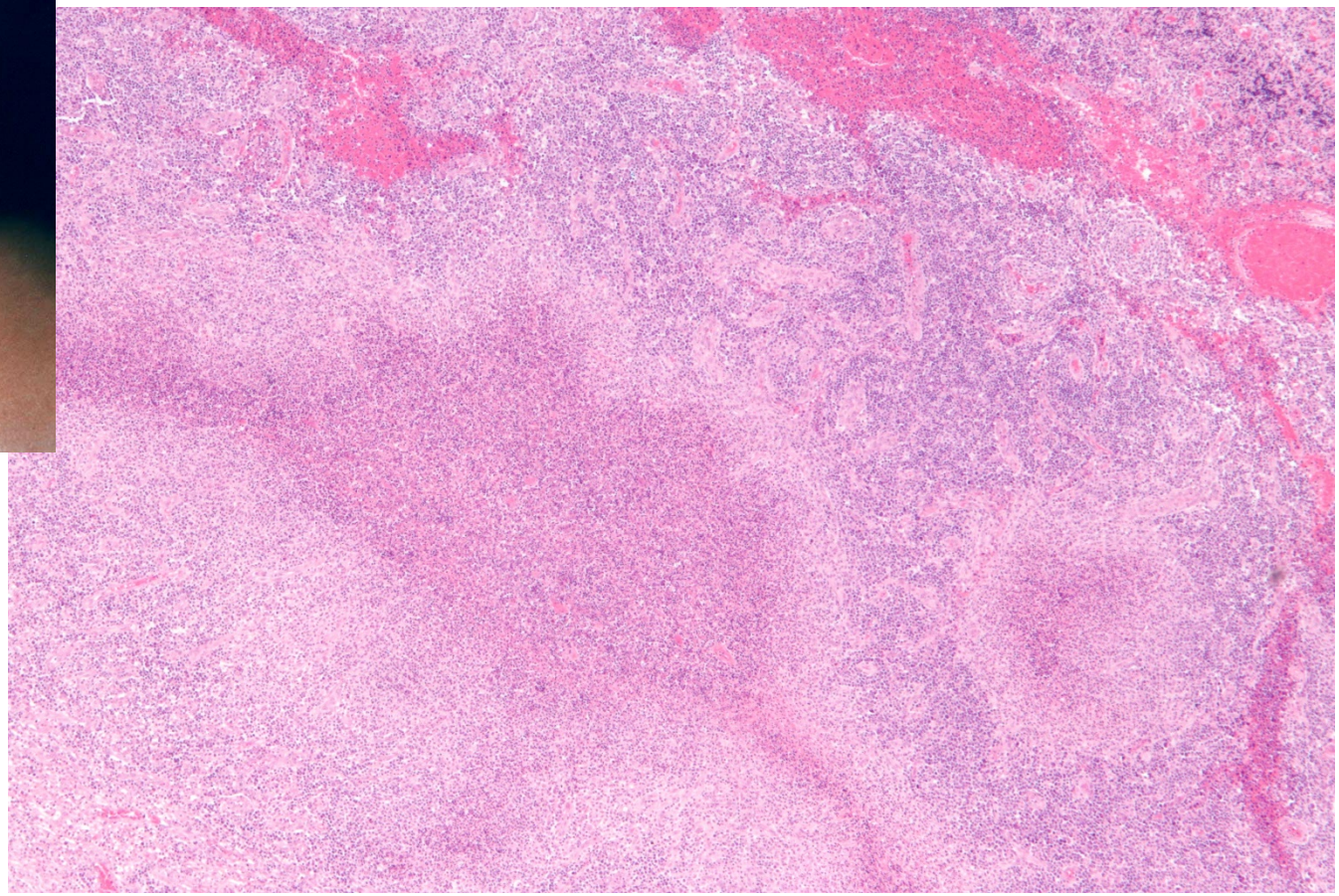
# Leprosy





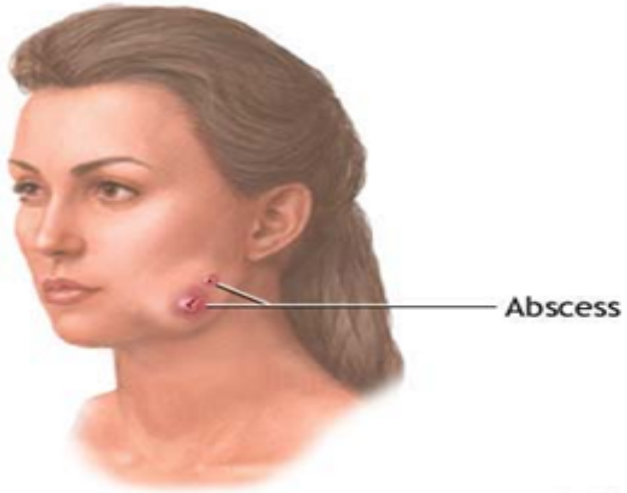
# Cat-scratch disease

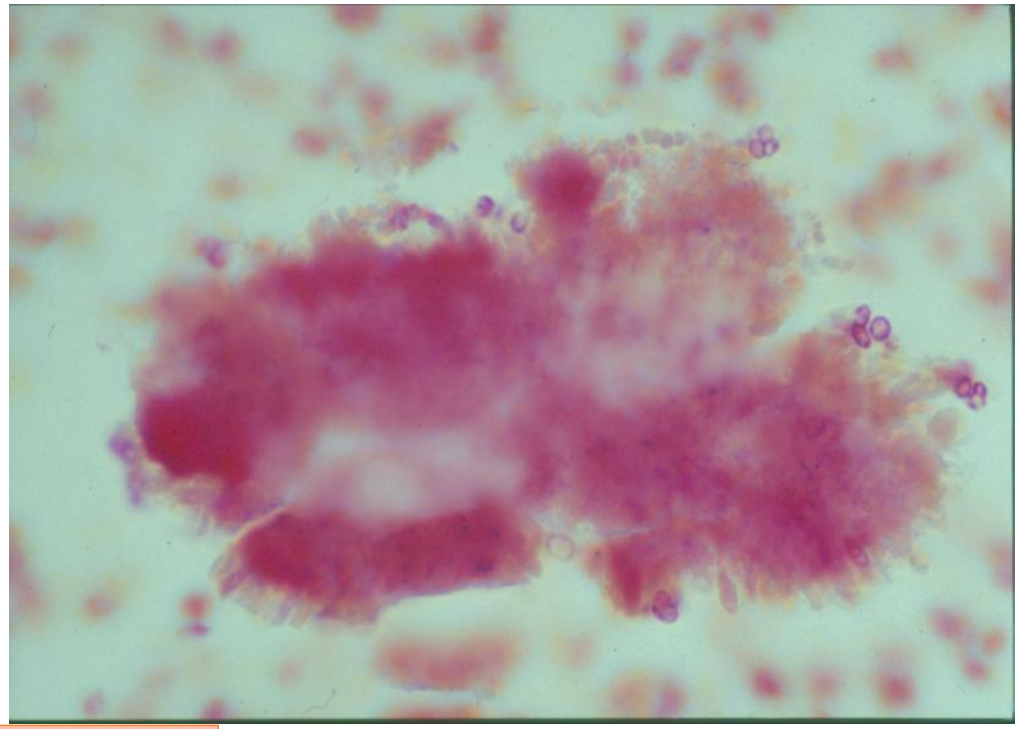
- Gram-negative bacillus
- Rounded or stellate granuloma containing central granular debris and neutrophils



# Actinomycosis

**Actinomycosis is a long-term (chronic) granulomatous bacterial infection that commonly affects the face and neck**

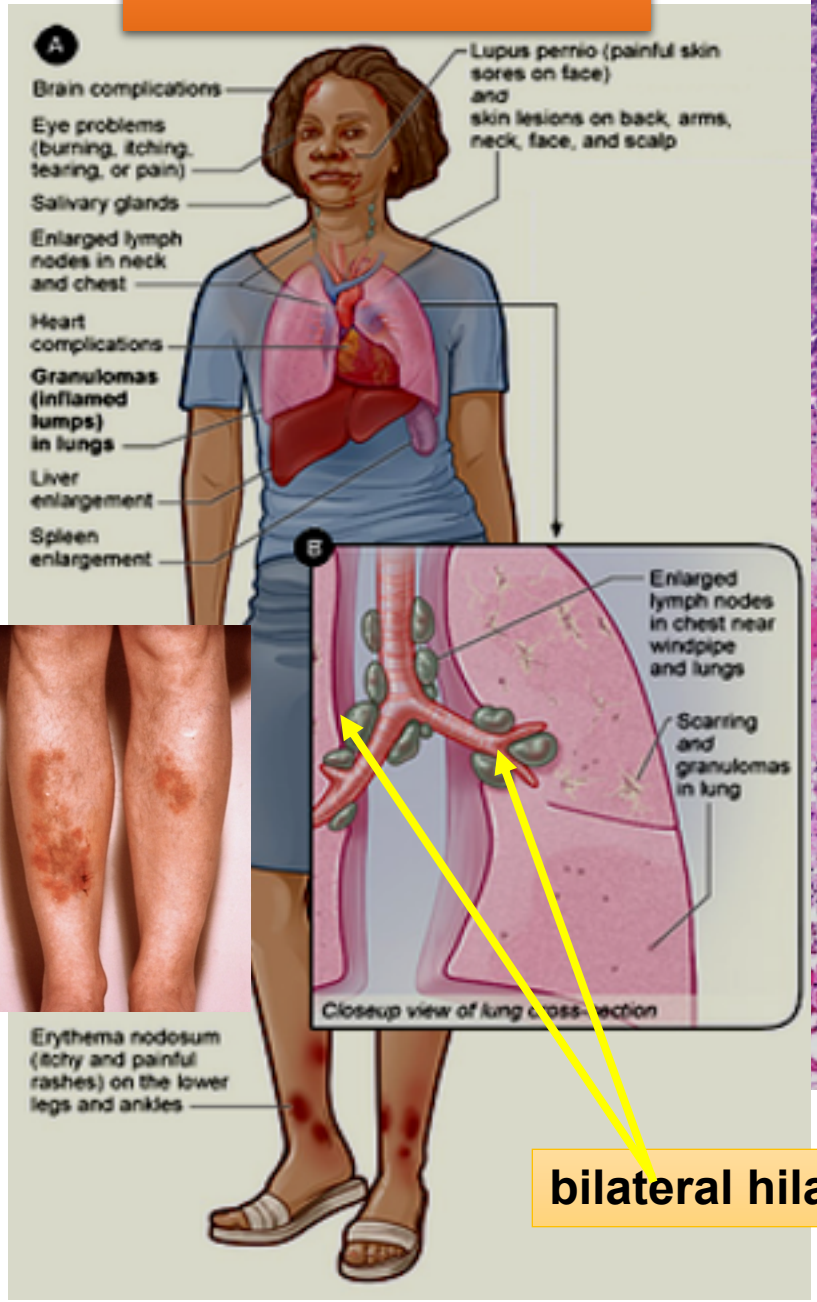


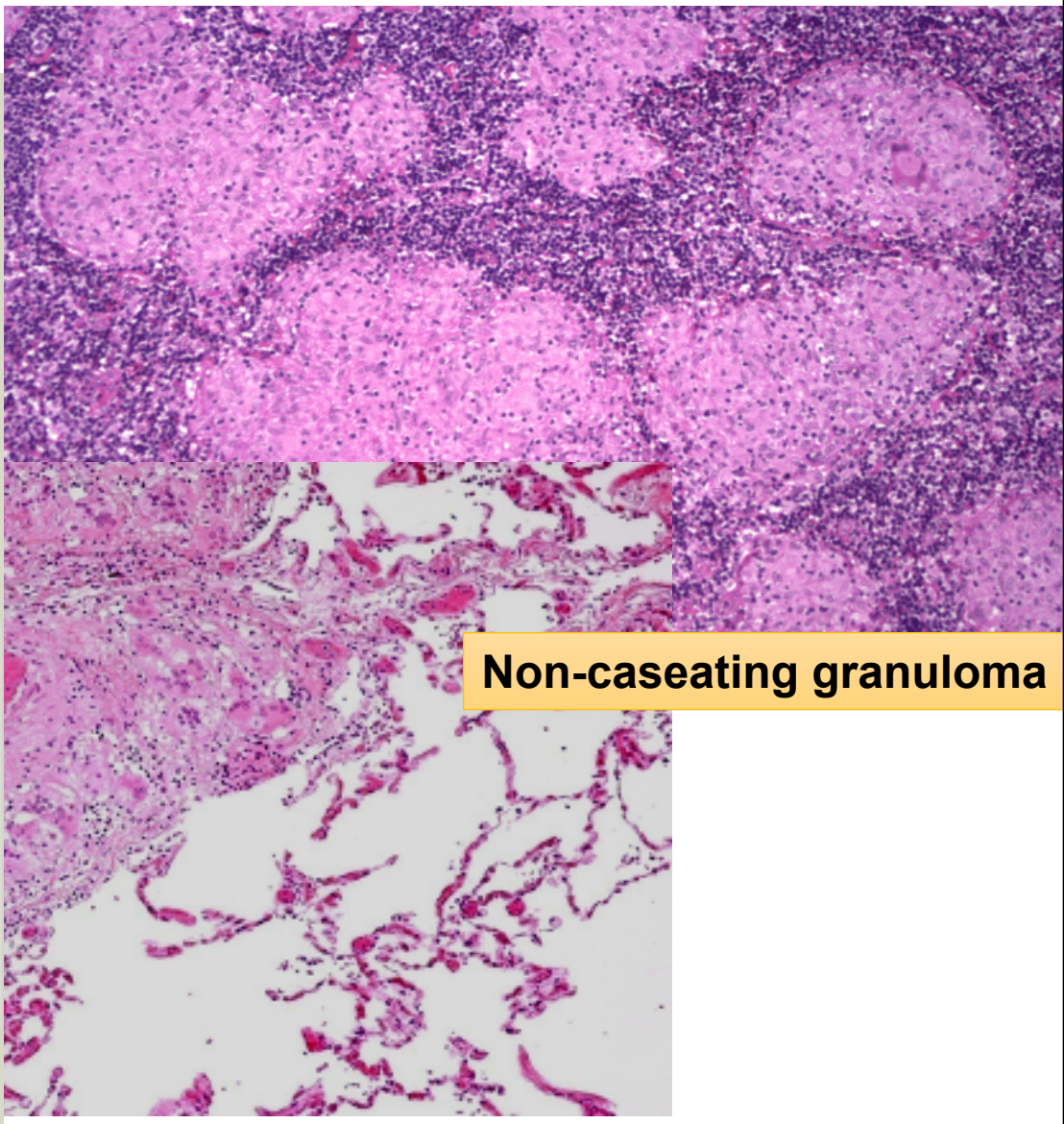



**Examination of drained fluid under a microscope shows "sulfur granules" in the fluid. They are yellowish granules made of clumped organisms.**

filamentous, gram-positive, non–acid-fast, anaerobic-to-microaerophilic bacteria

# Sarcoidosis



Non-caseating granuloma

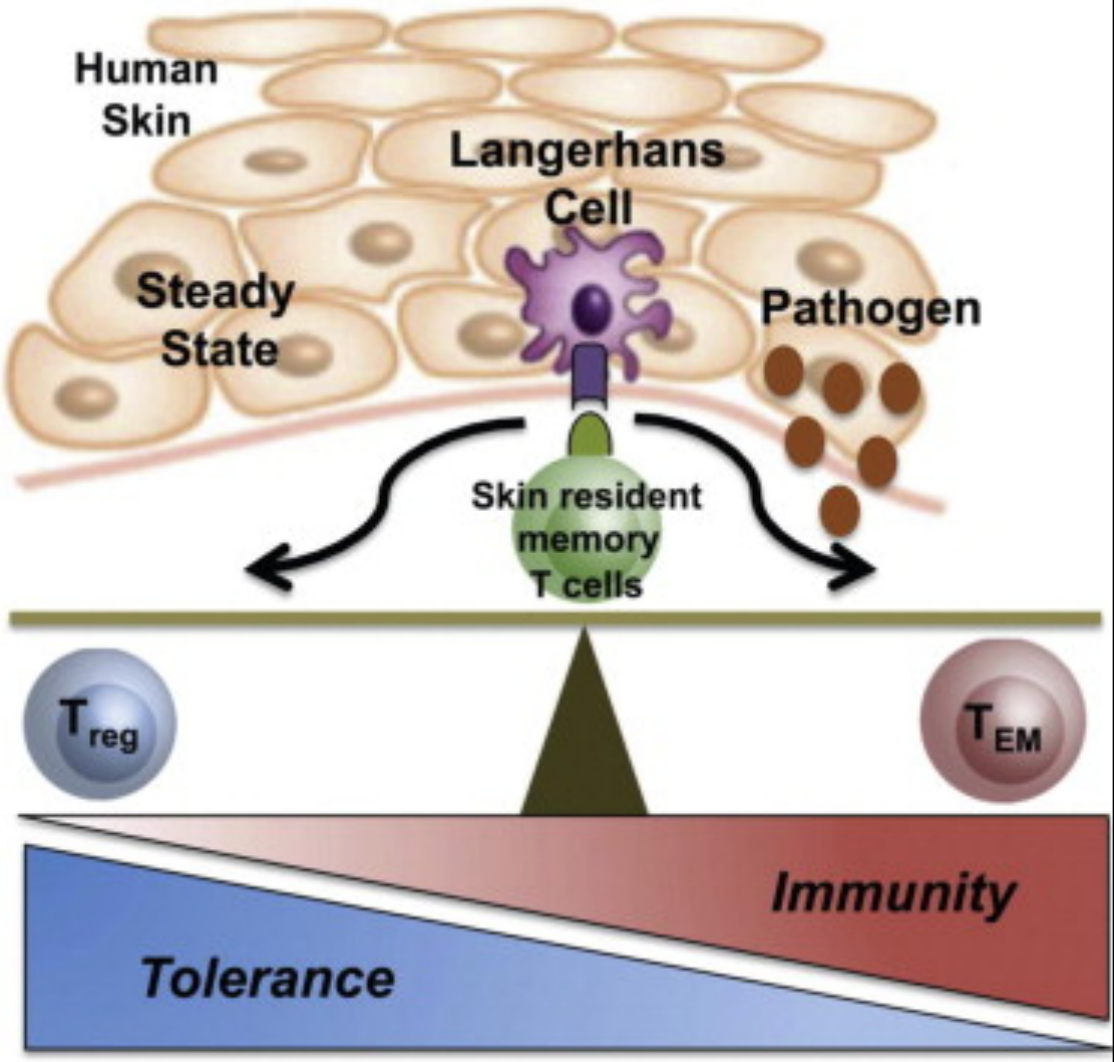
bilateral hilar lymph nodes enlargement

# Match A and B

| A | B |
| --- | --- |
| 1) The most important cell in granulomatous inflammation | a. IFN-γ |
| 2) A cytokines that is important in activating macrophages and transforming them into epithelioid cells | b. Langhans cells |
| 3) Multinucleated cell in TB | c. Epitheliod histiocyes |
| 4) Antigen presenting cells | d. Cord factor |
| 5) pathogenesis of immune type granulomatous inflammation | e. Langerhan's cells |
| 6) Microscopic finding of TB | f. Type IV hypersensitivity reaction |
| 7) Found in the cell wall of TB | g. Caseating granuloma |

# Langerhan's cells

- Antigen presenting cells



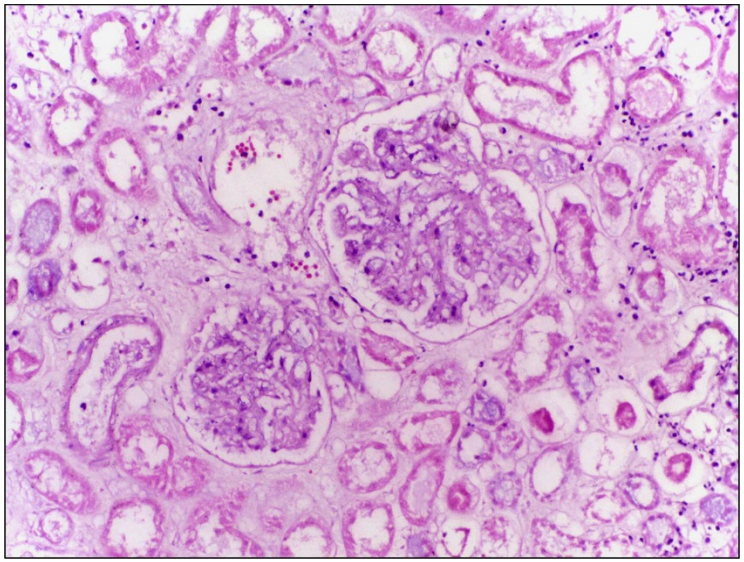
- Which of the following diseases does not cause granulomatous inflammation

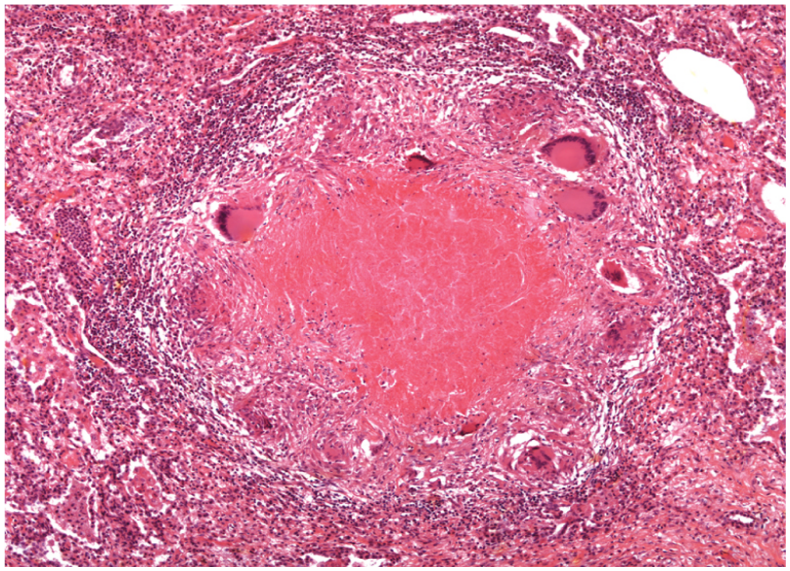
a) Cat-scratch disease
b) Actinomycosis
c) Sarcoidosis
d) Leishmaniasis
**e) Staphylococcus infection**

# What are the causes of caseous necrosis?

- Caseous necrosis is caused by tuberculosis, leprosy, and fungal infections.

- How does caseous necrosis differ from coagulative necrosis under the microscope?
  - In caseous necrosis, there is total loss of tissue structure, whereas in coagulative necrosis, cell outlines are retained.





- What is the origin of epithelioid cells?
  They are transformed macrophages.
- Do you know the difference between granulation tissue and granulomatous inflammation?
  Granulation tissue contains new small blood vessels, fibroblasts, and mononuclear cells in an edematous extracellular matrix; it is part of the repair response. A granuloma is a circumscribed collection of epithelioid cells, usually surrounded by lymphocytes; it is a form of chronic inflammation.

- What are the causes of granulomatous inflammation?
- Causes are
  - (1) bacterial (e.g., *Mycobacterium tuberculosis, M. leprae, Treponema pallidum*)
  - (2) parasitic (e.g., schistosomiasis)
  - (3) fungal (e.g., histoplasmosis, blastomycosis)
  - (4) inorganic dusts (e.g., silicosis, berylliosis)
  - (5) foreign body
  - (6) unknown (e.g., sarcoidosis).

- **How are giant cells formed in granulomas?**
  **Giant cells are formed by fusion of macrophages.**

- **What are the other cells in a granuloma?**
  **Lymphocytes, mainly CD4+, that caused the granulomatous reaction are present. Healing granulomas are surrounded by fibroblasts.**

- **In TB do granulomas in different organs look different?**
  **No, all granulomas look similar.**

# *TAKE HOME MESSAGES:*

- Granulomatous inflammation is a distinctive pattern of chronic inflammation characterized by aggregates epithelioid macrophages
- Damaging stimuli which provoke a granulomatous inflammatory response include: Microorganisms which are of low inherent pathogenicity but which excite an immune response.

- Granuloma are produced in response to:
  - Bacterial infection
  - parasitic infection: e.g. Schistosoma infection
  - Certain fungi cannot be dealt with adequately by neutrophils, and thus excite granulomatous reactions.
  - Non-living foreign material deposited in tissues, e.g. keratin from ruptured epidermal cyst.
  - Unknown factors, e.g. in the disease 'sarcoidosis' and Crohn's diseas