

# GRANULOMATOUS INFLAMMATION

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# OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT:

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

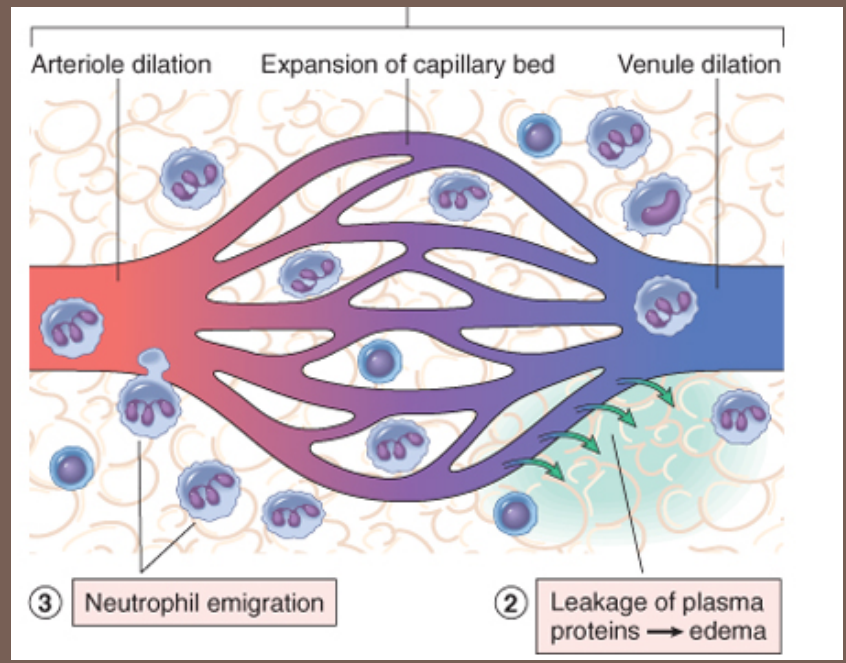
- **Define Granulomatous inflammation.**
- **Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance.**
- **Understands the pathogenesis of granuloma formation.**
- **Identify the two types of granulomas, which differ in their pathogenesis.**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

Define Granulomatous inflammation.

# Inflammation

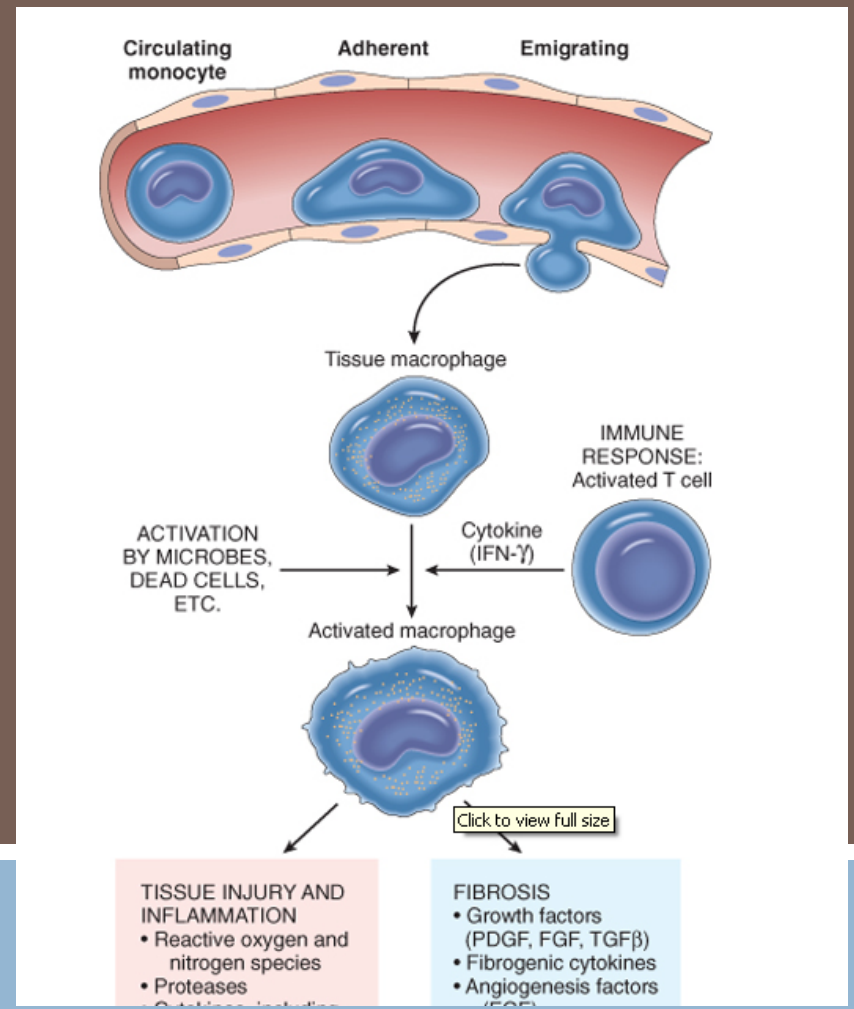
## Acute inflammation

Neutrophils



## Chronic inflammation

Macrophage, Lymphocytes & Plasma cells

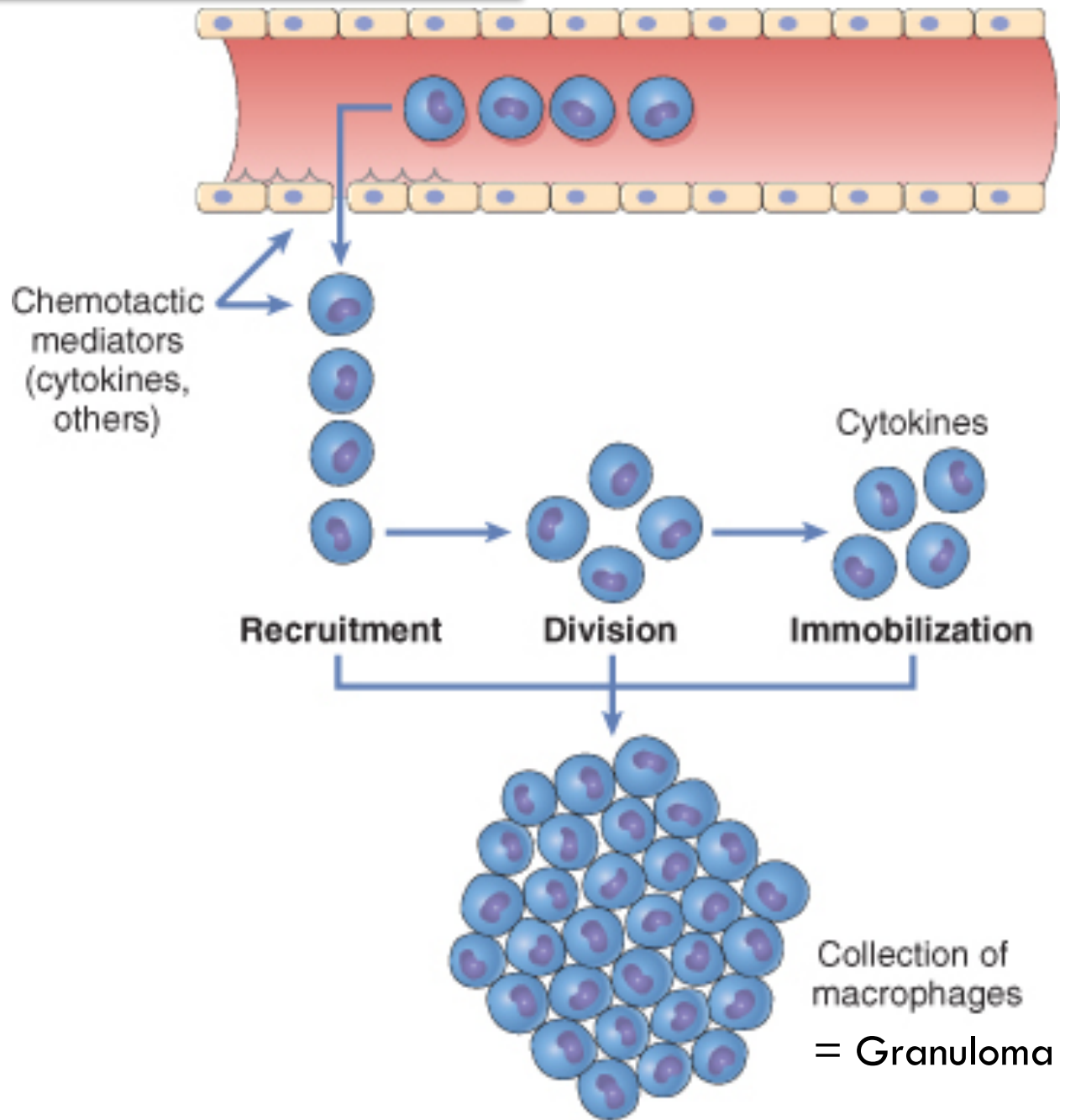


# GRANULOMATOUS INFLAMMATION

**A form of chronic inflammation characterized by the formation of granulomas.**



© Define Granulomatous inflammation.

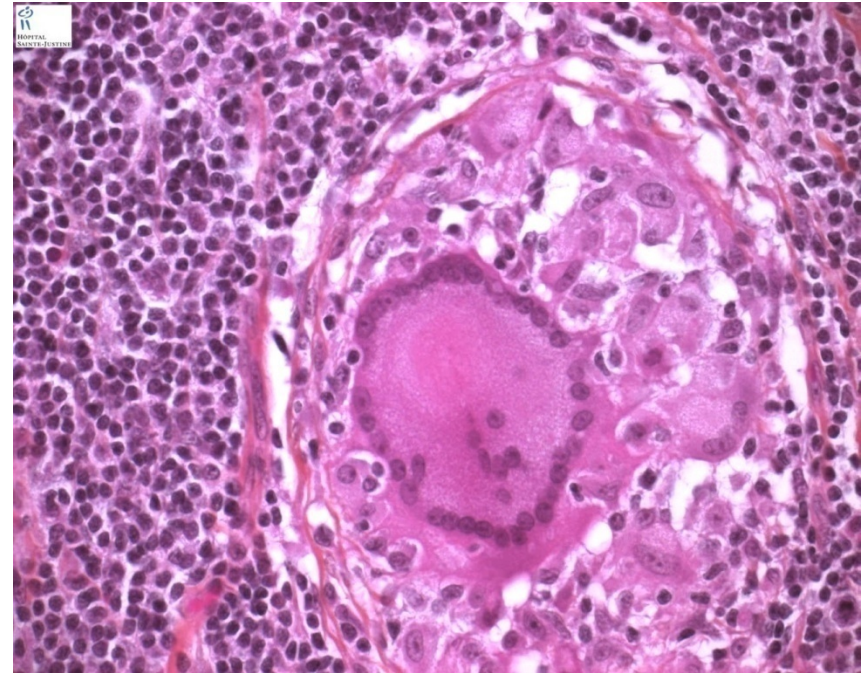
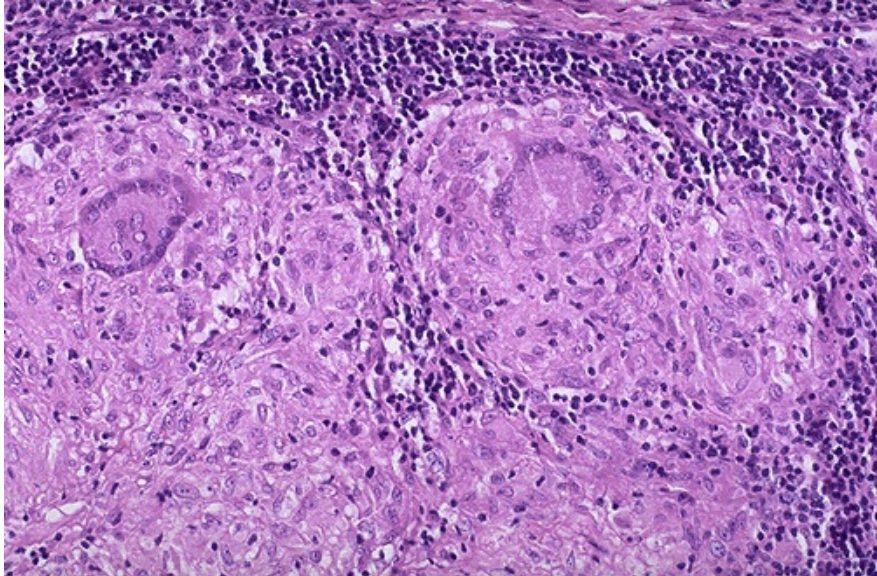


# Why is it important?

- ❑ 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

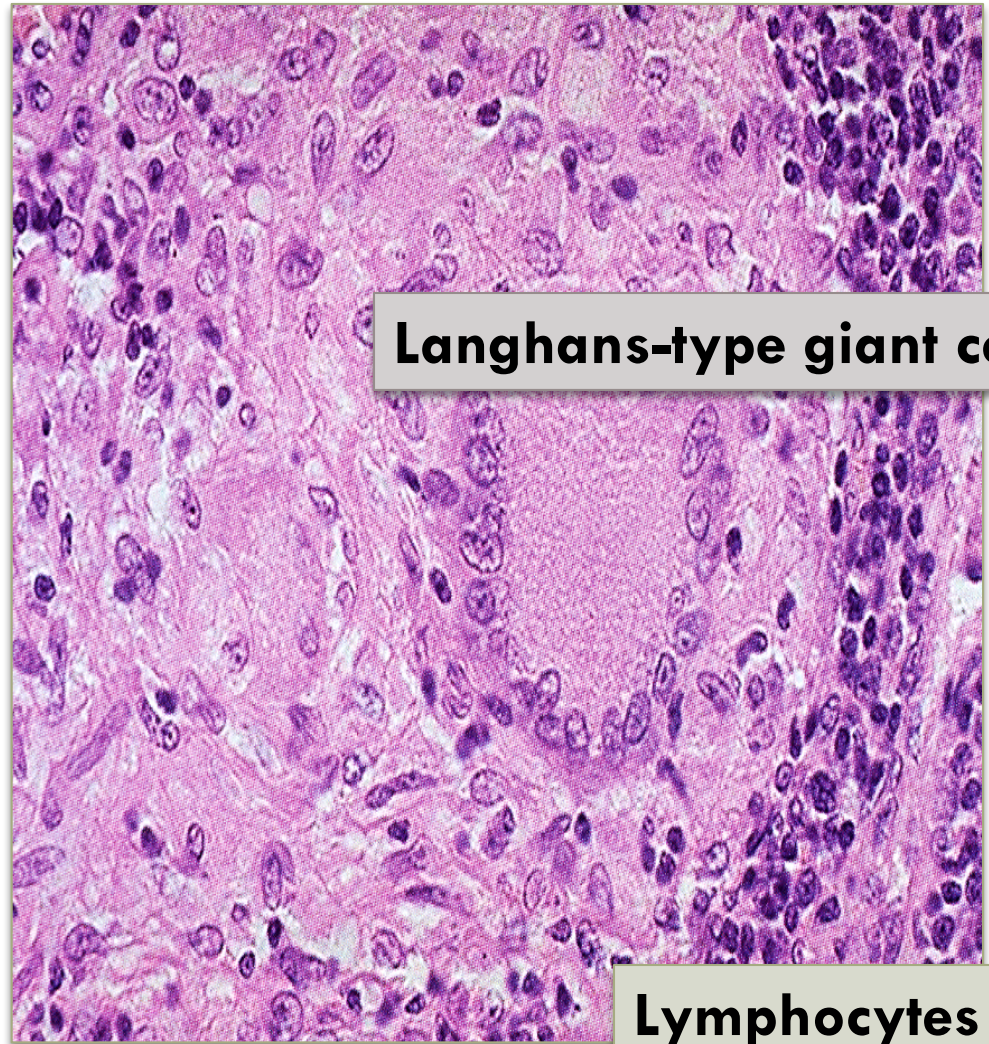




# Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance

microscopic aggregation  
of activated  
macrophages

## Granuloma

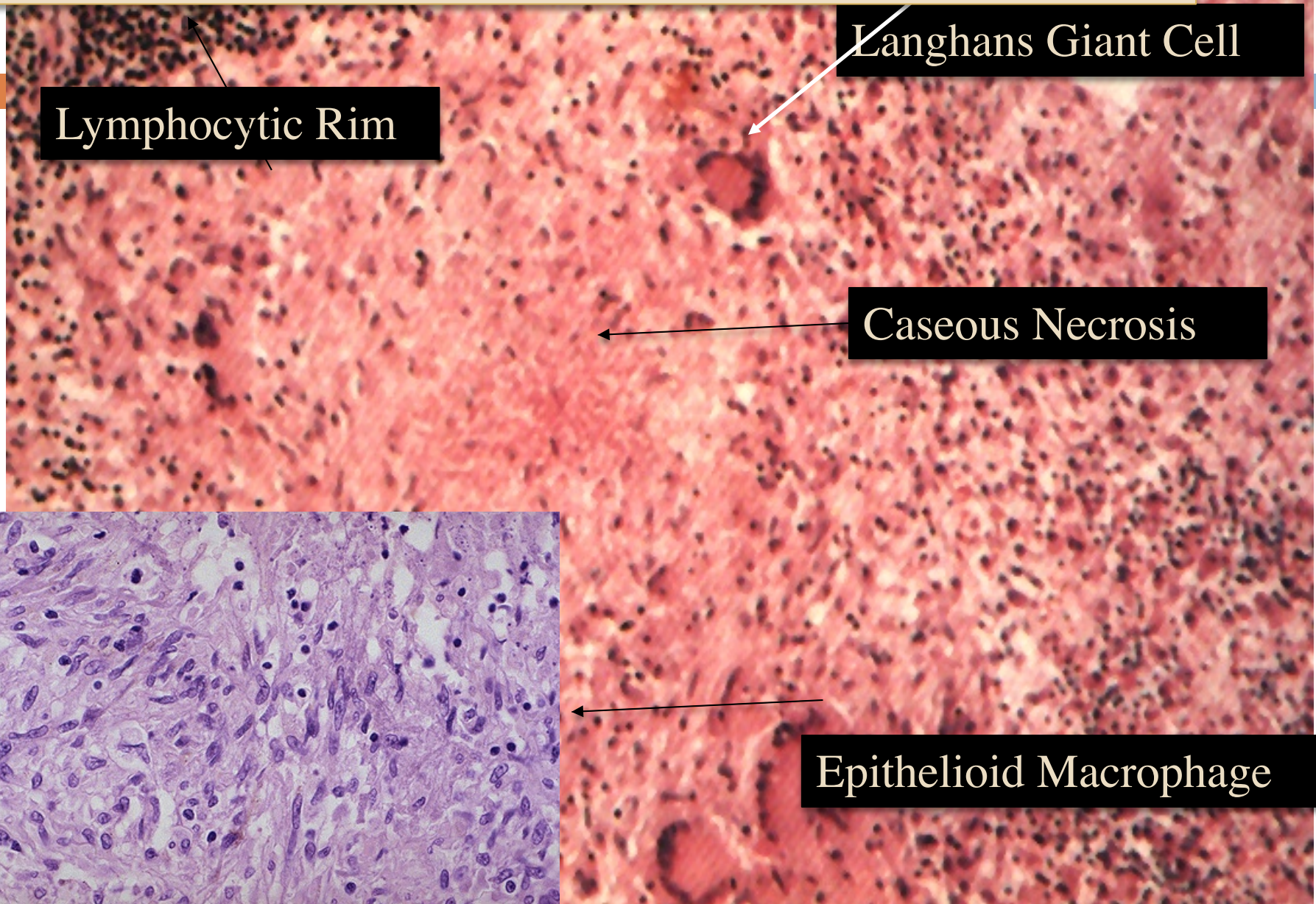


Langhans-type giant cell

Lymphocytes



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



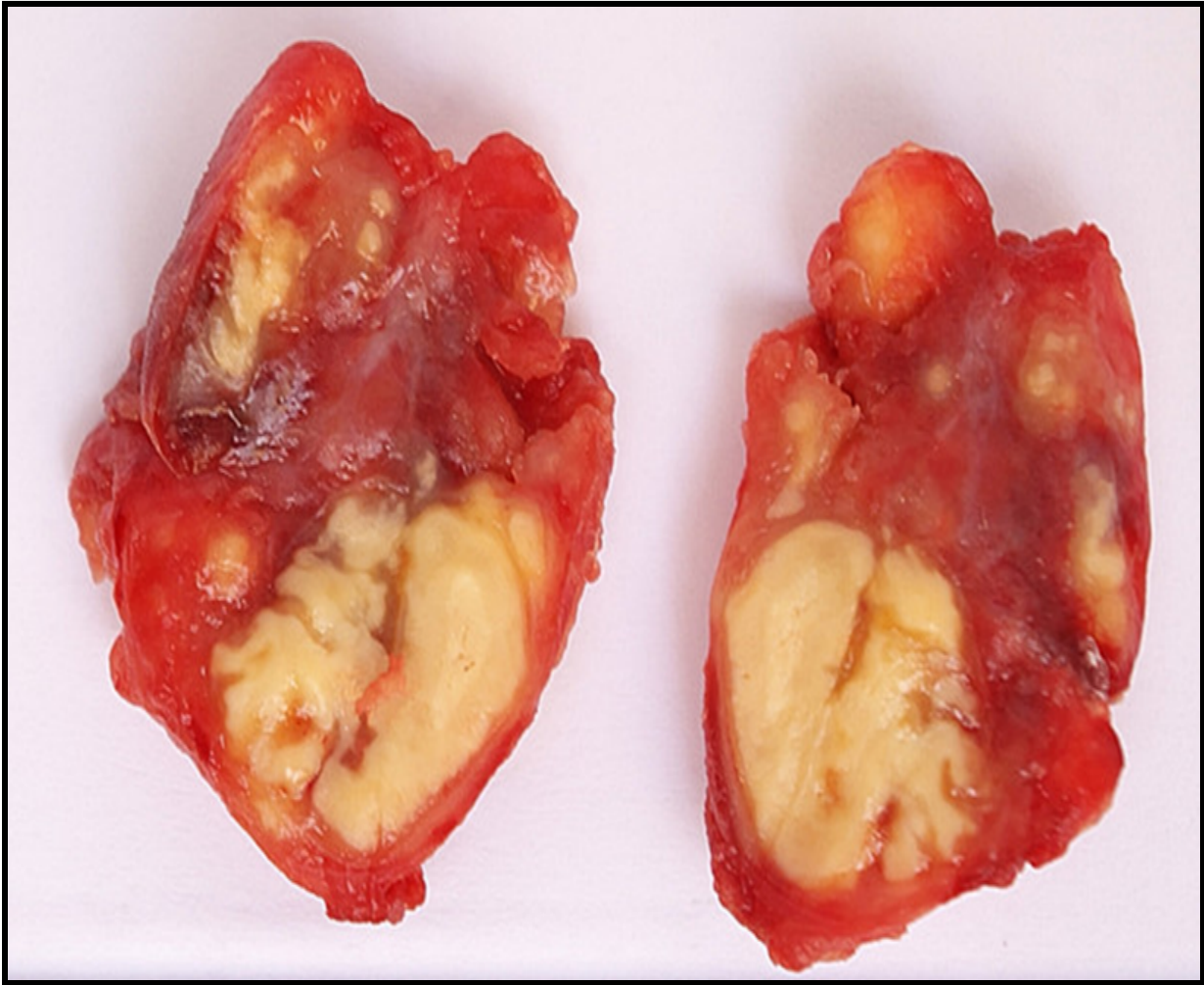
Lymphocytic Rim

Langhans Giant Cell

Caseous Necrosis

Epithelioid Macrophage

**Recognize the morphology of granulomas**

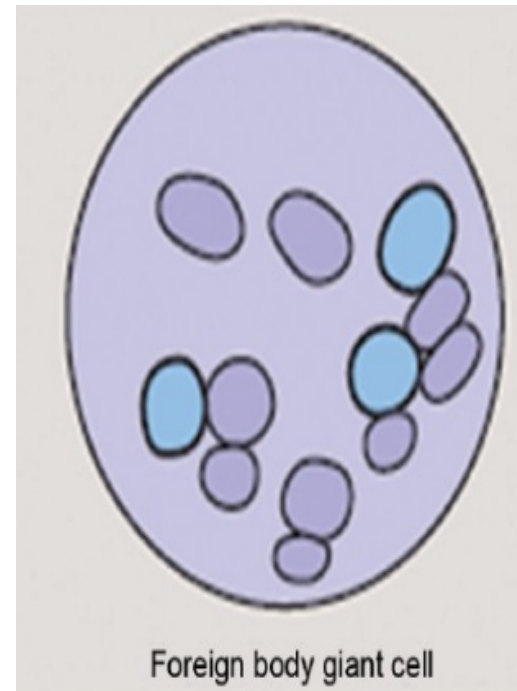
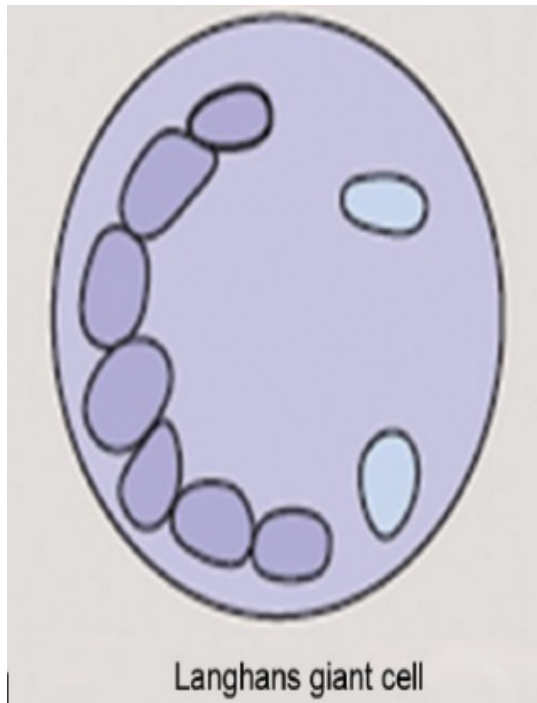


***Section of a lymph node with caseation necrosis***



# 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**).



# 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.



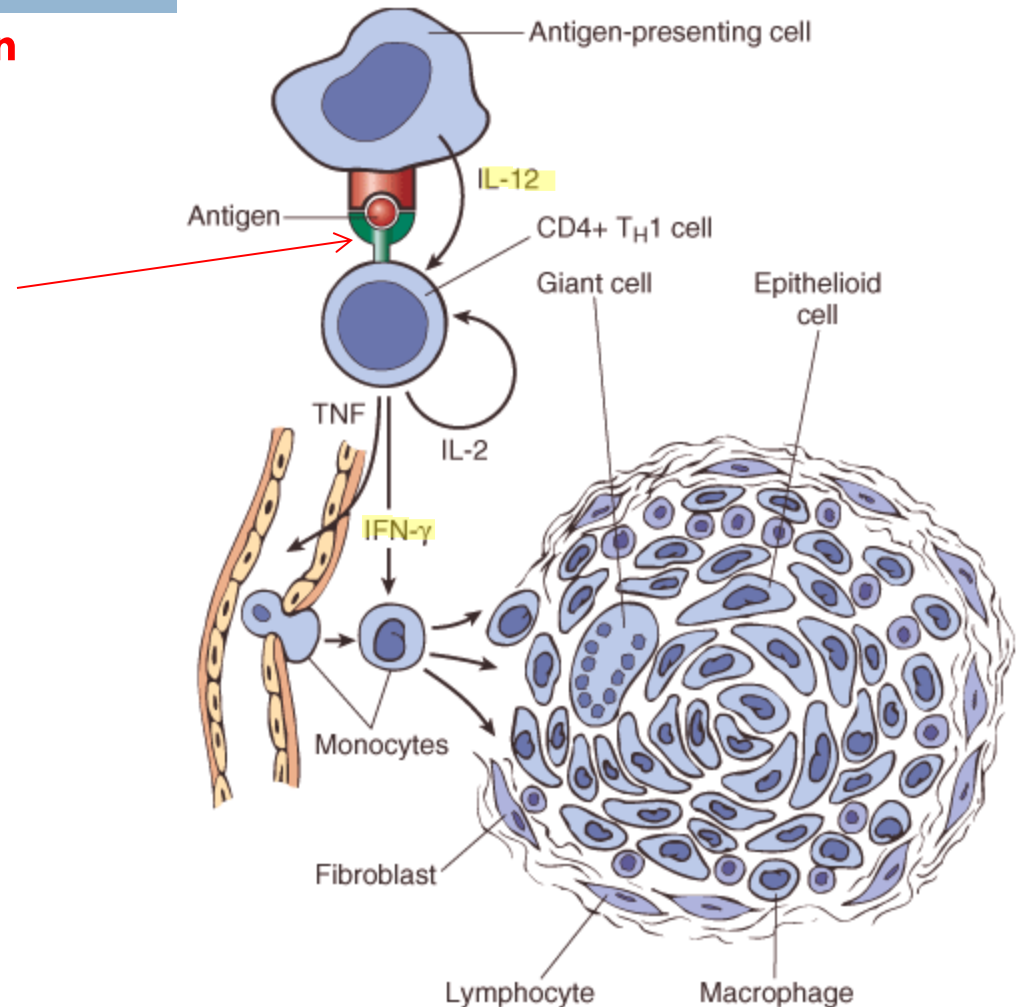
# Understands the pathogenesis of granuloma formation

## Granulomatous Inflammation Mechanism

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

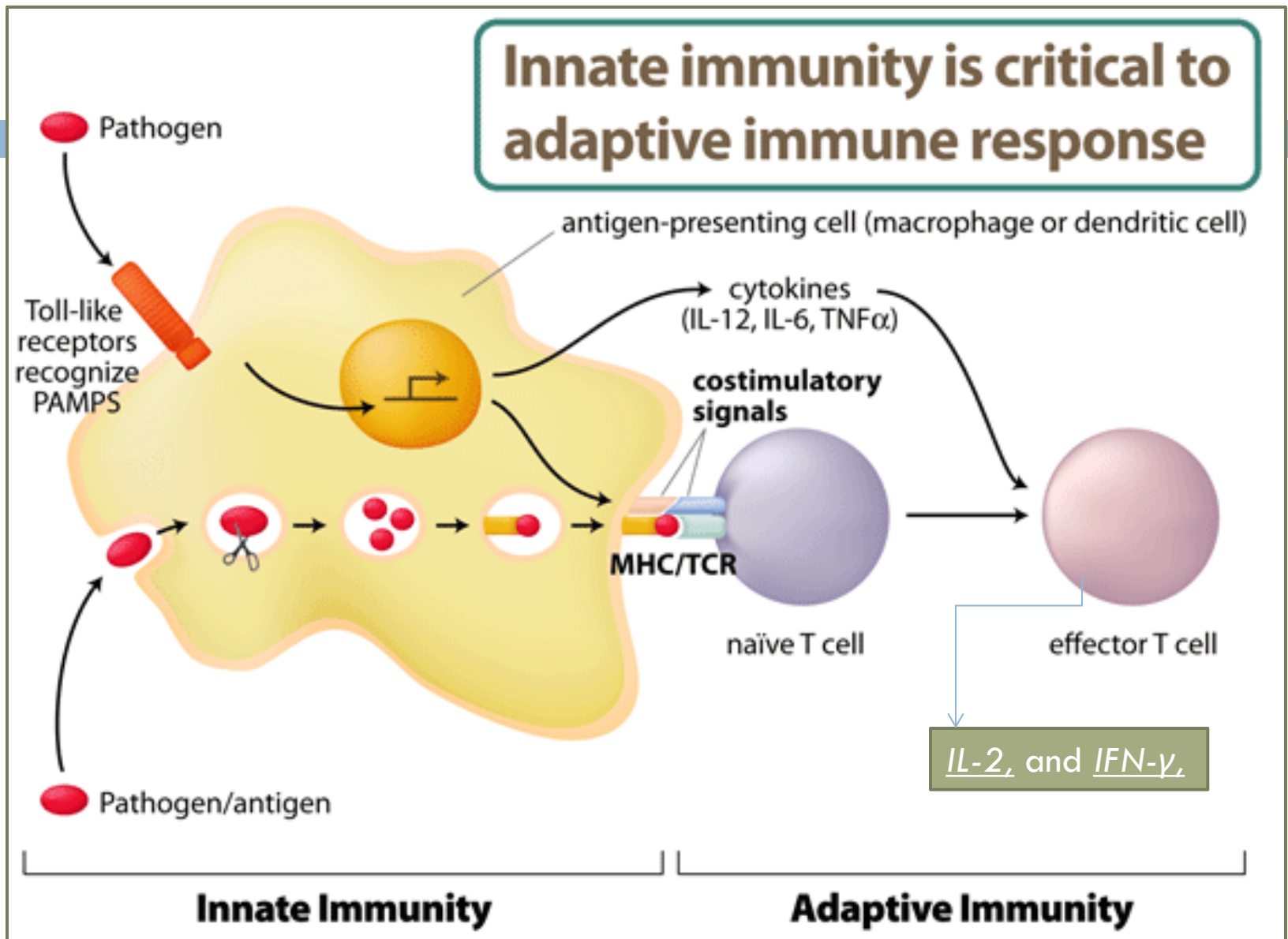
➤ deposition of a **indigestible** antigenic material

***IFN- $\gamma$***  released by the **CD4+ T cells of the  $T_H1$  subset is crucial in activating macrophages.**



Type IV hypersensitivity

# ◎ Understands the pathogenesis of granuloma formation



## ◎ Understands the pathogenesis of granuloma formation

### Epithelioid cell granulomas

1. When macrophages have successfully phagocytosed the injurious agent but it survives inside them.
2. When an active T lymphocyte-mediated cellular immune response occurs. Lymphokines produced by activated T lymphocytes inhibit migration of macrophages and cause them to aggregate in the area of injury and form granulomas.

◎ 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.

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

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

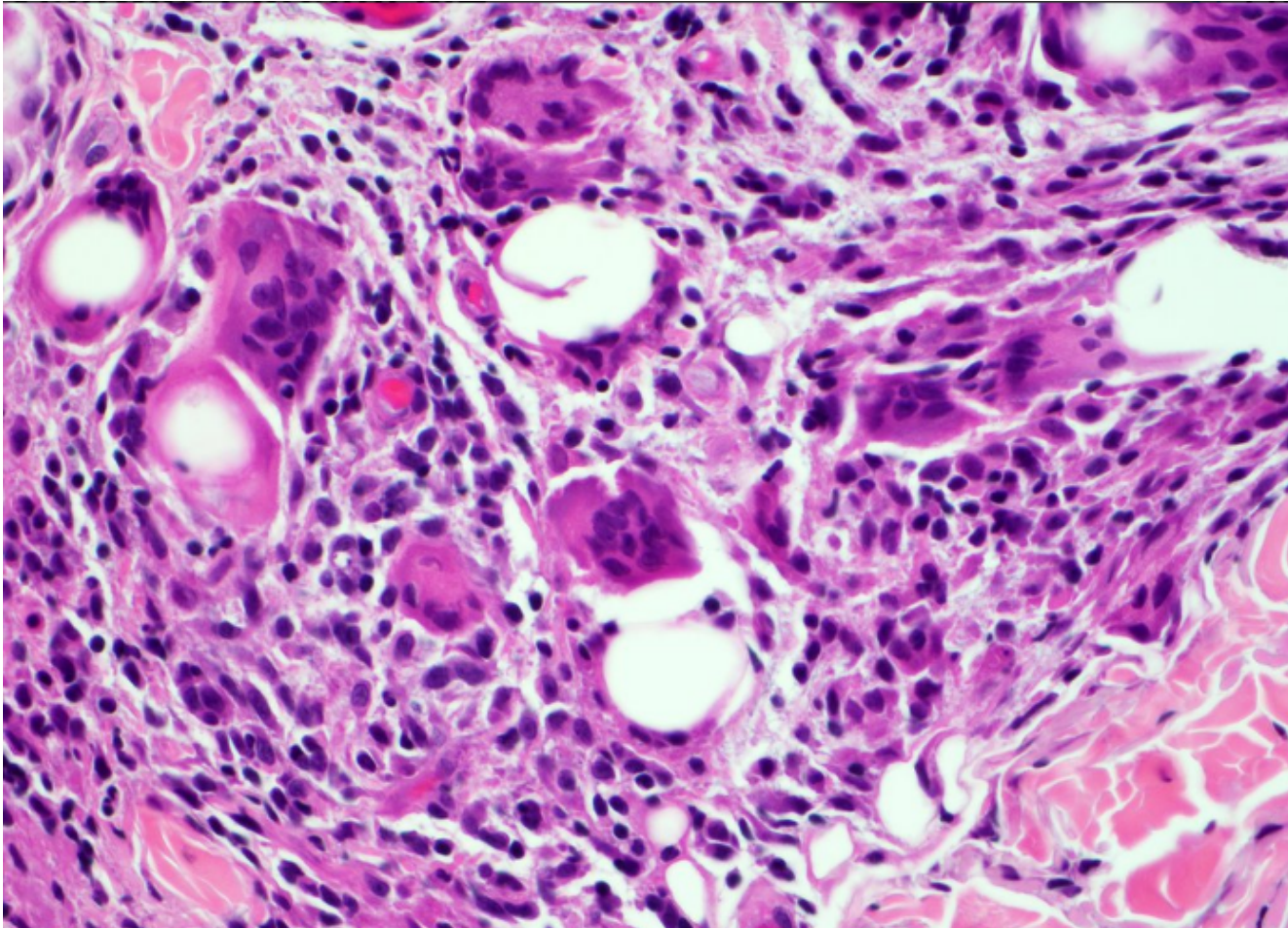
The foreign material can usually be identified in the center of the granuloma, by polarized light (appears refractile).

## Immune granuloma

are caused by insoluble particles, typically 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



# ◎ List the common causes of Granulomatous Inflammation

## Causes

### Non-immune granuloma

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

**unknown**  
Sarcoidosis  
Crohn's disease

### Immune granuloma:

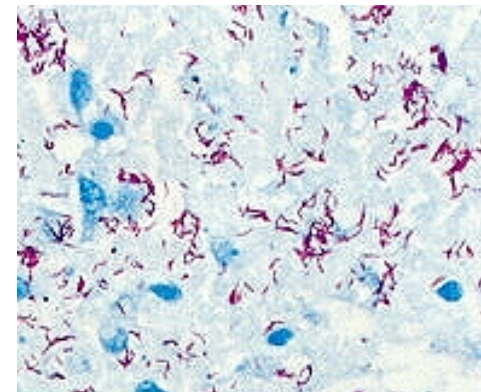
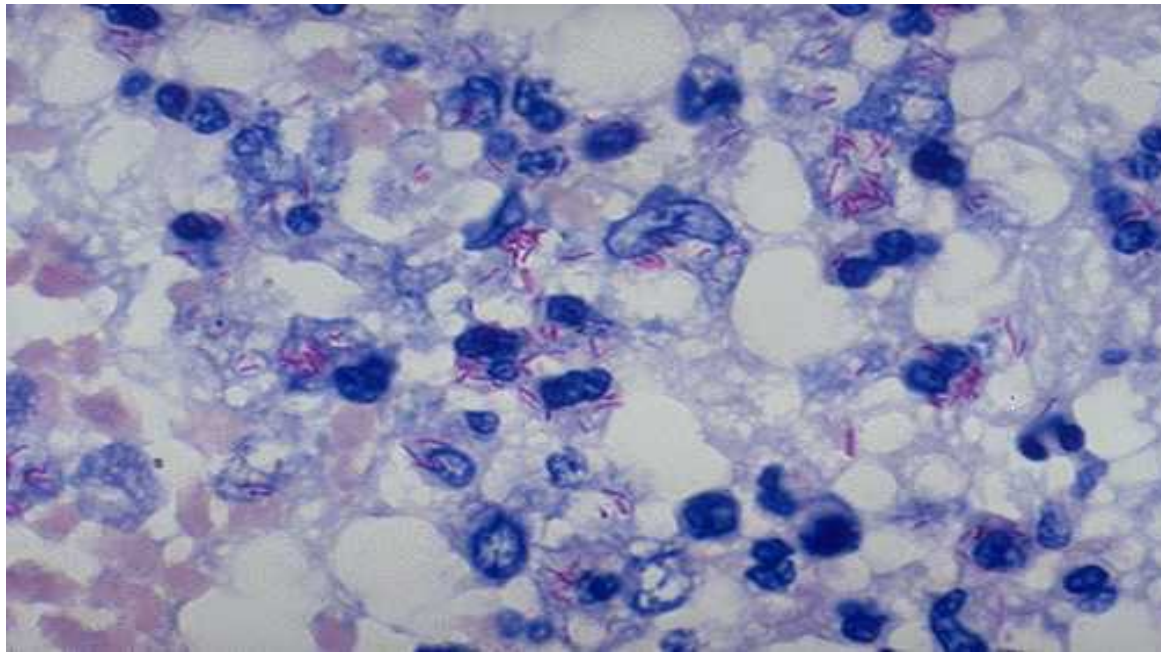
- ◎ **Bacteria**
  - **Tuberculosis**
  - **Leprosy**
  - **Actinomycosis**
  - **Cat-scratch disease**
- ◎ **Parasites**
  - **Schistosomiasis**
  - **Leishmaniasis**
- ◎ **Fungi**
  - **Histoplasmosis**
  - **Blastomycosis**
- ◎ **Metal/Dust**
  - **Berylliosis**



## ◎ List the common causes of Granulomatous Inflammation

### Tuberculosis: *Mycobacterium tuberculosis*

- 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).



## Pathogenesis of TB

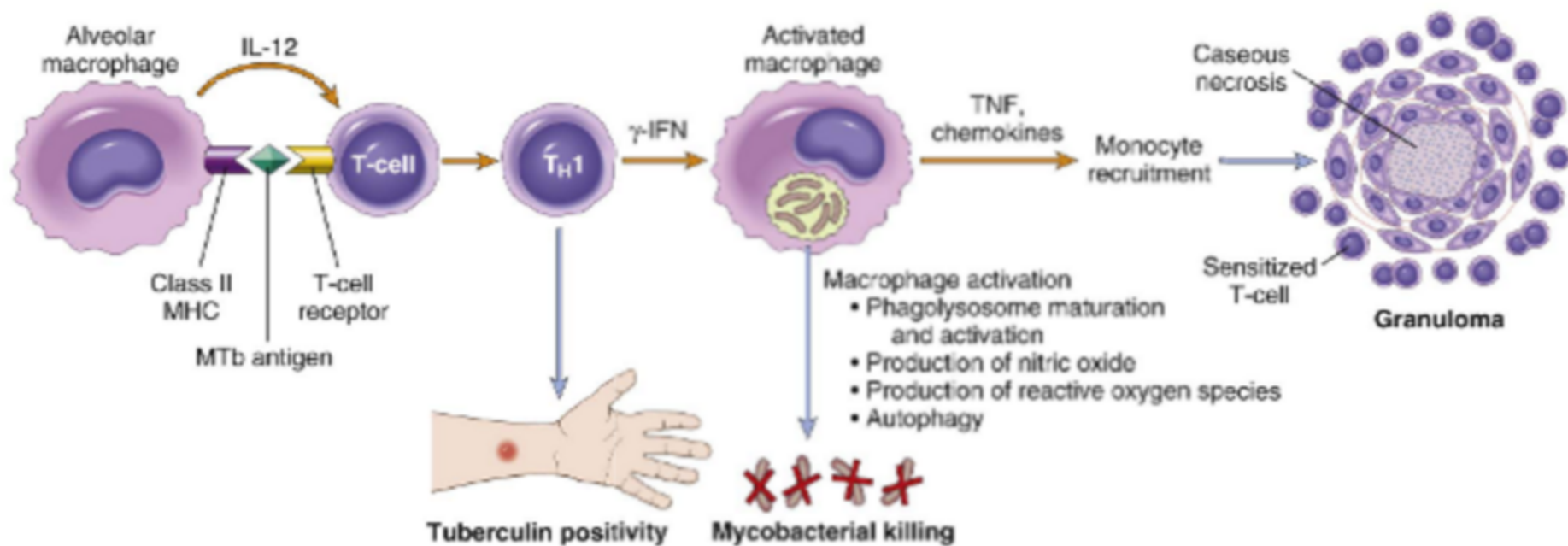
- Cord factor is a glycolipid molecule found in the cell wall of *Mycobacterium tuberculosis* and similar species.
- It protects *M. tuberculosis* from the defenses of the host and prevents fusion between phagosomal vesicles
- Cord factor presence increases the production of the cytokines interleukin-12 (IL-12), IL-1 $\beta$ , IL-6 and TNF which are all pro-inflammatory cytokines important for granuloma formation



### A. INFECTION BEFORE ACTIVATION OF CELL MEDIATED IMMUNITY



### B. INITIATION AND CONSEQUENCES OF CELL MEDIATED IMMUNITY

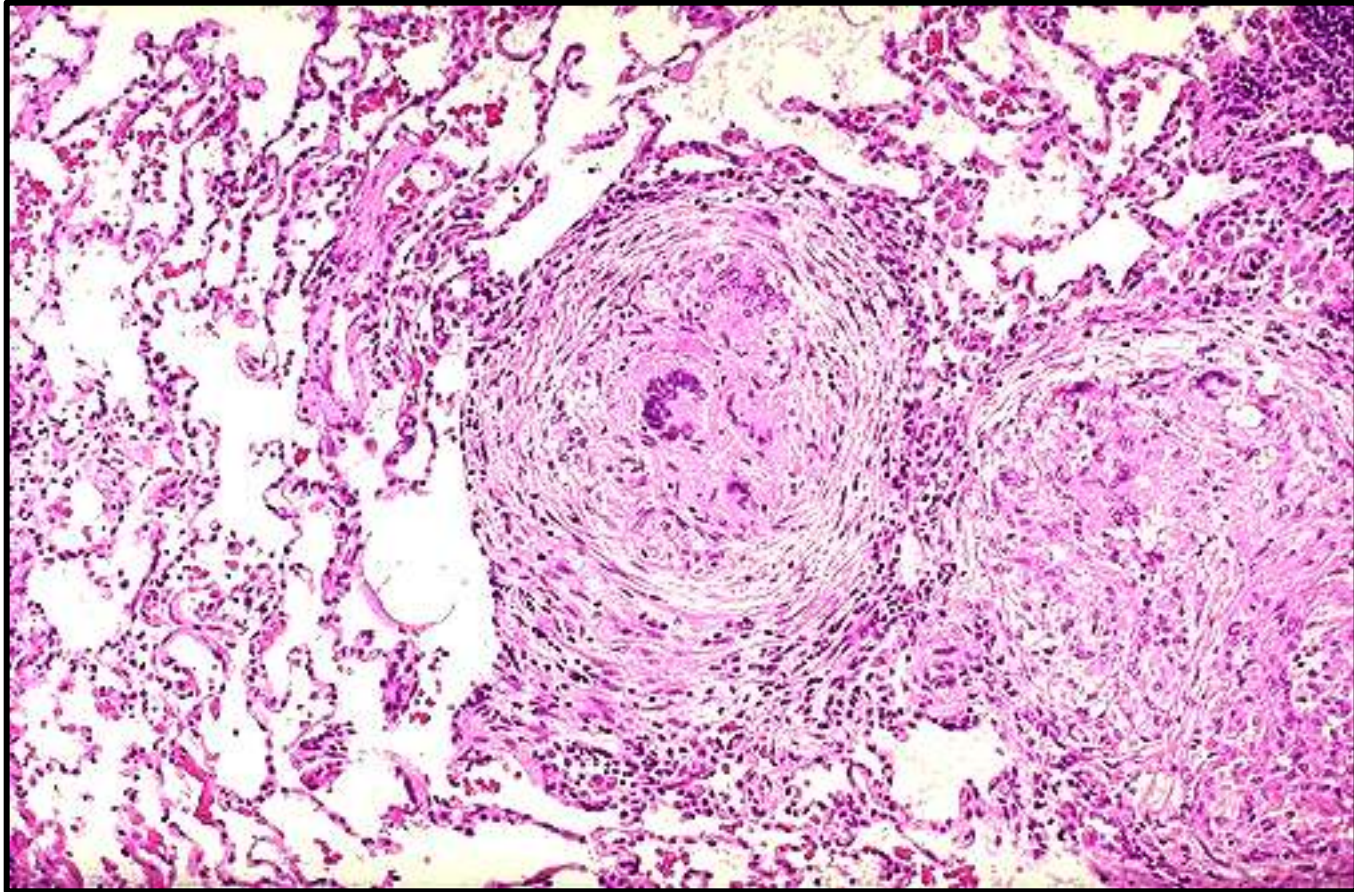


© List the common causes of Granulomatous Inflammation

# Tuberculosis

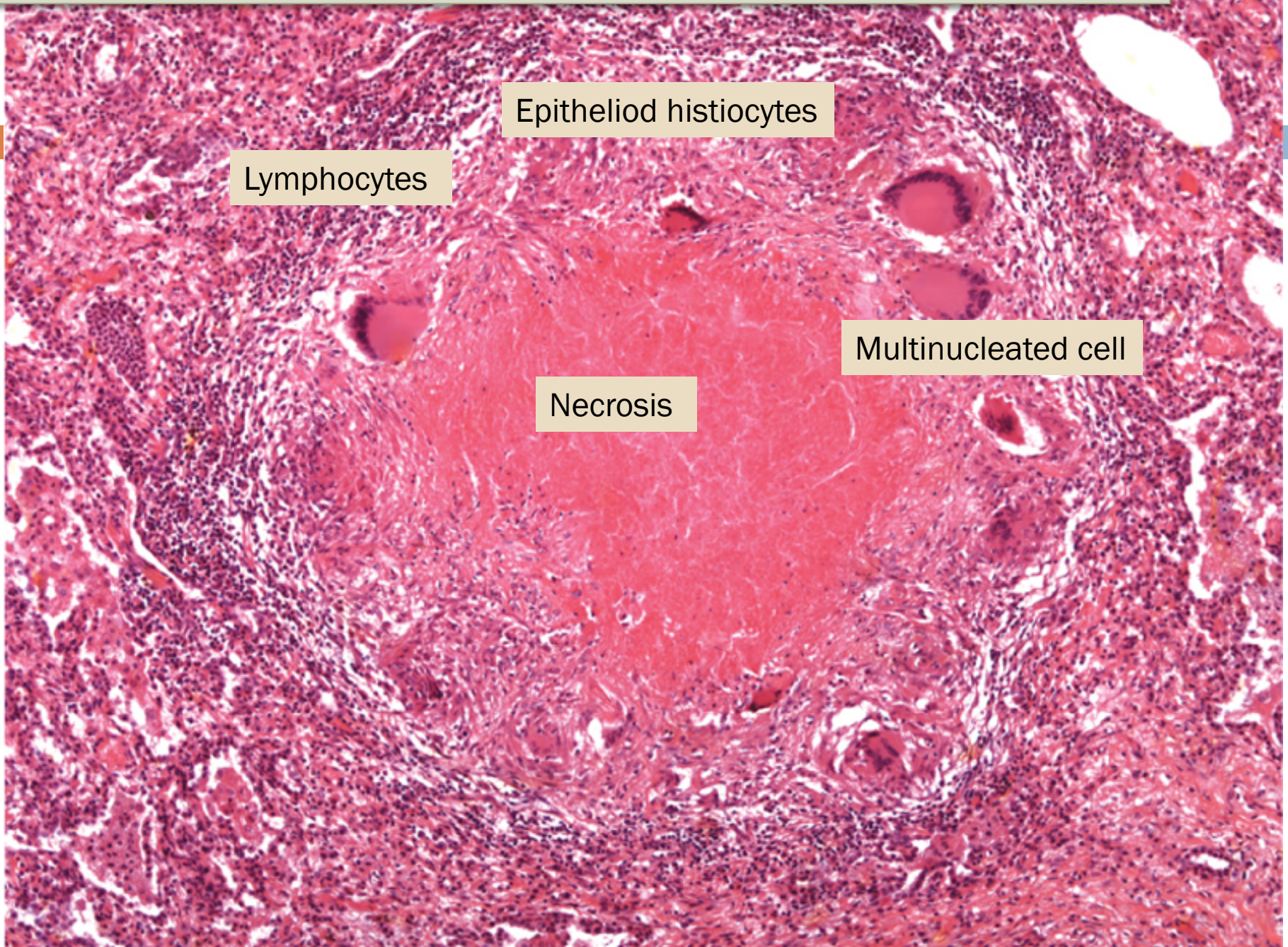


# © List the common causes of Granulomatous Inflammation





© List the common causes of Granulomatous Inflammation



Lymphocytes

Epithelioid histiocytes

Necrosis

Multinucleated cell



# Symptoms of Tuberculosis

Grey lines = Specific  
Colored lines = Overlapping

**(Established)  
pulmonary tuberculosis**

Poor appetite

**Miliary tuberculosis**

Productive cough

**Return of  
dormant  
tuberculosis**

Night sweats

Weakness

Cough with  
increasing mucus  
Coughing  
up blood

**Primary  
pulmonary  
tuberculosis**

Fever

Structural  
abnormalities

Dry cough

Weight loss

**Extrapulmonary  
tuberculosis**

*Common sites:*

**Tuberculous  
pleuritis**

Meninges

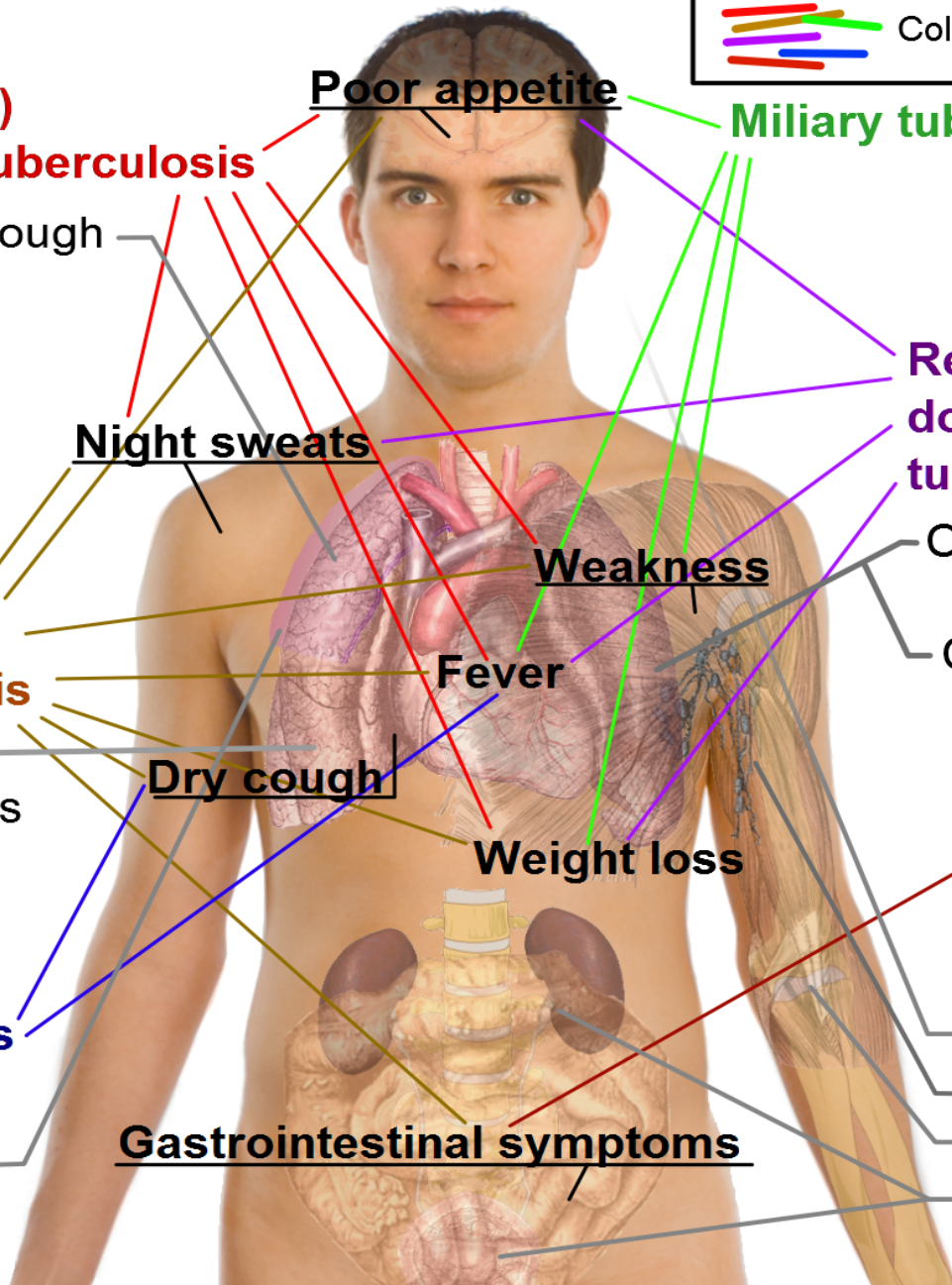
Lymph nodes

Bone and joint sites

Genitourinary tract

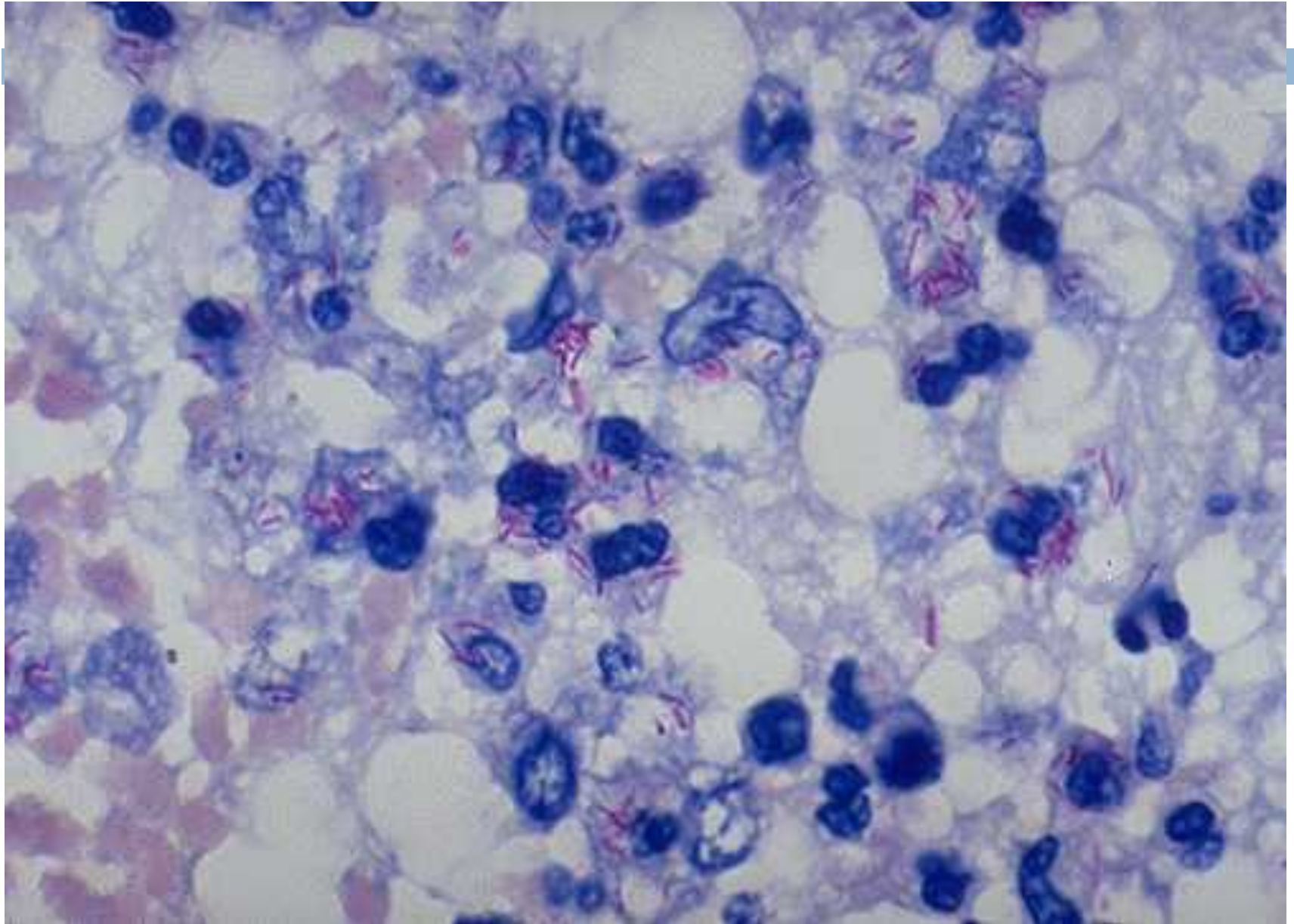
Chest pain

Gastrointestinal symptoms



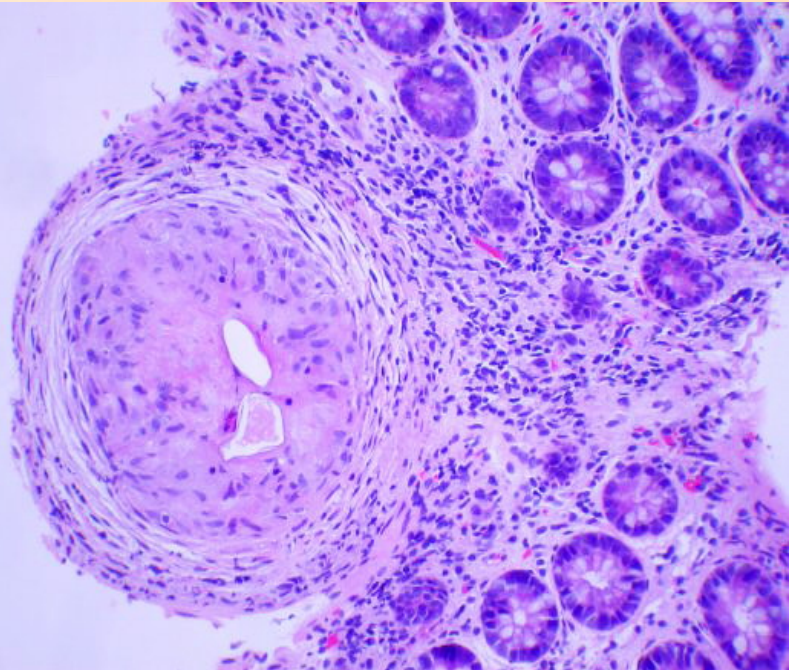
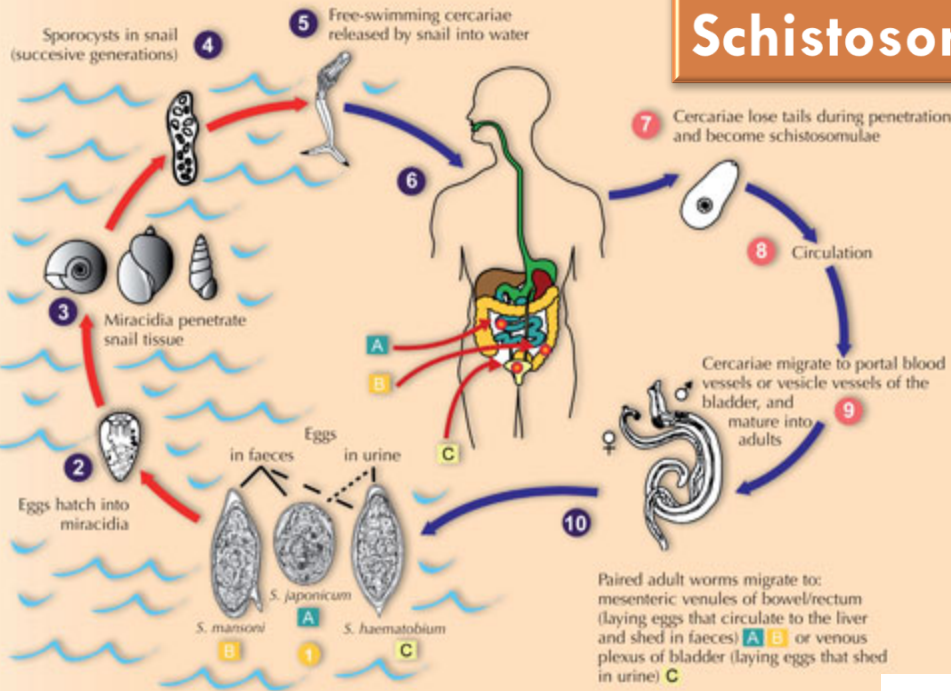
© List the common causes of Granulomatous Inflammation

Sputum , TB bacilli

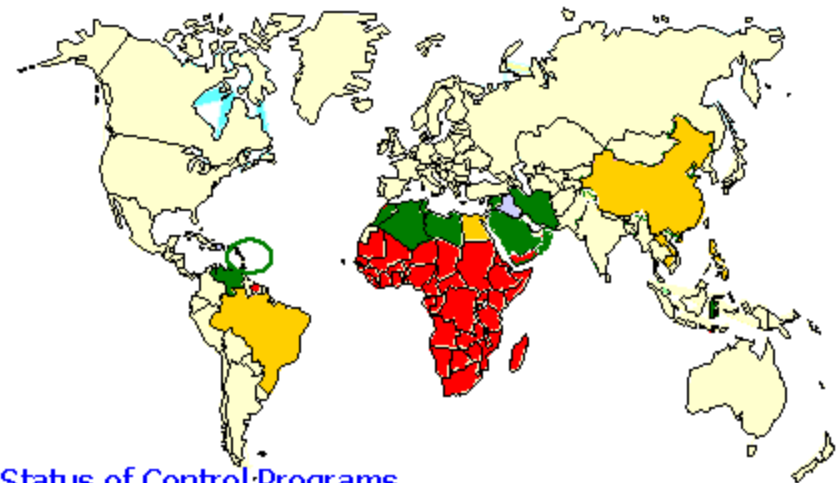




# Schistosomiasis



## Global Distribution of Schistosomiasis

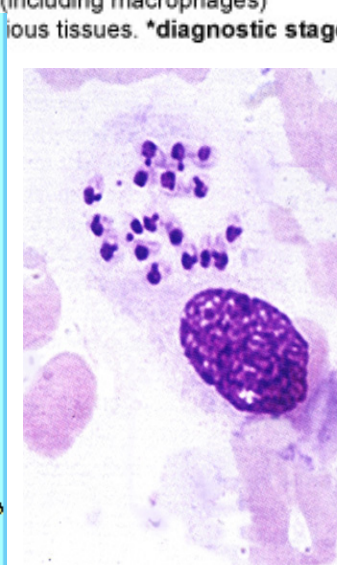
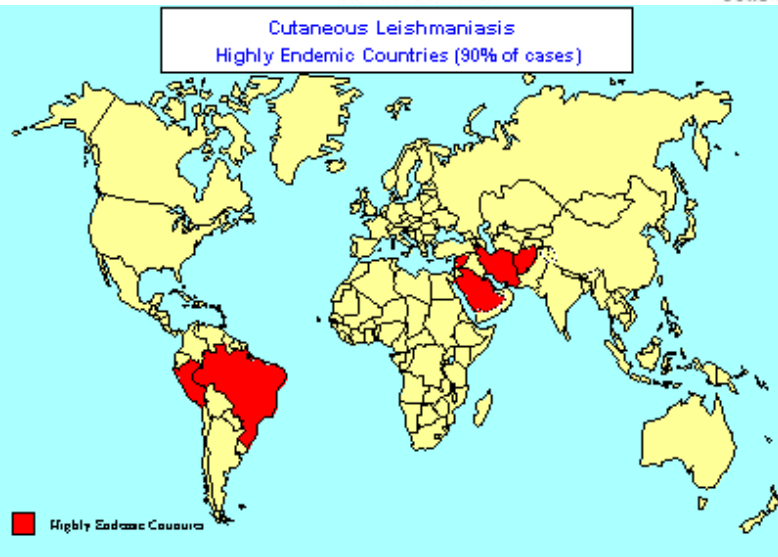
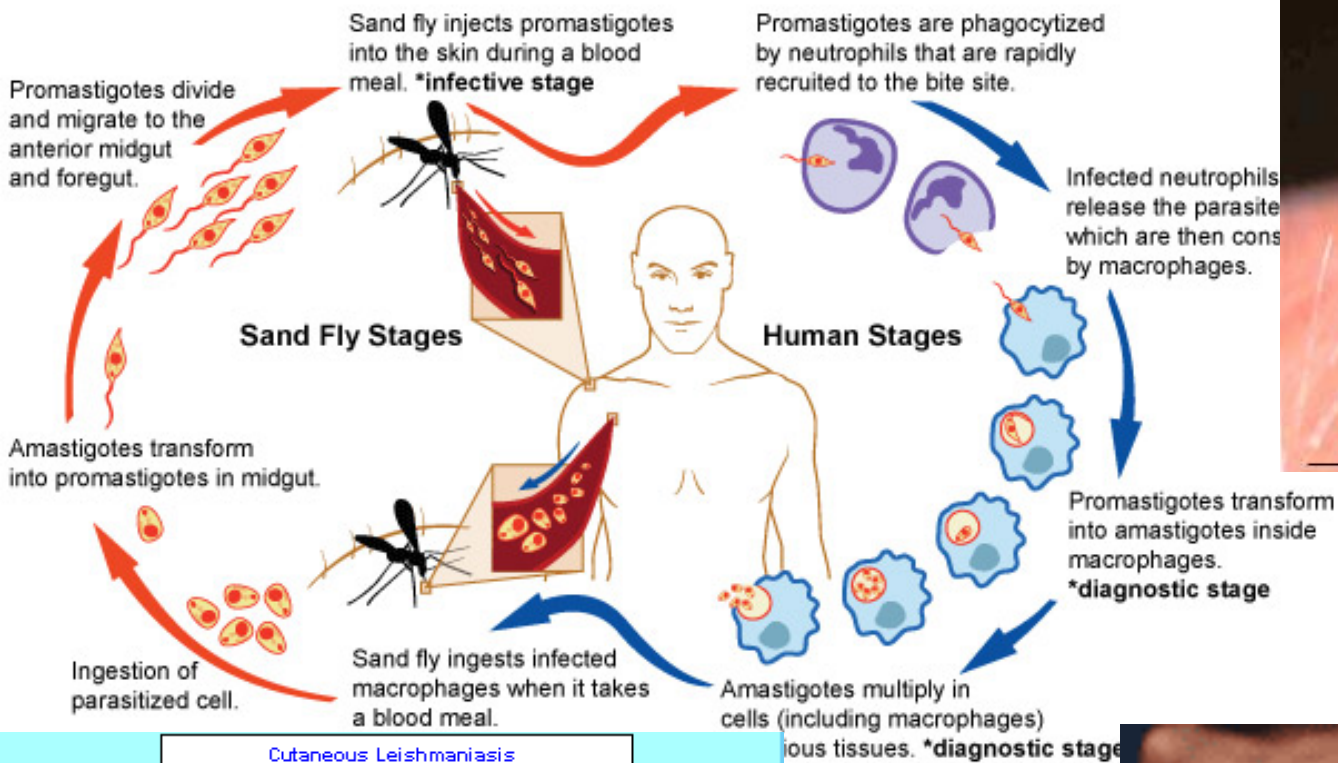


### Status of Control Programs

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

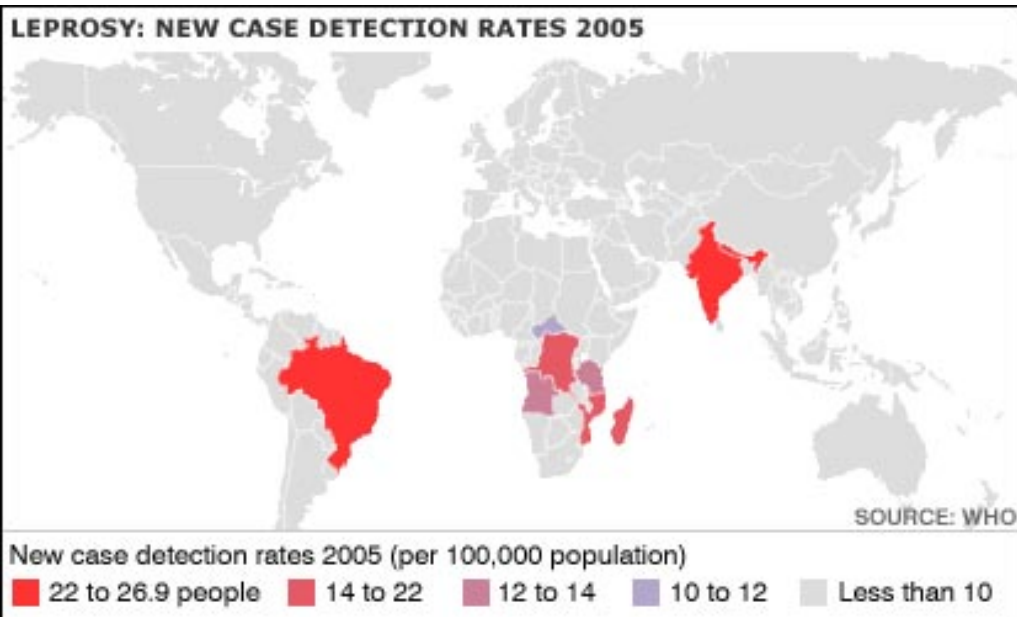


# Leishmaniasis



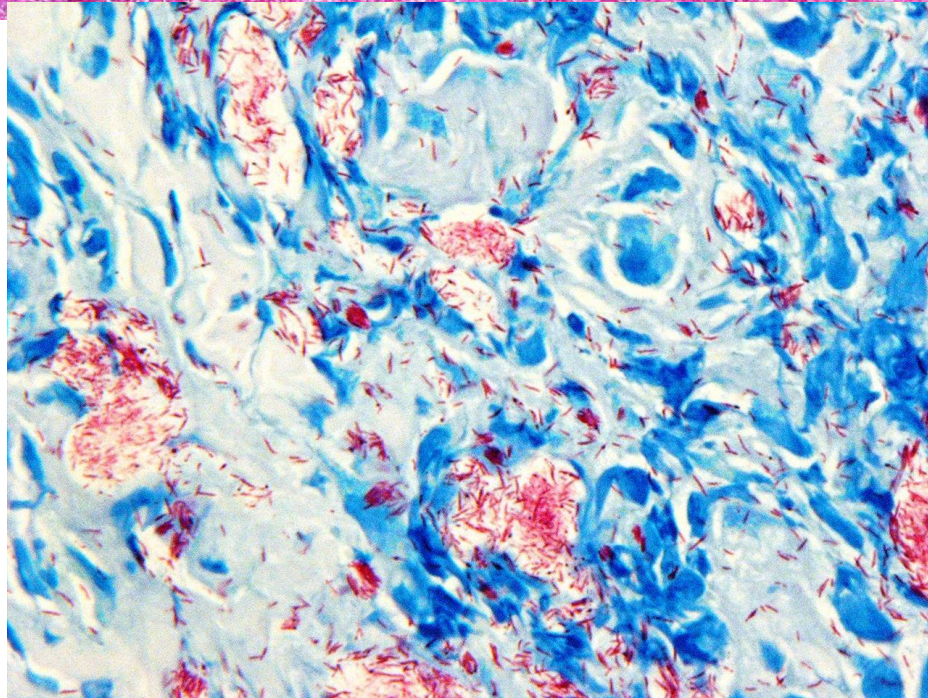
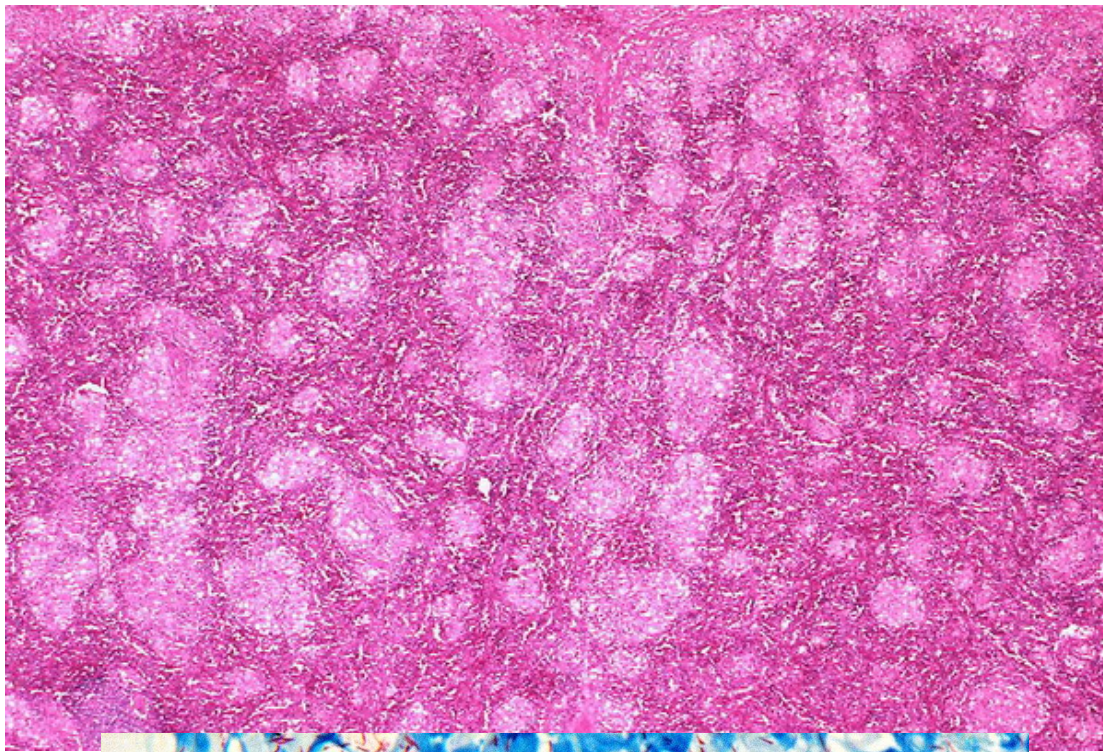


# Leprosy



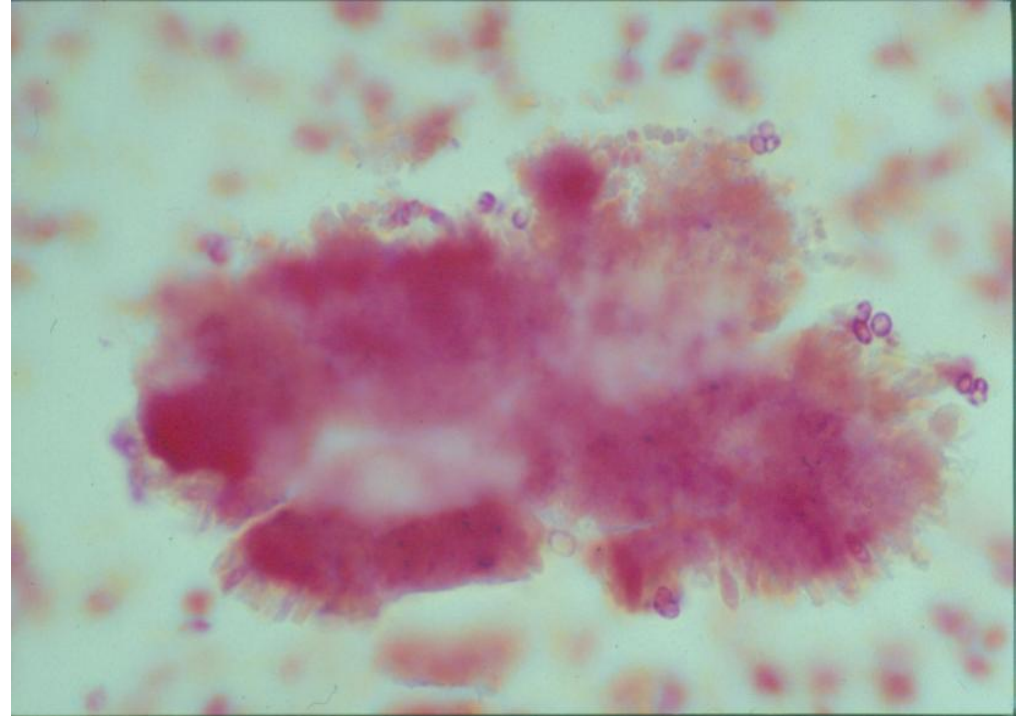
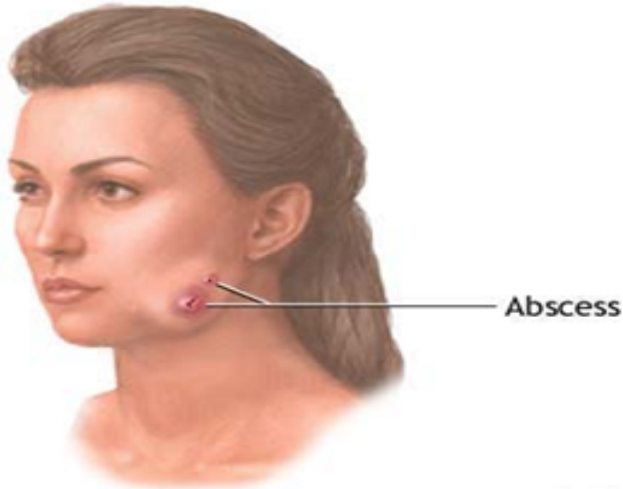


# Leprosy



## Actinomyces

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

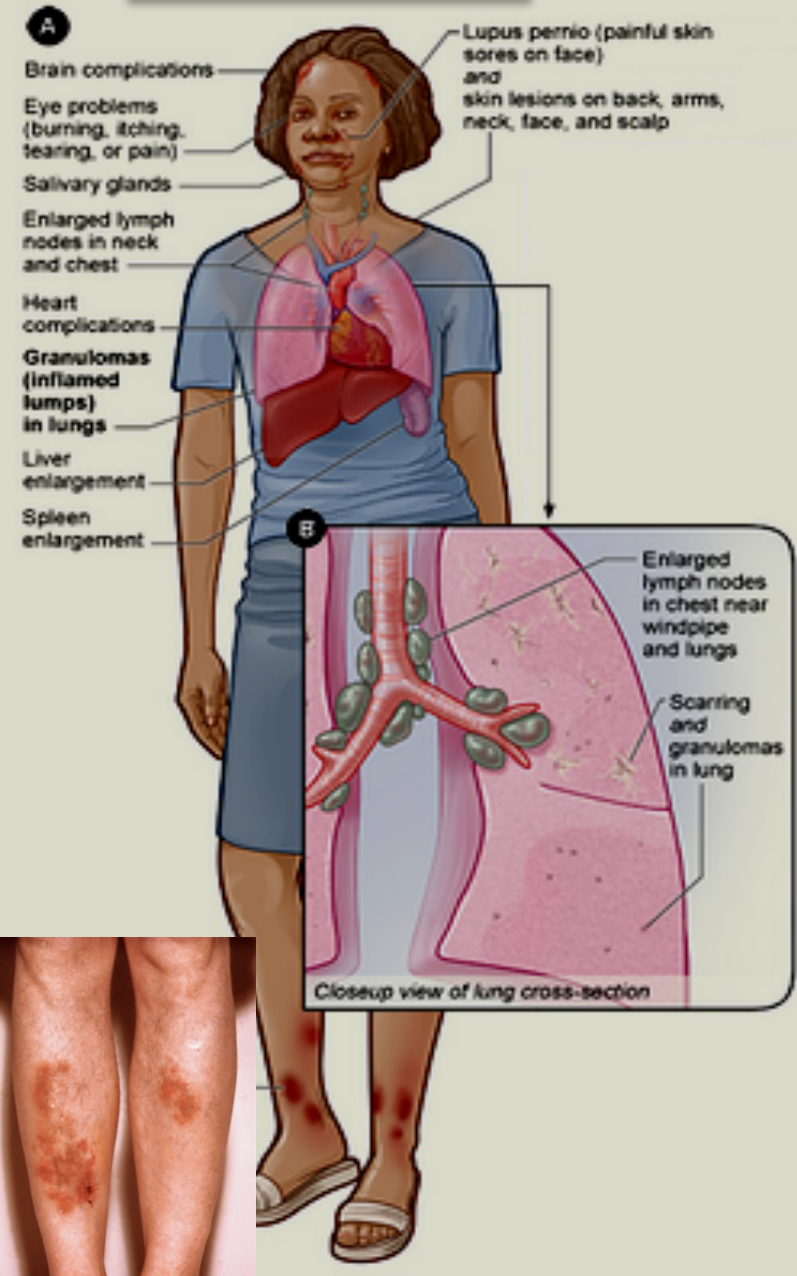


Examination of drained fluid under a microscope shows "sulfur granules" in the fluid. They are yellowish granules made of clumped organisms.

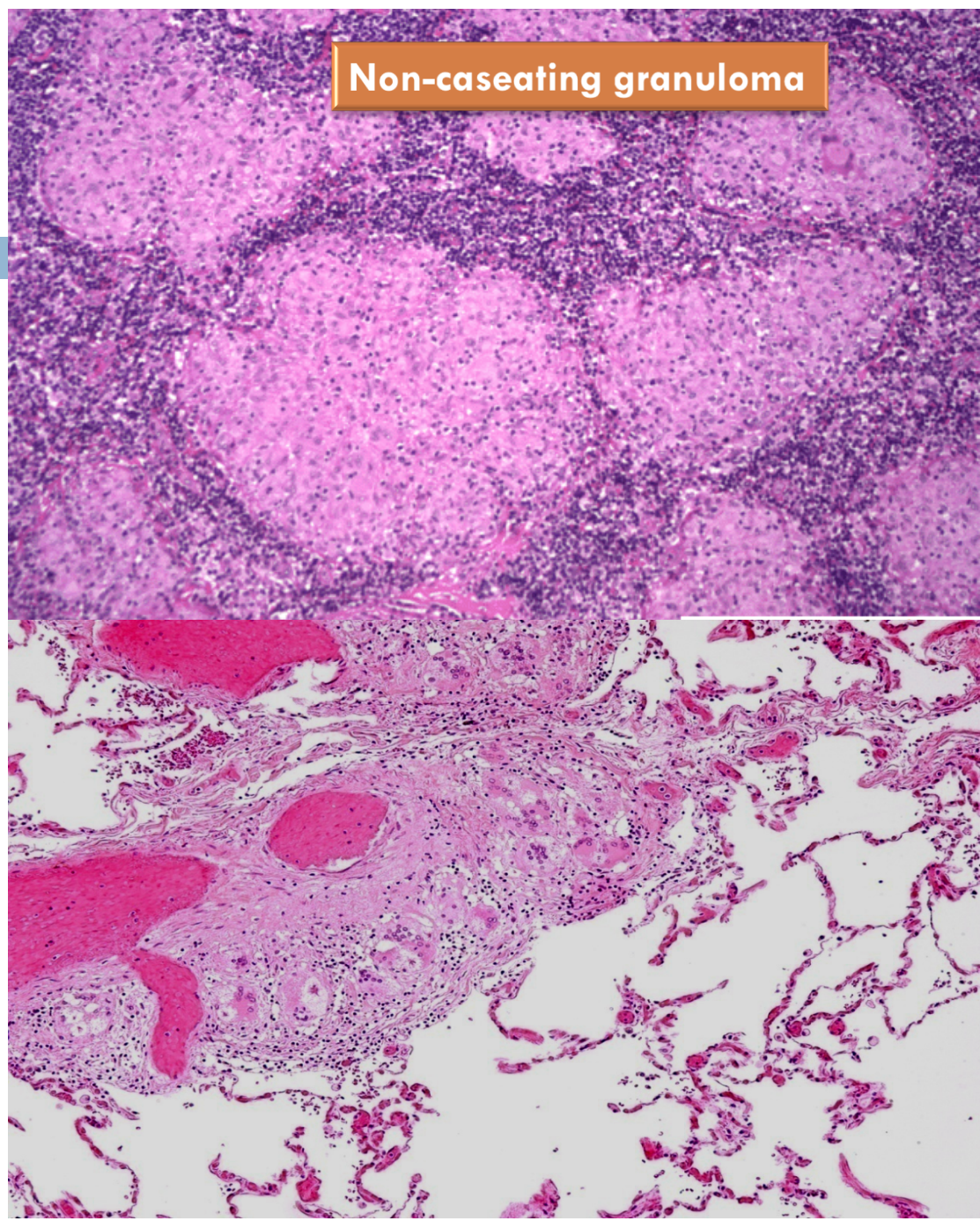
filamentous, gram-positive, non-acid-fast, anaerobic-to-microaerophilic bacteria



# Sarcoidosis



## Non-caseating granuloma



# Match A and B

**A**

- 1) The most important cell in granulomatous inflammation
- 2) A cytokines that is important in activating macrophages and transforming them into epithelioid cells
- 3) Multinucleated cell in TB
- 4) Antigen presenting cells
- 5) pathogenesis of immune type granulomatous inflammation
- 6) Microscopic finding of TB
- 7) Found in the cell wall of TB

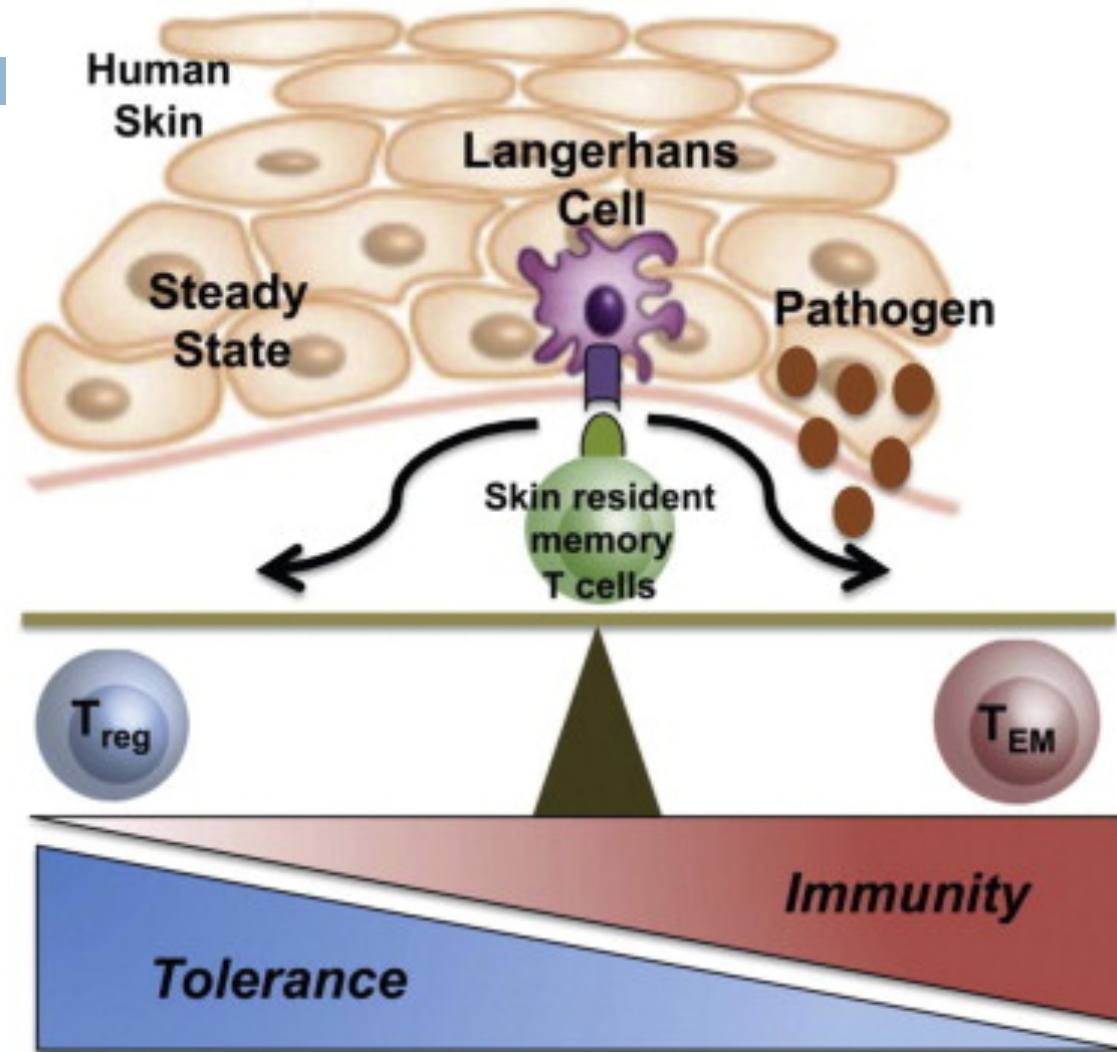
**B**

- a. **IFN- $\gamma$**
- b. **Langhans cells**
- c. **Epithelioid histiocytes**
- d. **Cord factor**
- e. **Langerhan's cells**
- f. **Type IV hypersensitivity reaction**
- 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.
- Granulomata 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 disease