

GRANULOMATOUS INFLAMMATION

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OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT:

Upon completion of this lecture, the student should:

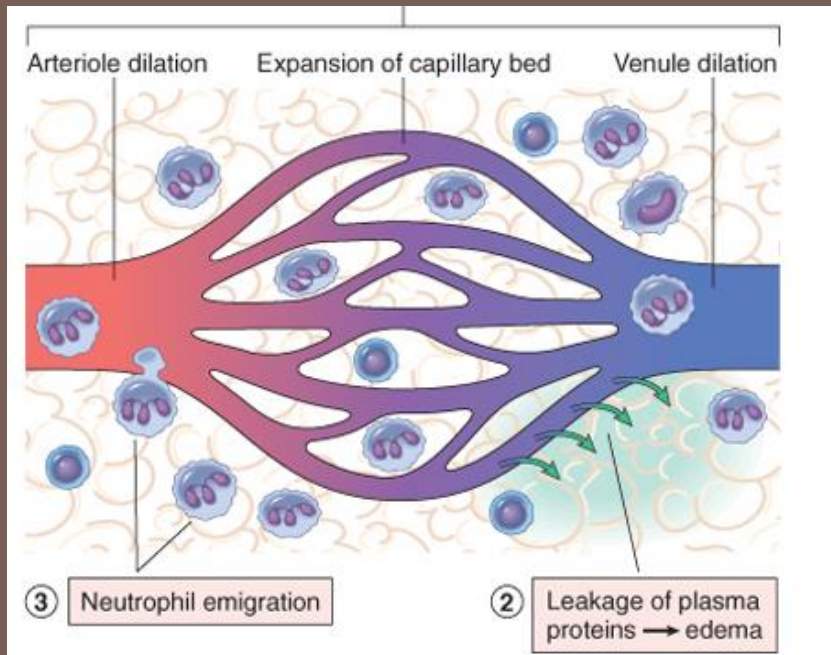
- **Define Granulomatous inflammation.**
- **Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance.**
- **Understands the pathogenesis of granuloma formation.**
- **Identify the two types of granulomas, which differ in their pathogenesis.**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

Define Granulomatous inflammation.

Inflammation

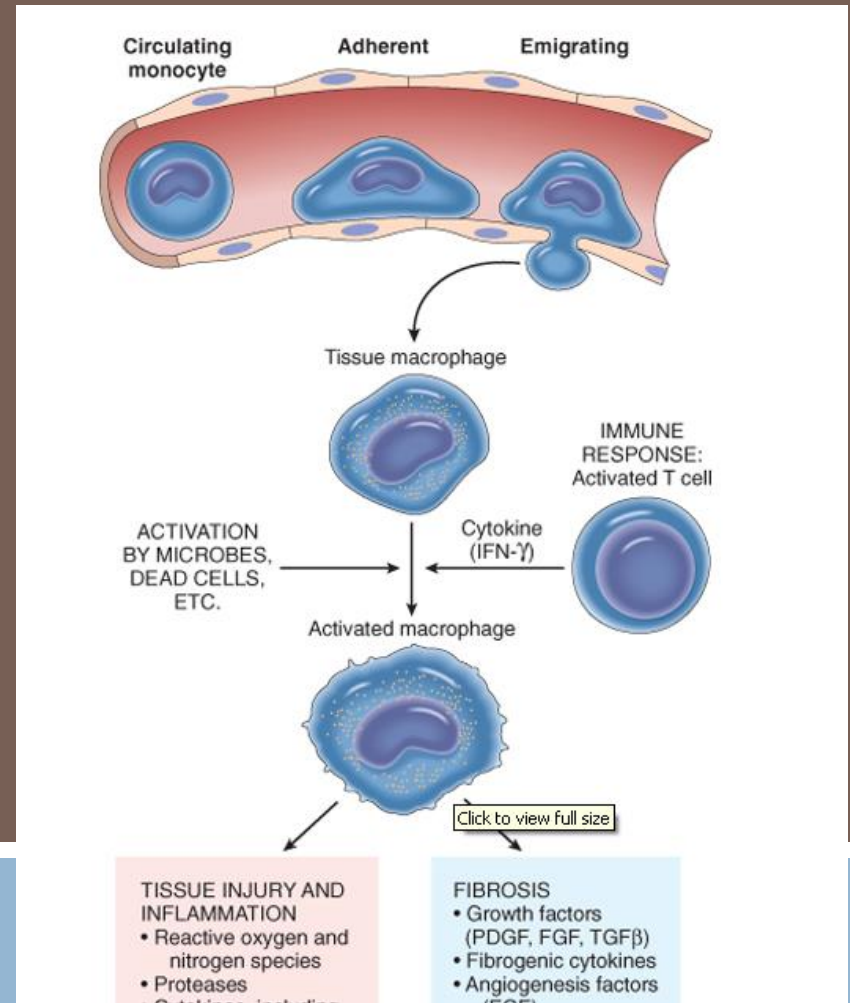
Acute inflammation

Neutrophils



Chronic inflammation

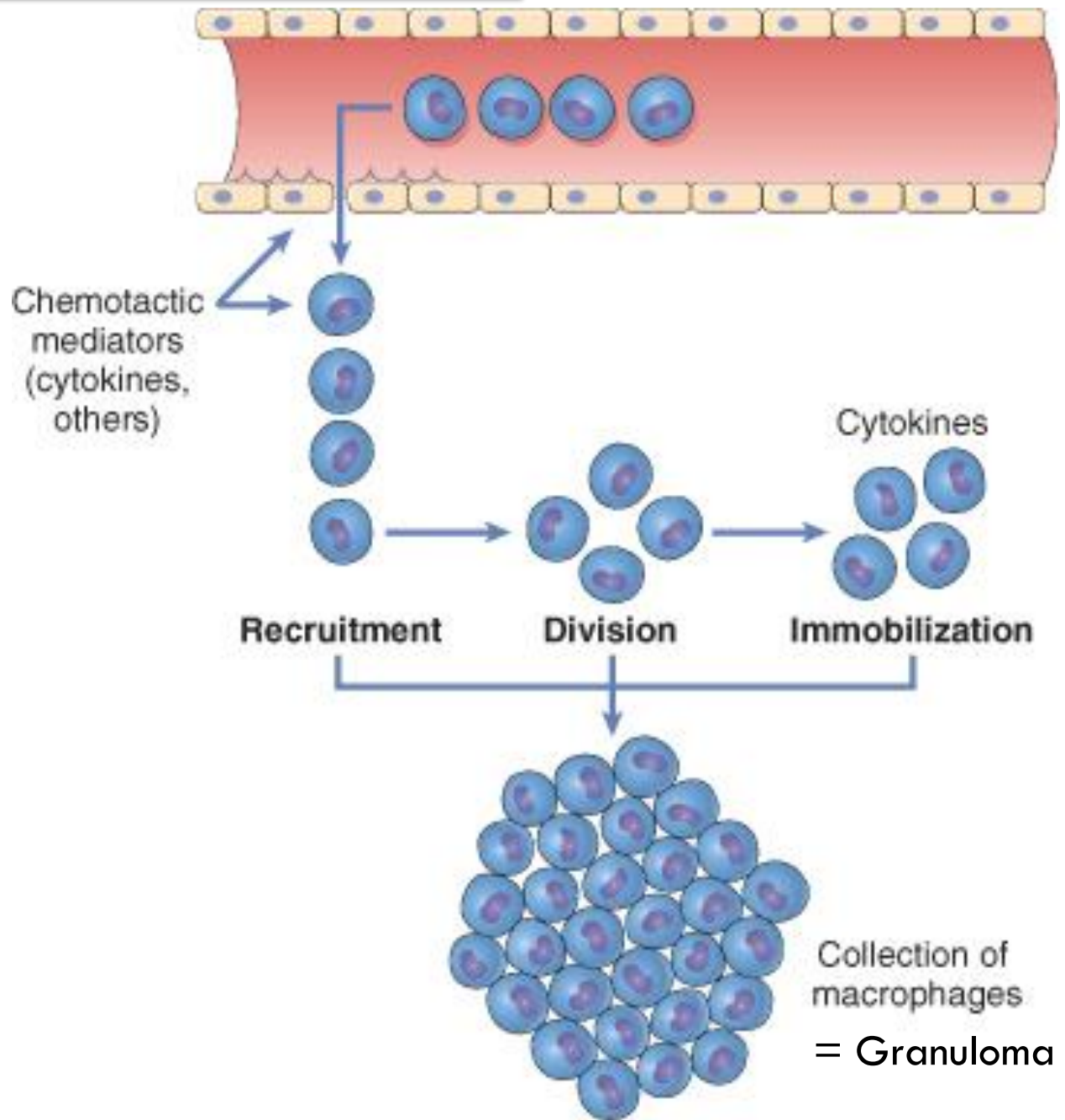
Macrophage, Lymphocytes & Plasma cells



GRANULOMATOUS INFLAMMATION

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

© Define Granulomatous inflammation.

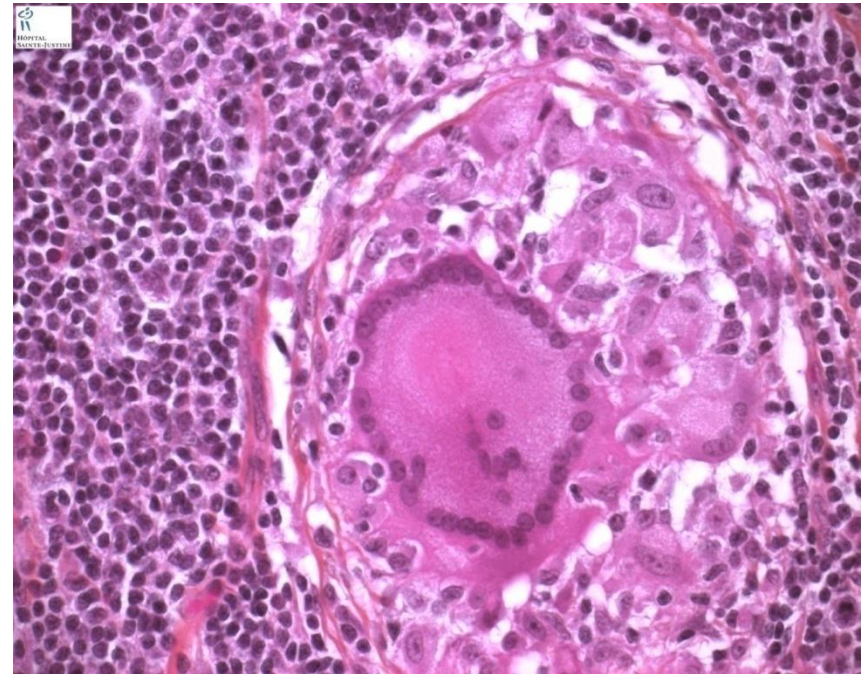
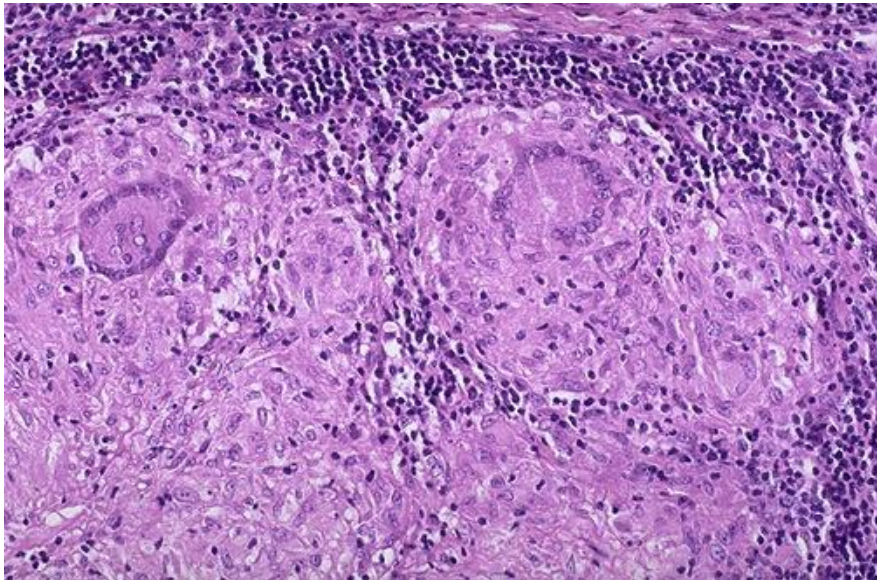


Why is it important?

- 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

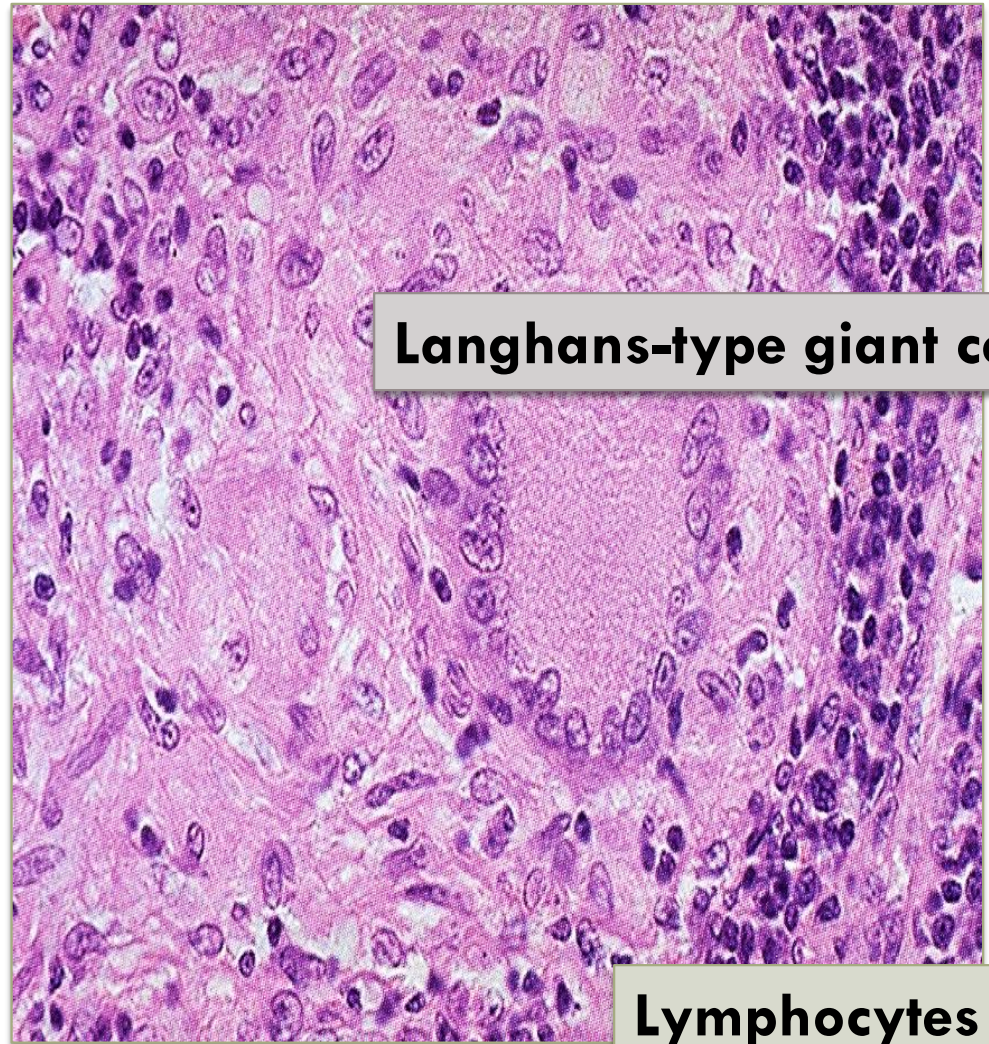
- Granuloma = Nodular collection of epithelioid macrophages surrounded by a rim of lymphocytes
- Epithelioid macrophages: squamous cell-like appearance



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

**microscopic aggregation
of activated
macrophages**

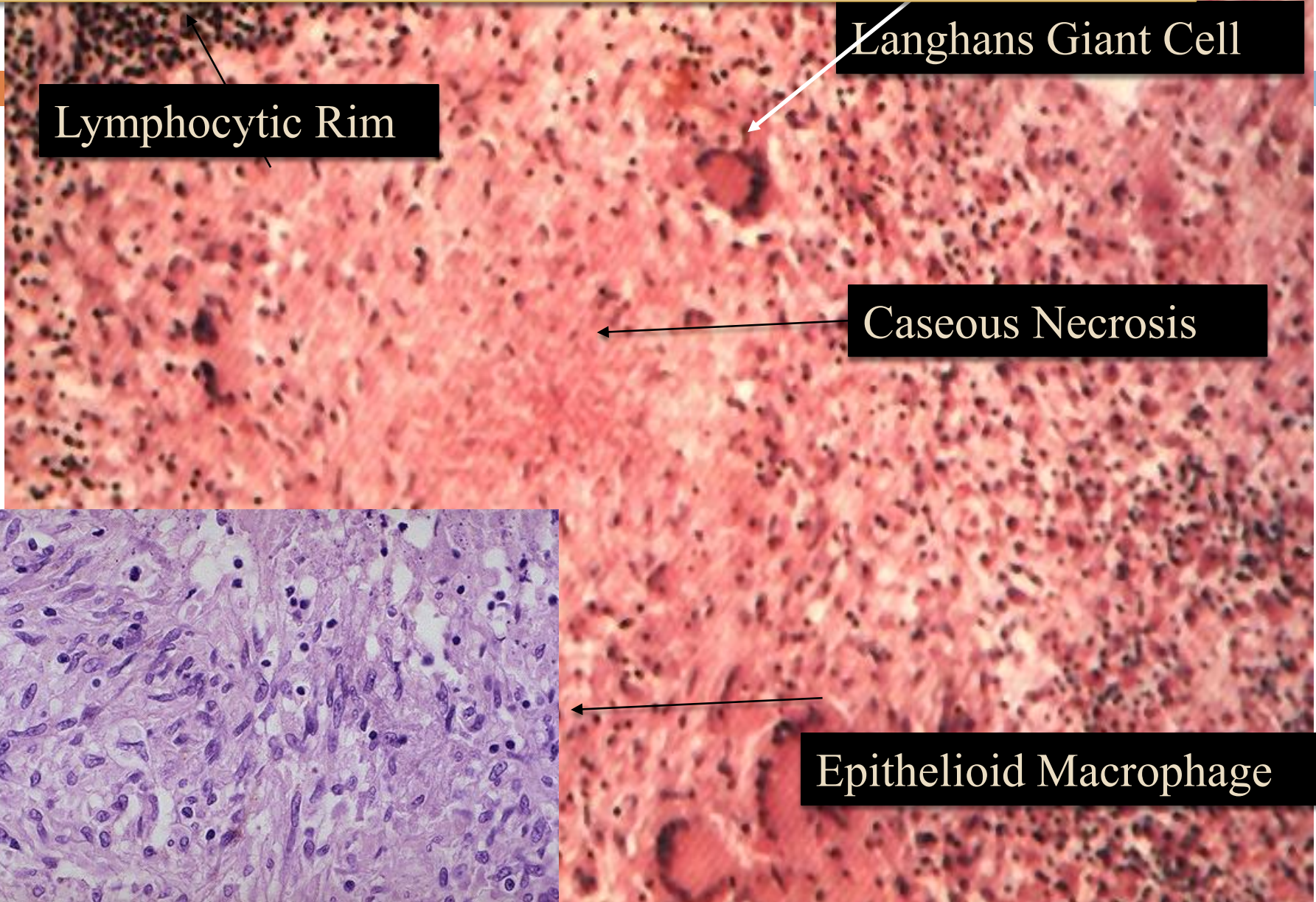
Granuloma



Langhans-type giant cell

Lymphocytes

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



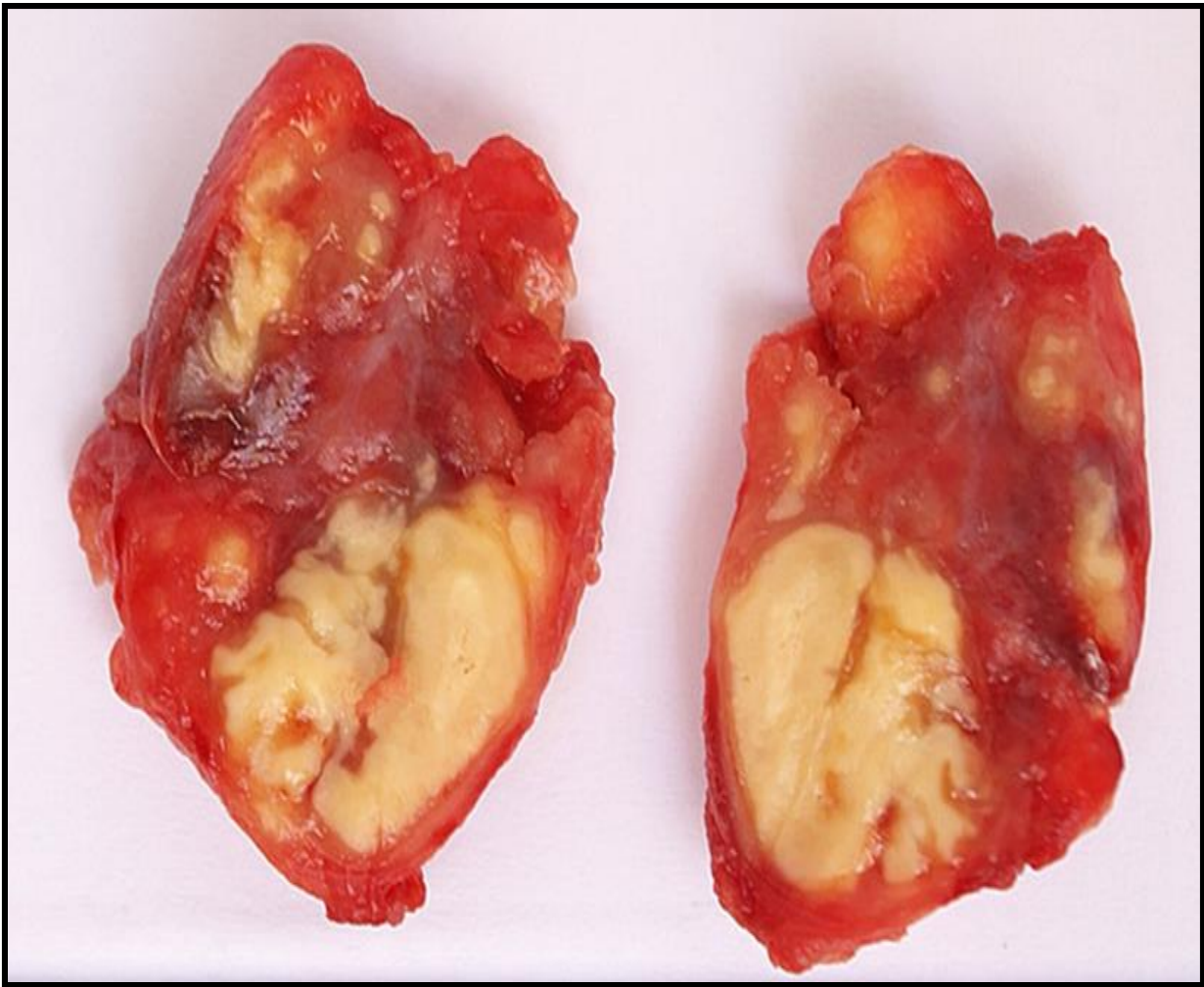
Lymphocytic Rim

Langhans Giant Cell

Caseous Necrosis

Epithelioid Macrophage

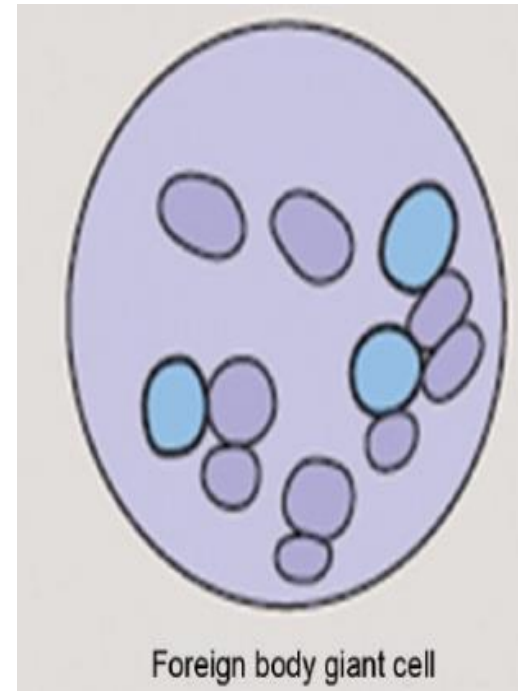
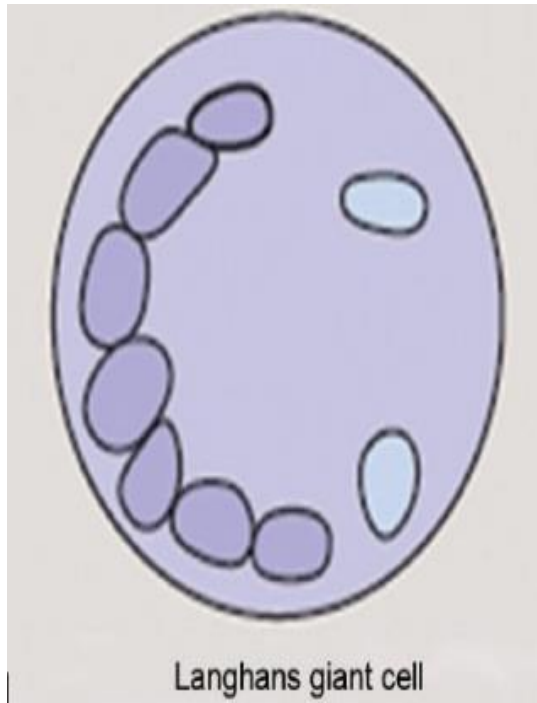
Recognize the morphology of granulomas



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.

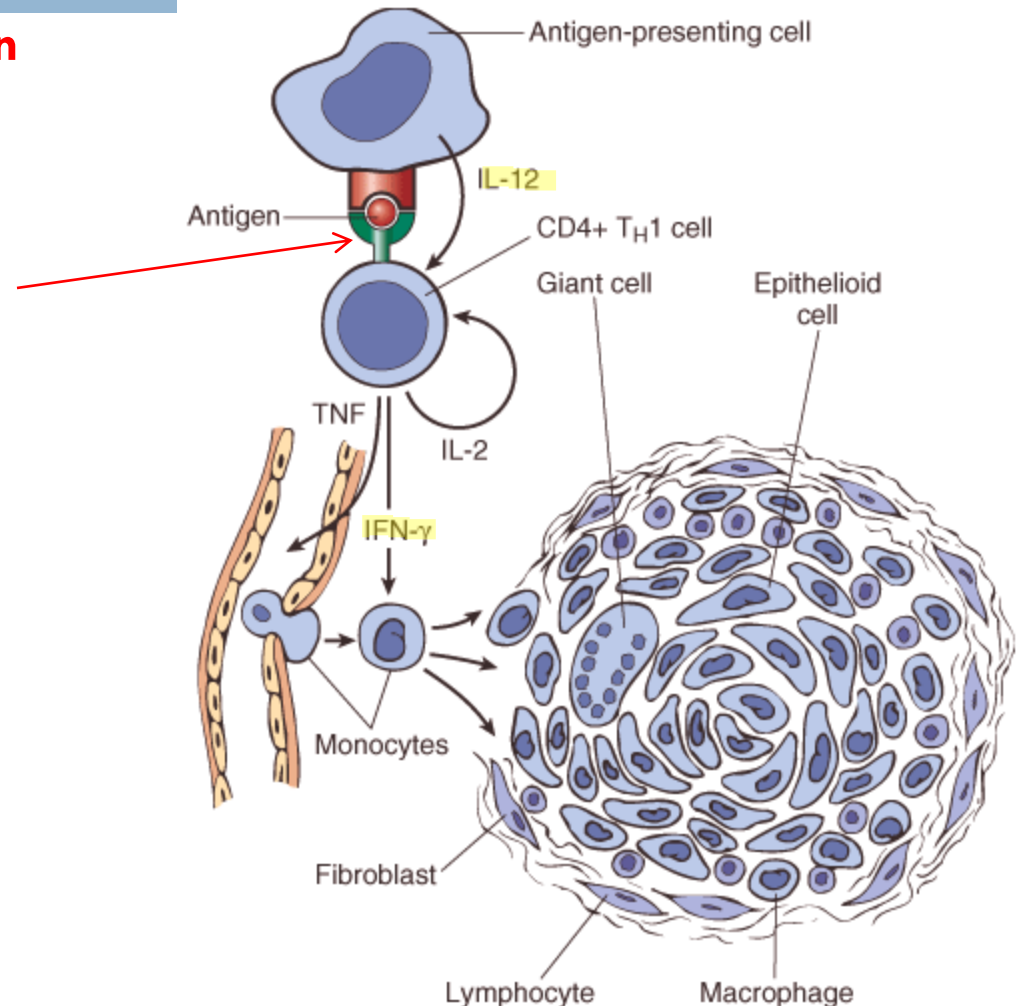
◎ Understands the pathogenesis of granuloma formation

Granulomatous Inflammation Mechanism

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

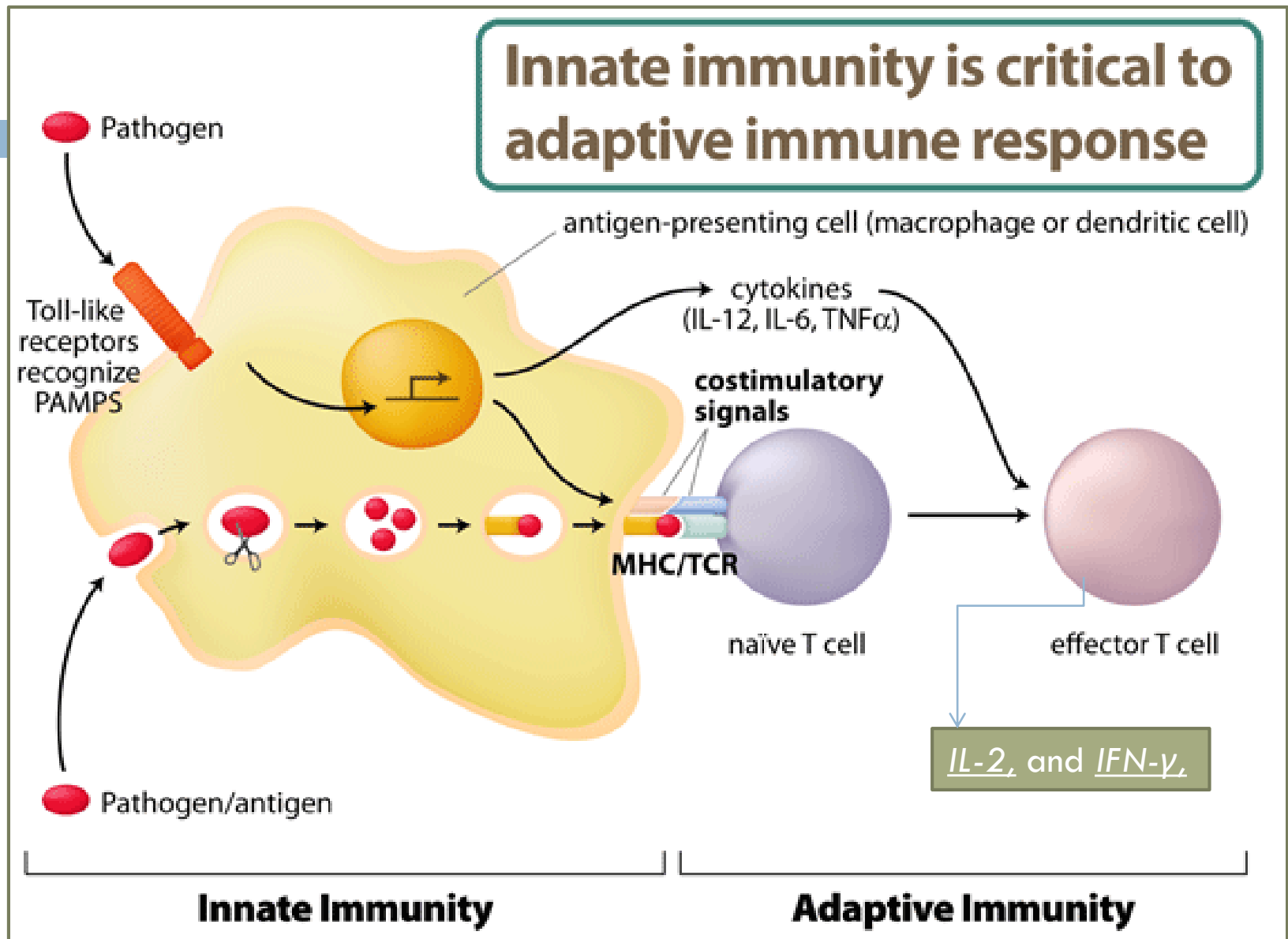
➤ deposition of a **indigestible** antigenic material

IFN- γ 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.**

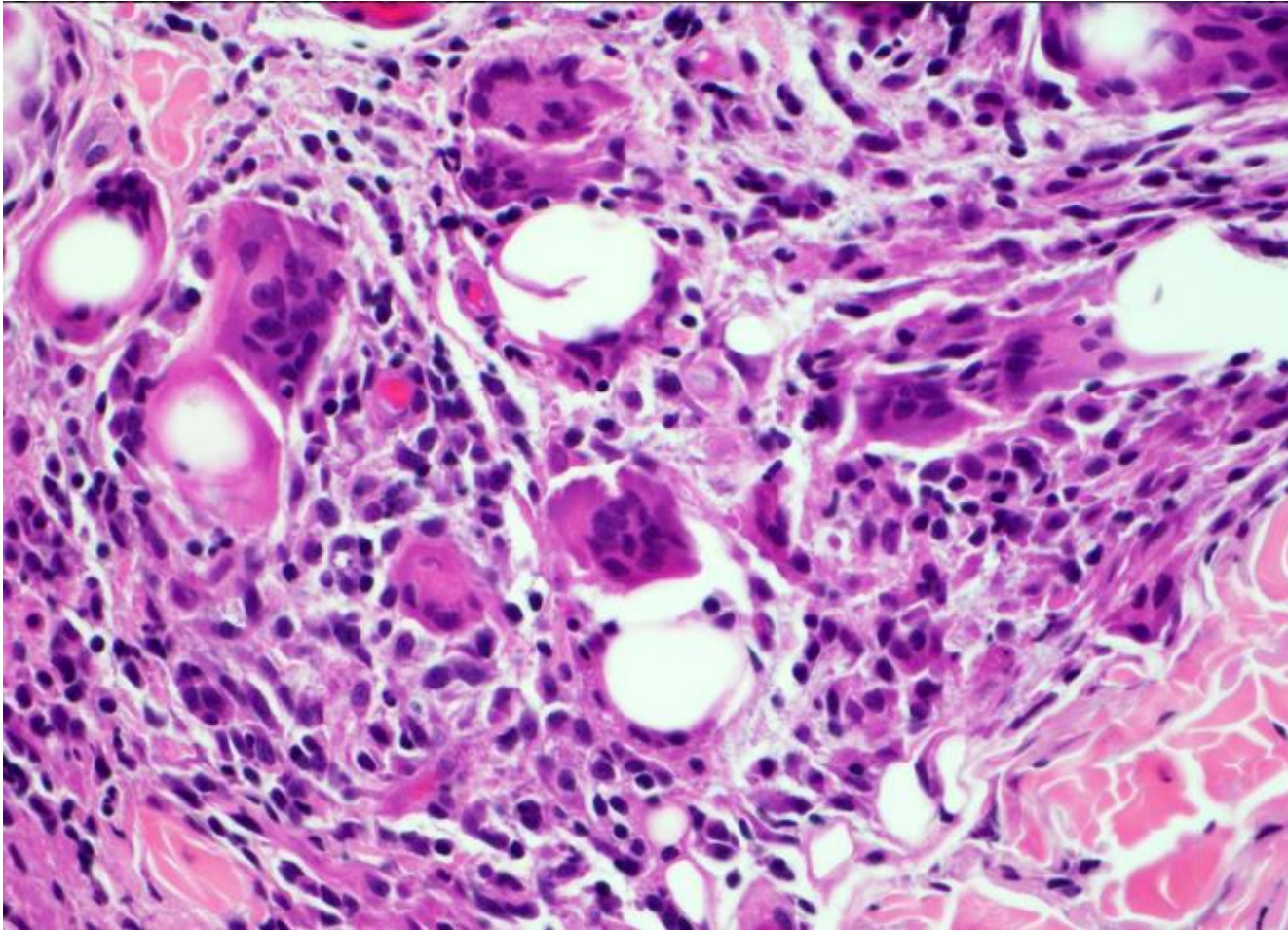
The foreign material can usually be identified in the center of the granuloma, by polarized light (appears refractile).

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

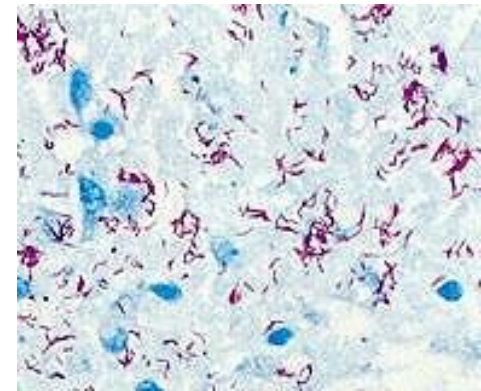
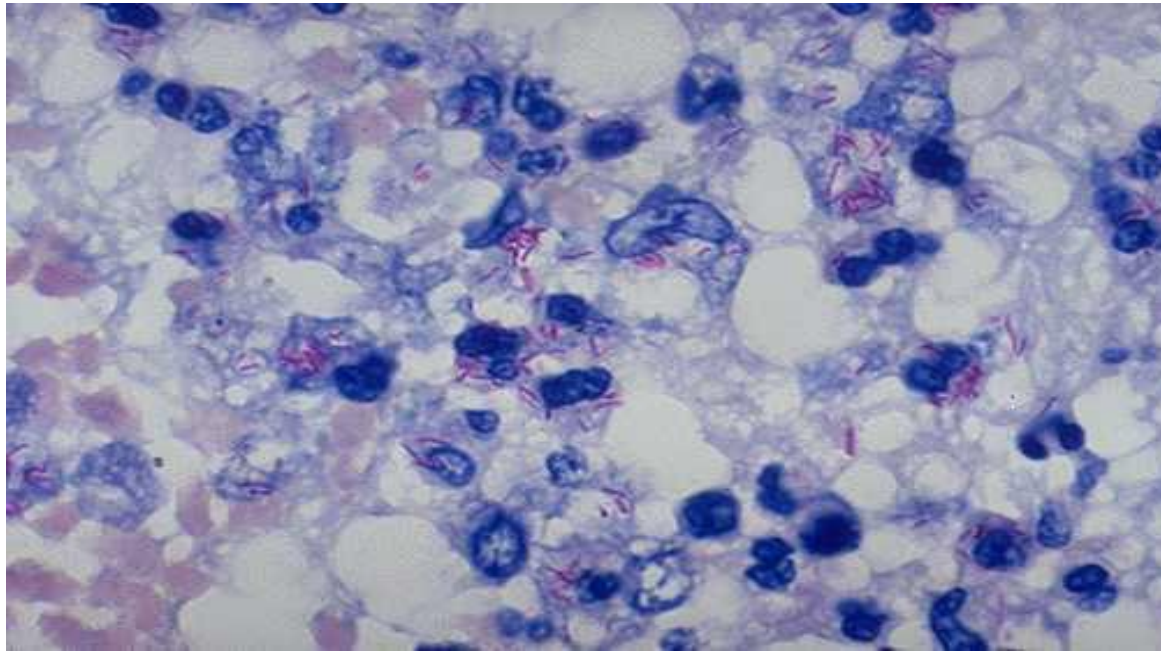
Immune granuloma:

- ◎ **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*

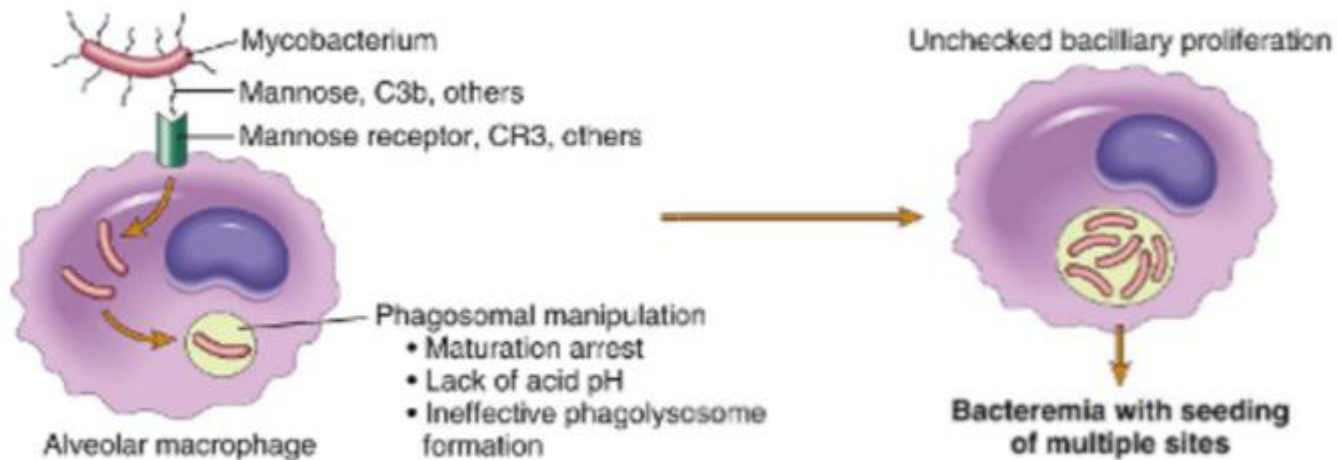
- Mycobacteria – ‘fungus like..
- slender rods
- acid fast bacilli [AFB] (i.e., they have a high content of complex lipids that readily bind the Ziehl-Neelsen [carbol fuchsin] stain and subsequently resist decolorization).



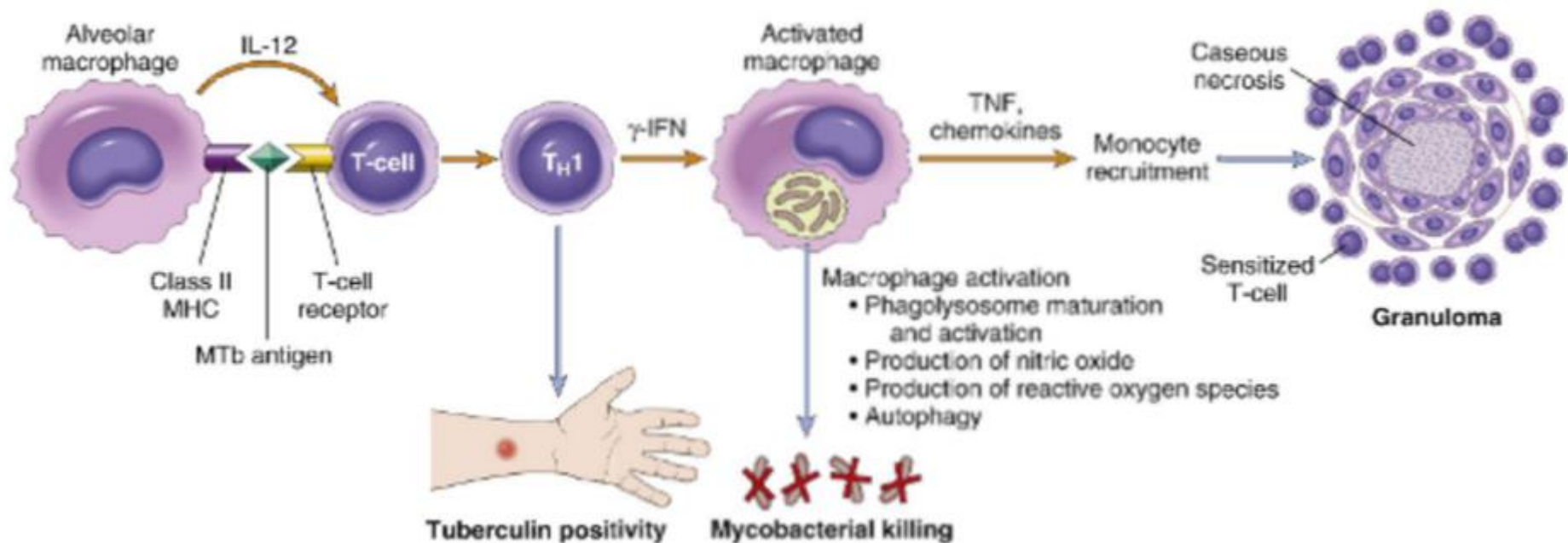
Pathogenesis of TB

- 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 β , 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

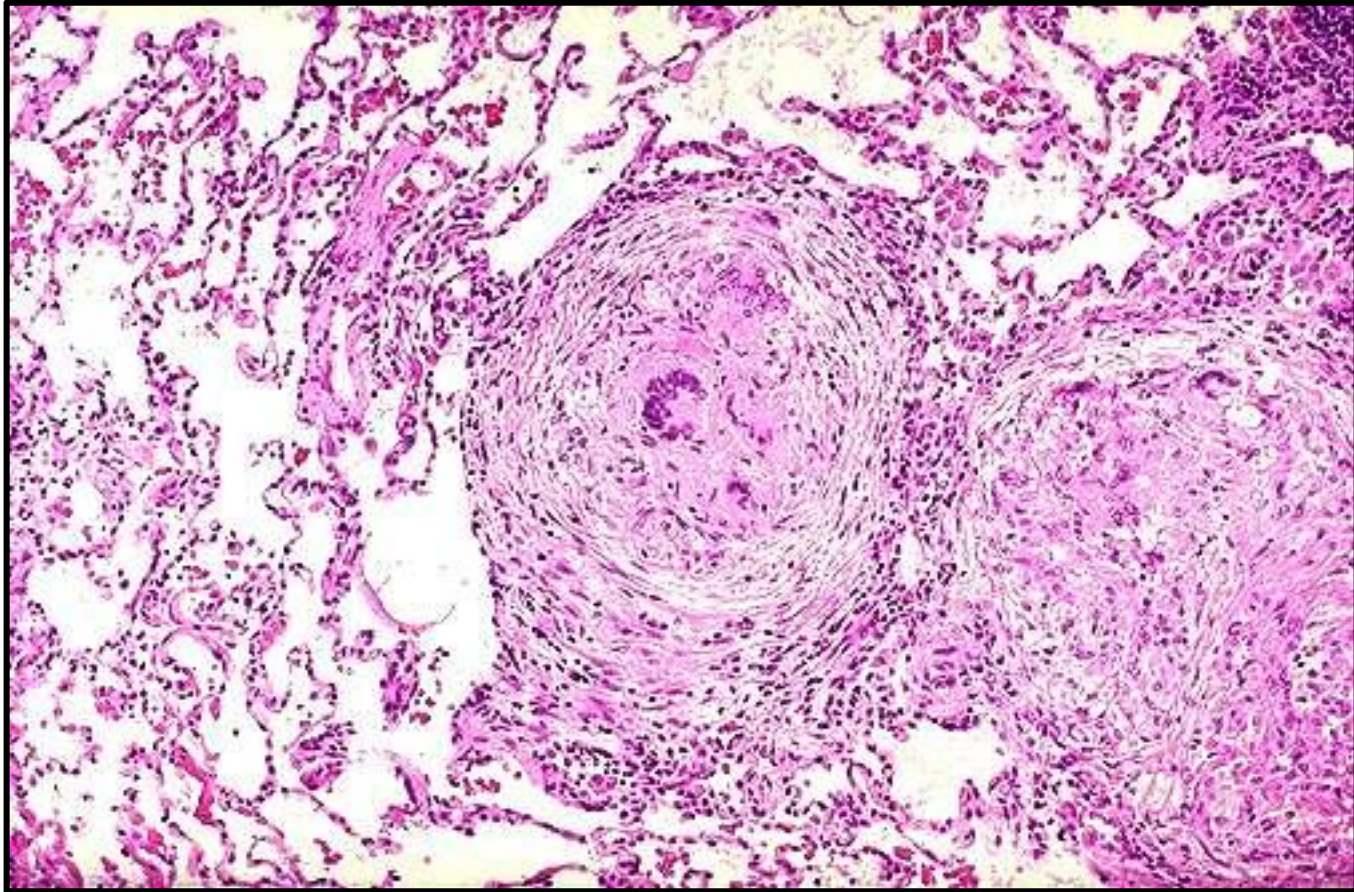


© List the common causes of Granulomatous Inflammation

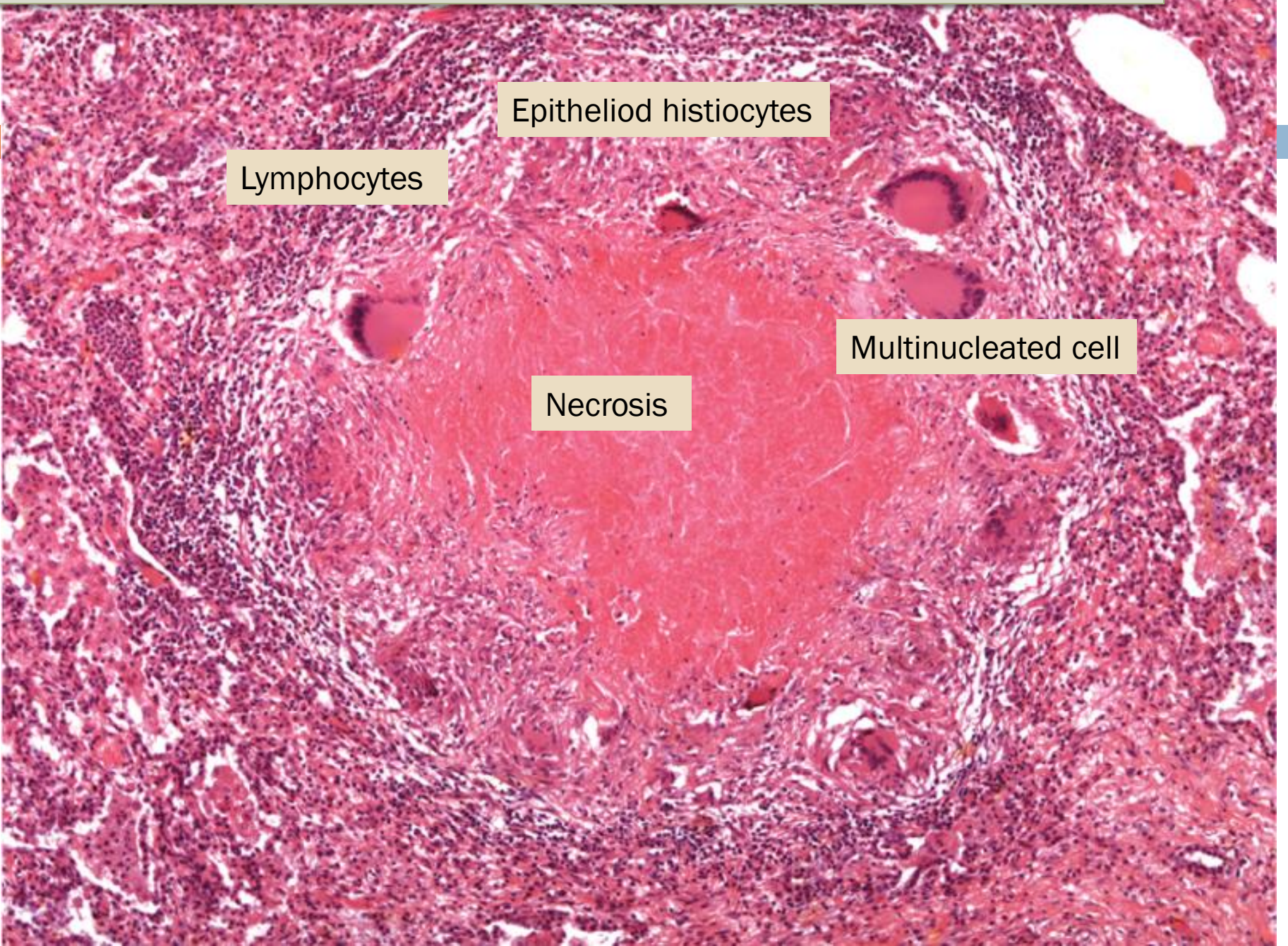
Tuberculosis



© List the common causes of Granulomatous Inflammation



© List the common causes of Granulomatous Inflammation



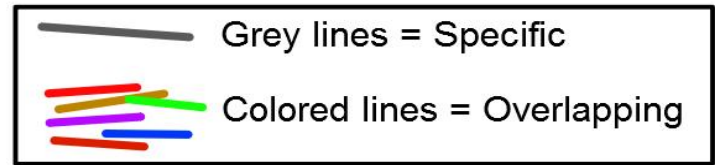
Lymphocytes

Epithelioid histiocytes

Necrosis

Multinucleated cell

Symptoms of Tuberculosis



**(Established)
pulmonary tuberculosis**

Poor appetite

Miliary tuberculosis

Productive cough

**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:

**Tuberculous
pleuritis**

Meninges

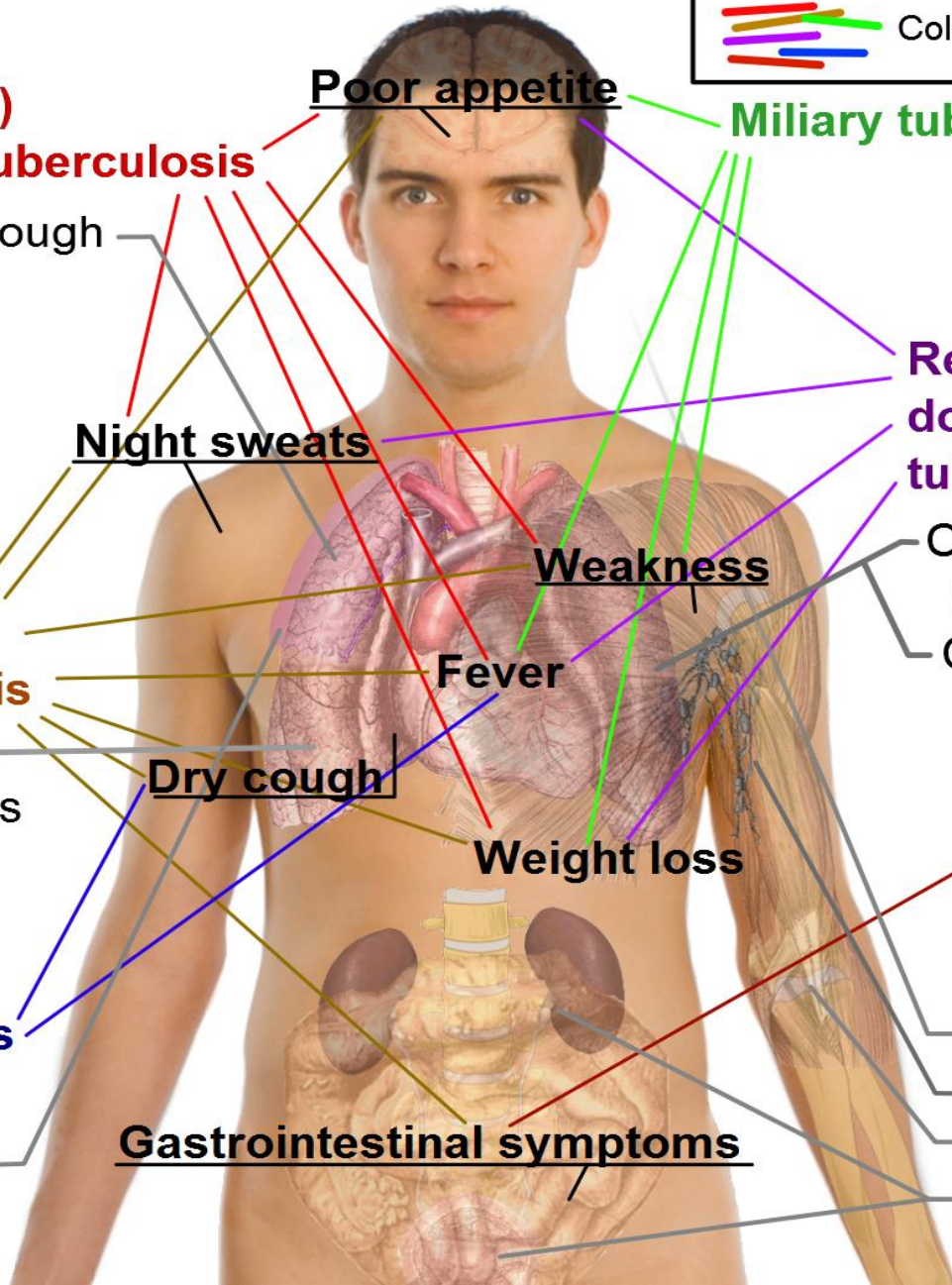
Lymph nodes

Bone and joint sites

Genitourinary tract

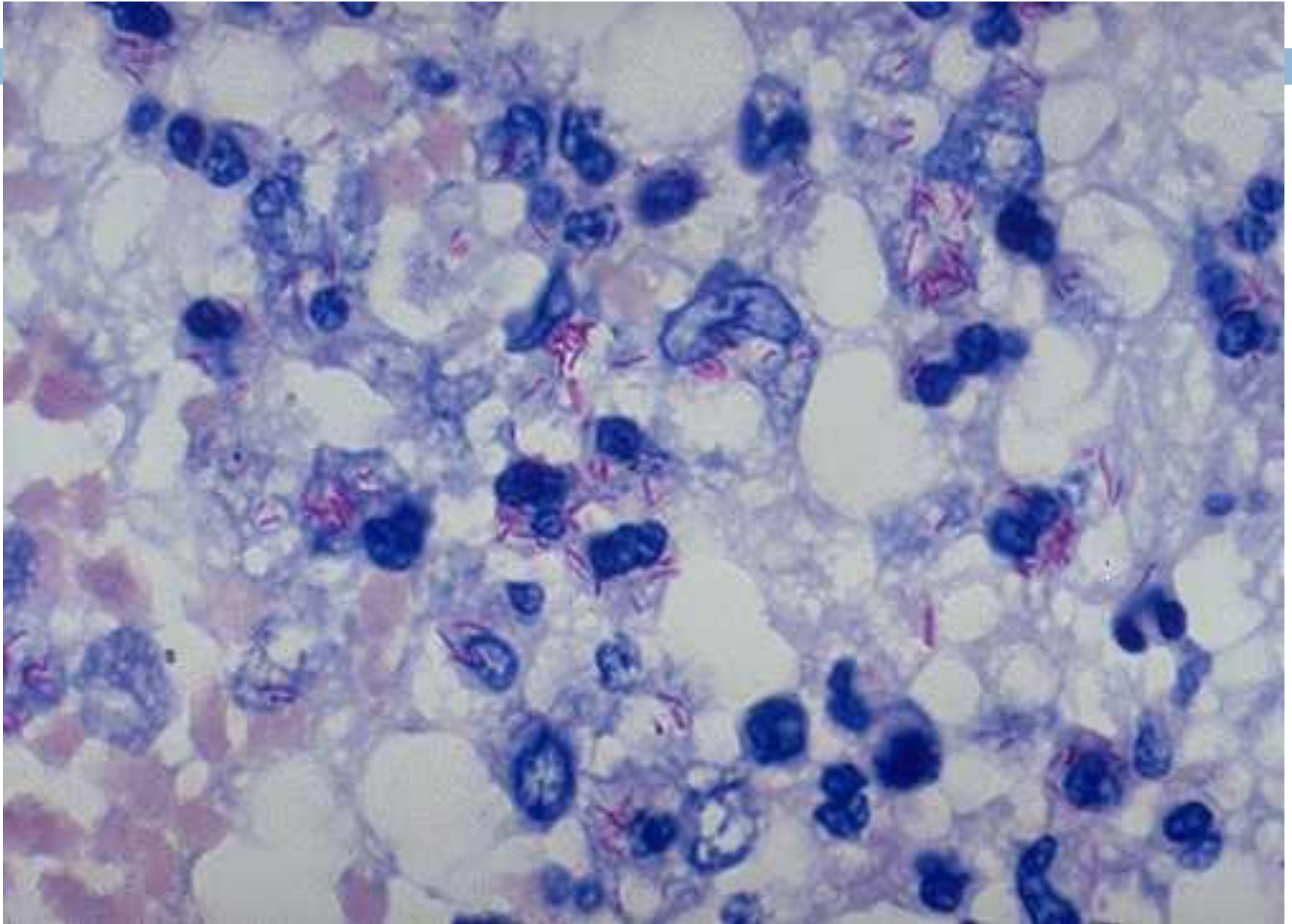
Chest pain

Gastrointestinal symptoms

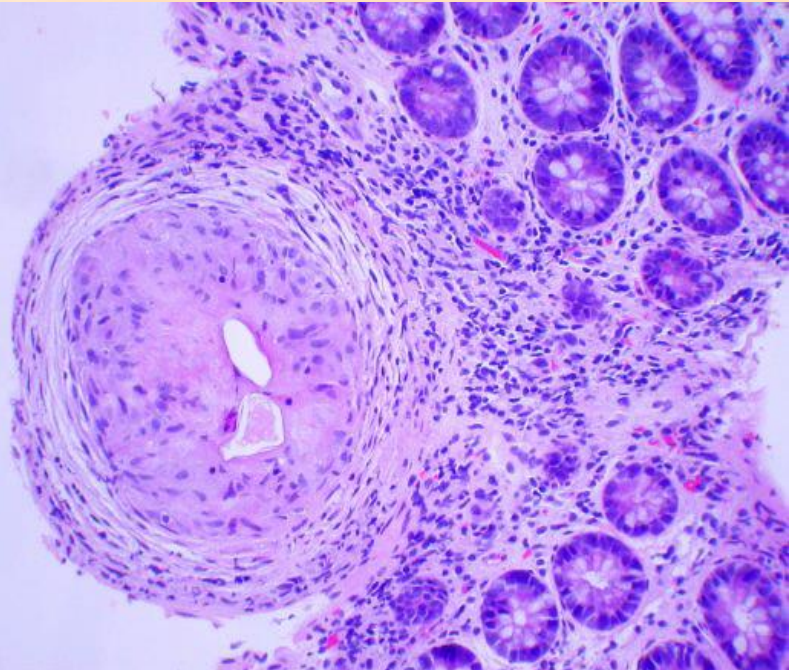
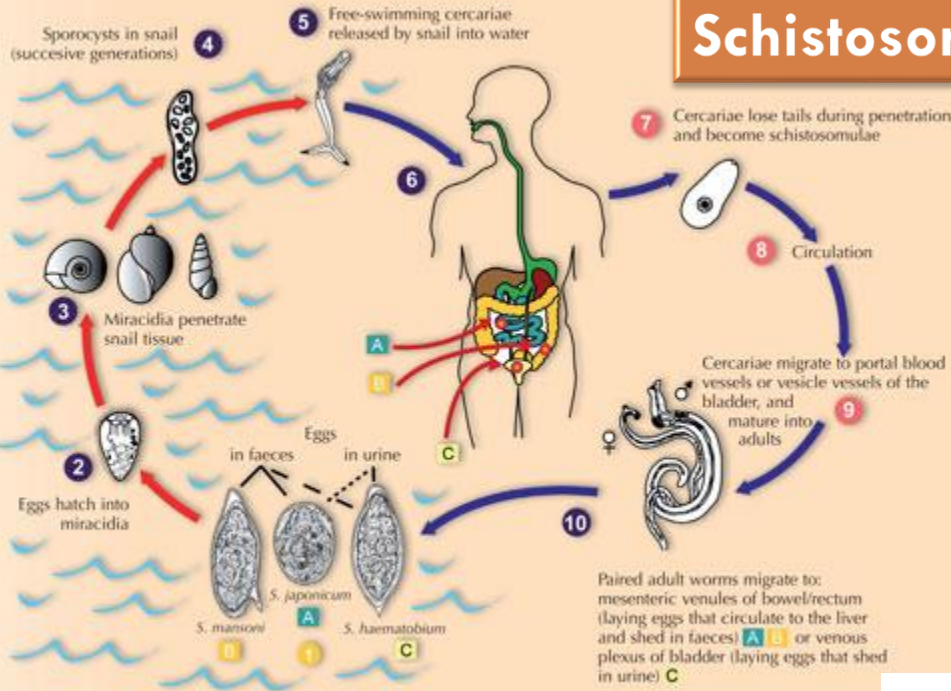


© List the common causes of Granulomatous Inflammation

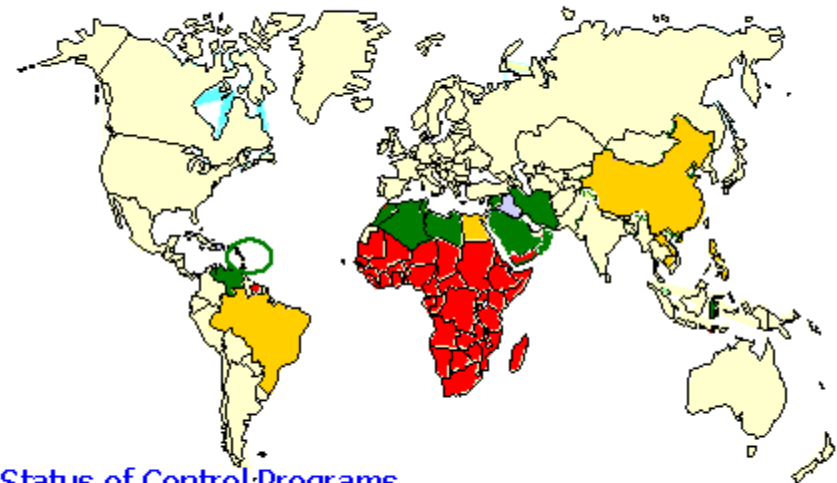
Sputum , TB bacilli



Schistosomiasis



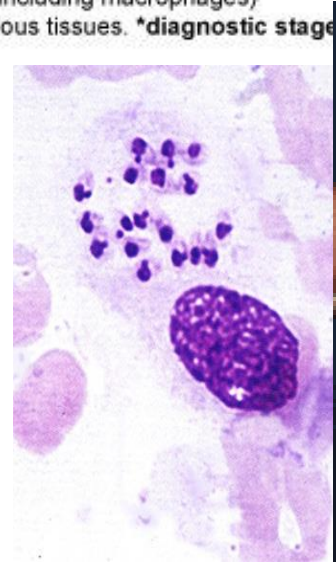
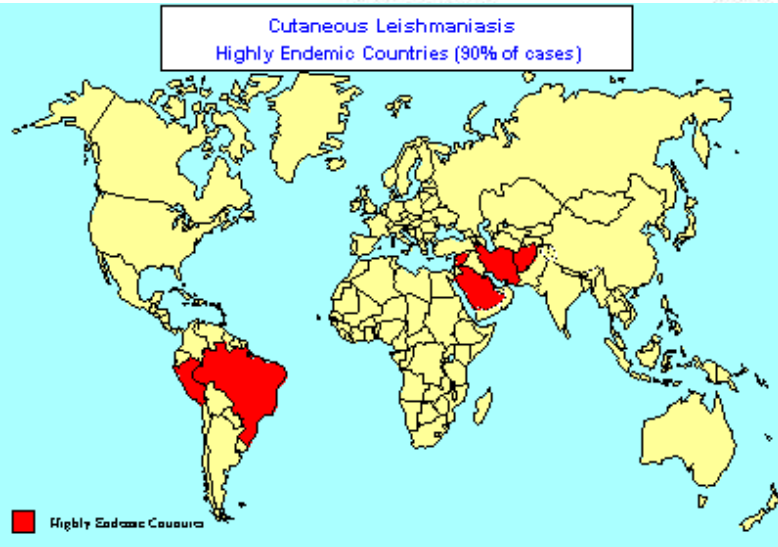
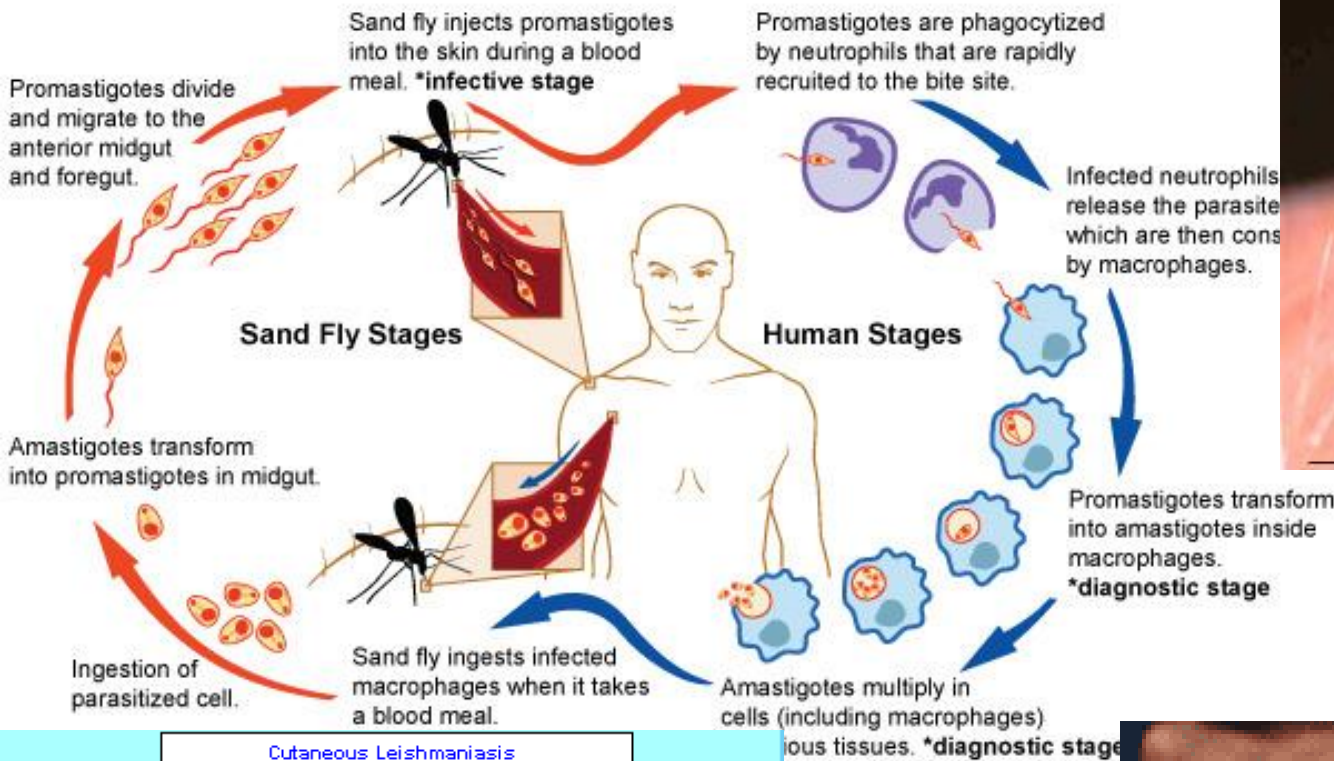
Global Distribution of Schistosomiasis



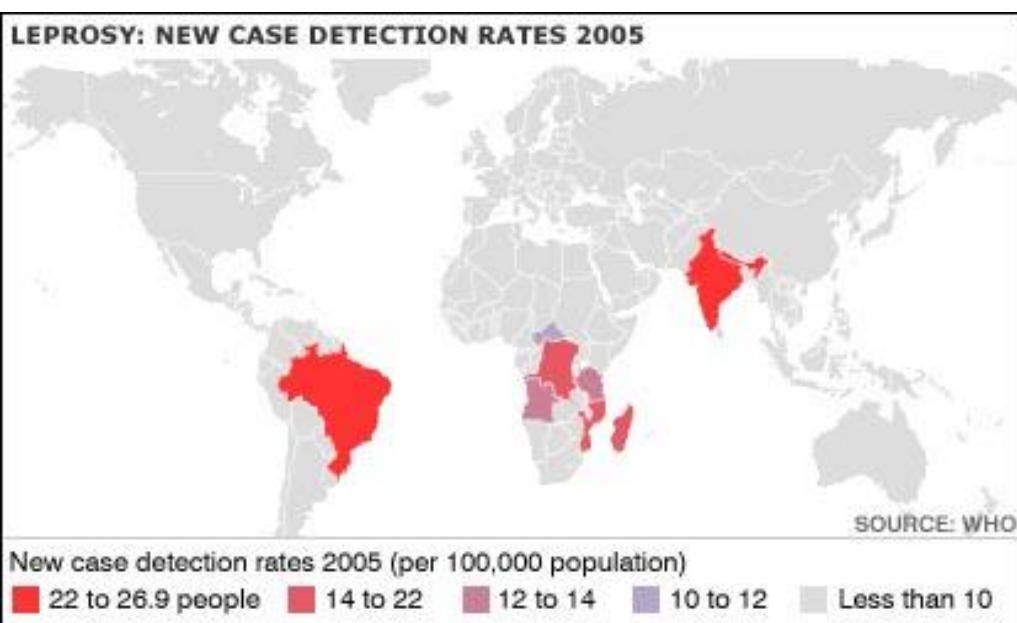
Status of Control Programs

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

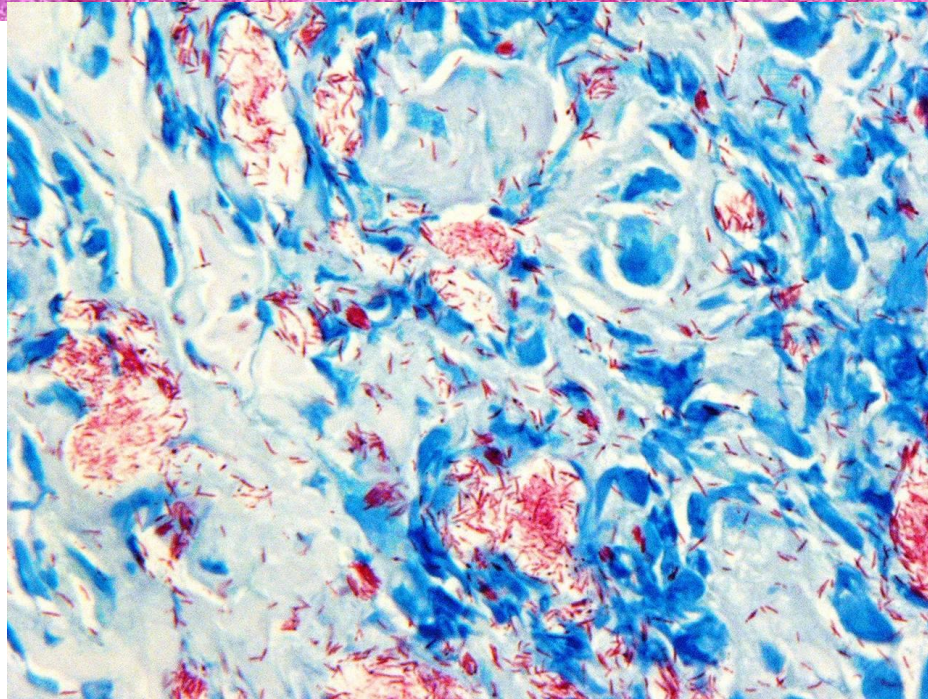
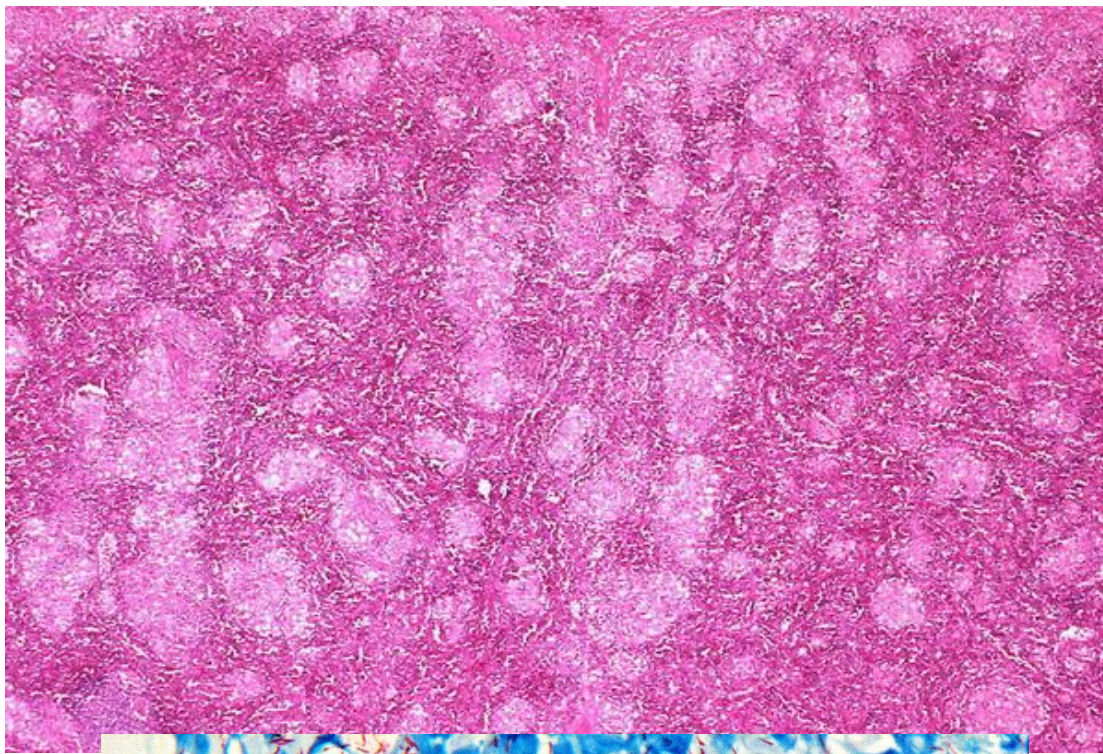
Leishmaniasis



Leprosy

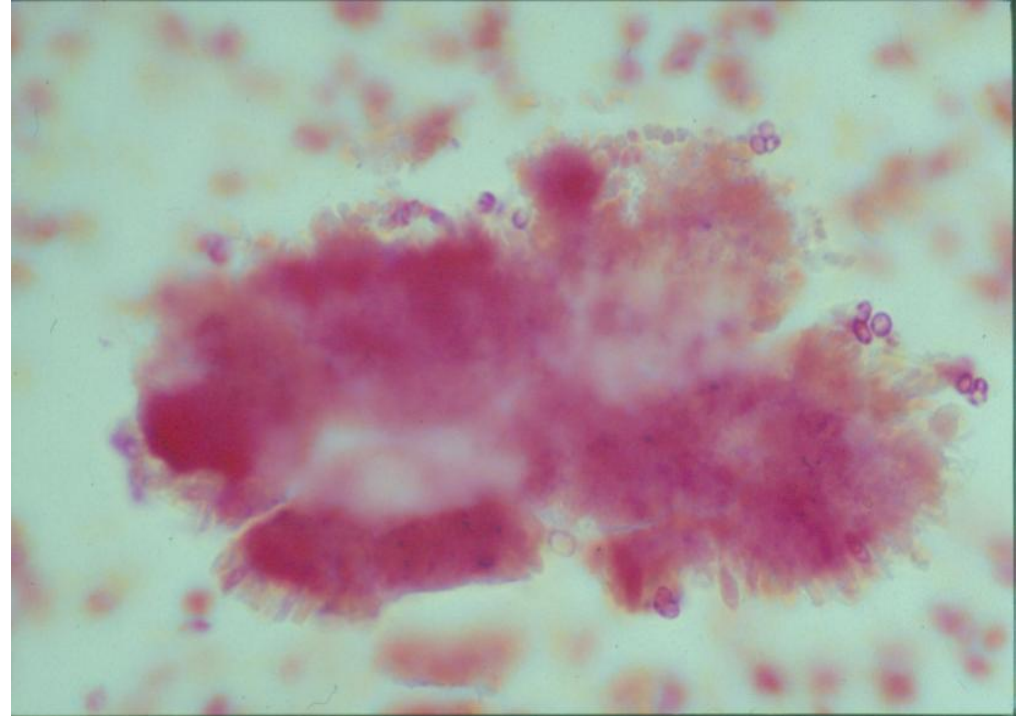
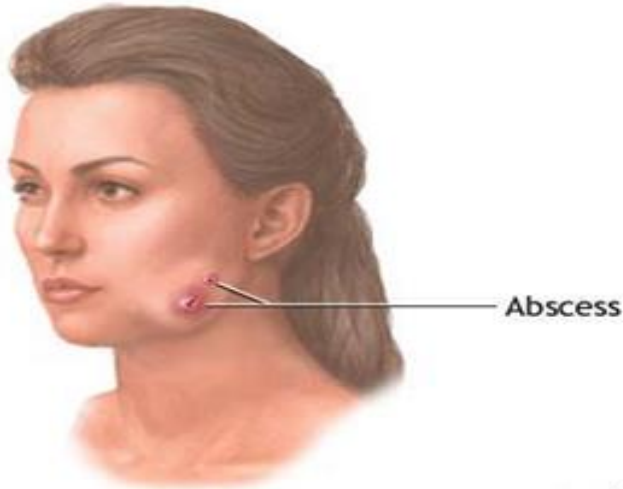


Leprosy



Actinomycosis

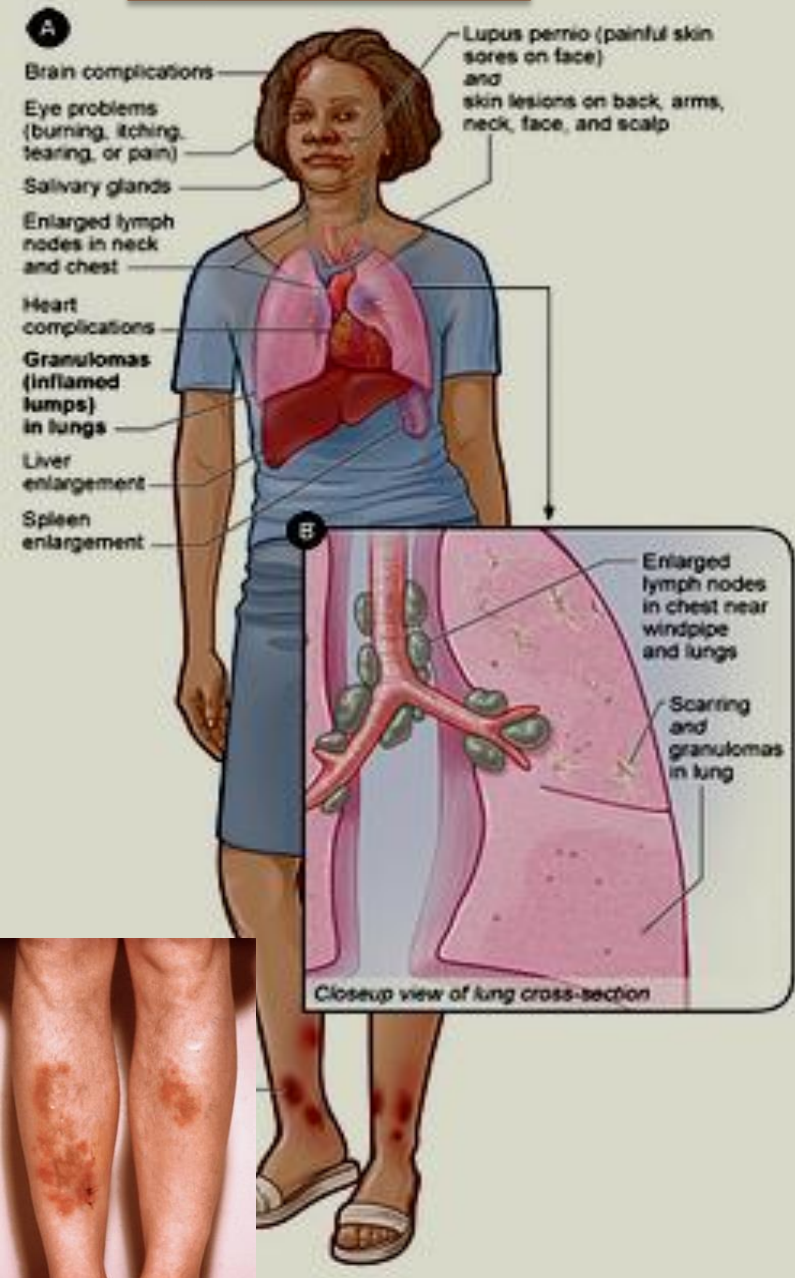
Actinomycosis is a long-term (chronic) granulomatous bacterial infection that commonly affects the face and neck



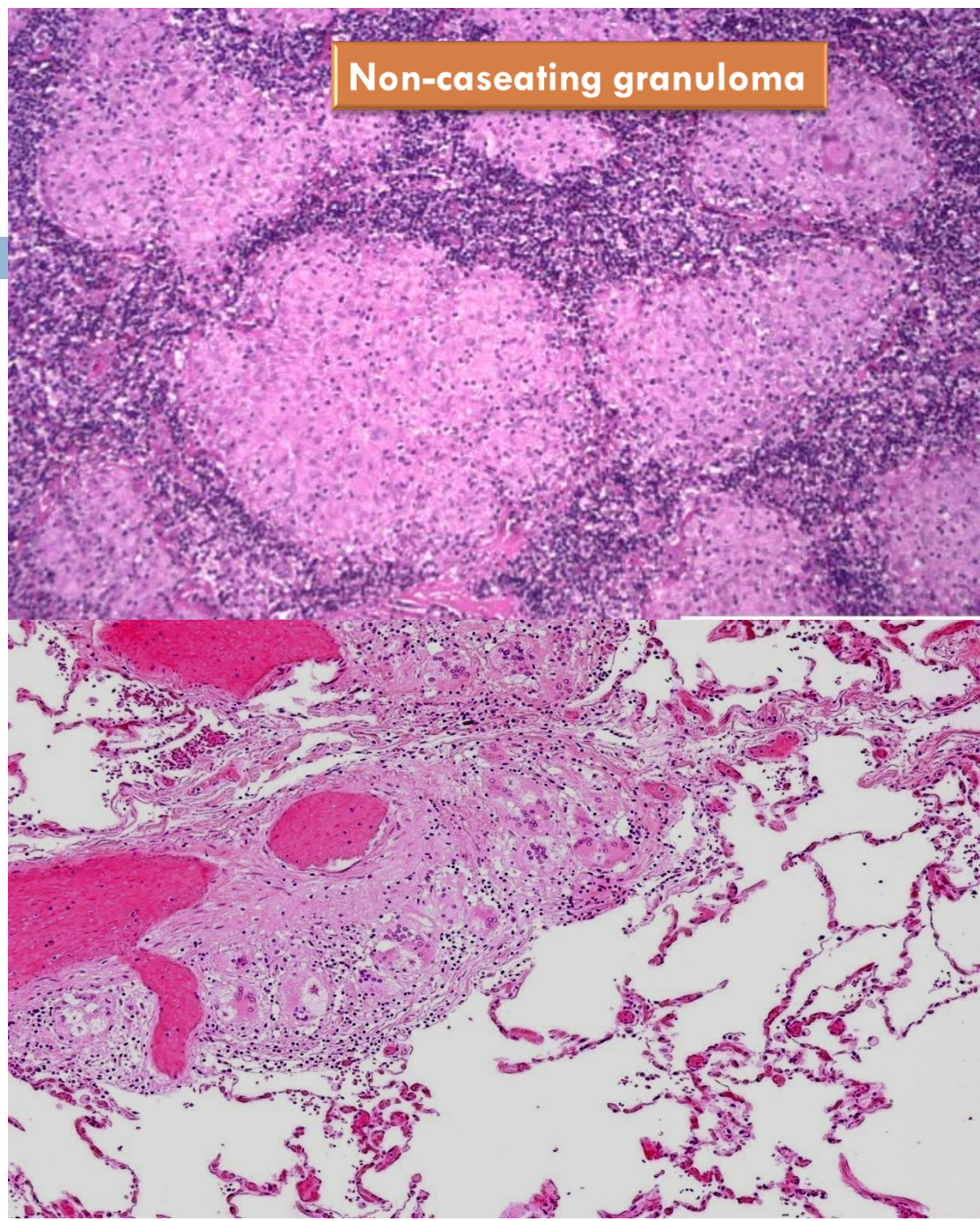
Examination of drained fluid under a microscope shows "sulfur granules" in the fluid. They are yellowish granules made of clumped organisms.

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

Sarcoidosis



Non-caseating granuloma



Match A and B

A

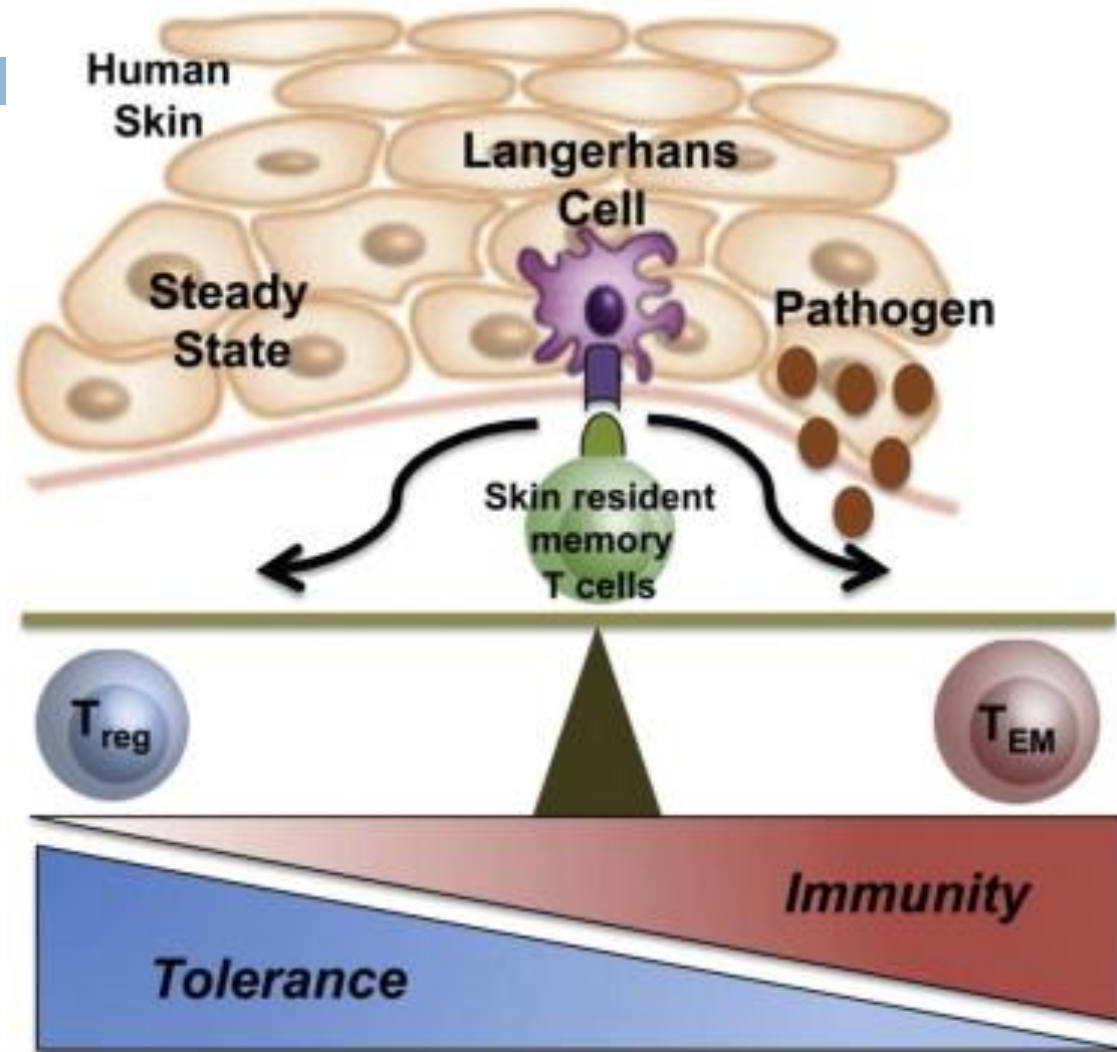
- 1) The most important cell in granulomatous inflammation
- 2) A cytokines that is important in activating macrophages and transforming them into epithelioid cells
- 3) Multinucleated cell in TB
- 4) Antigen presenting cells
- 5) pathogenesis of immune type granulomatous inflammation
- 6) Microscopic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

B

- a. **IFN- γ**
- 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