GRANULOMATOUS INFLAMMATION

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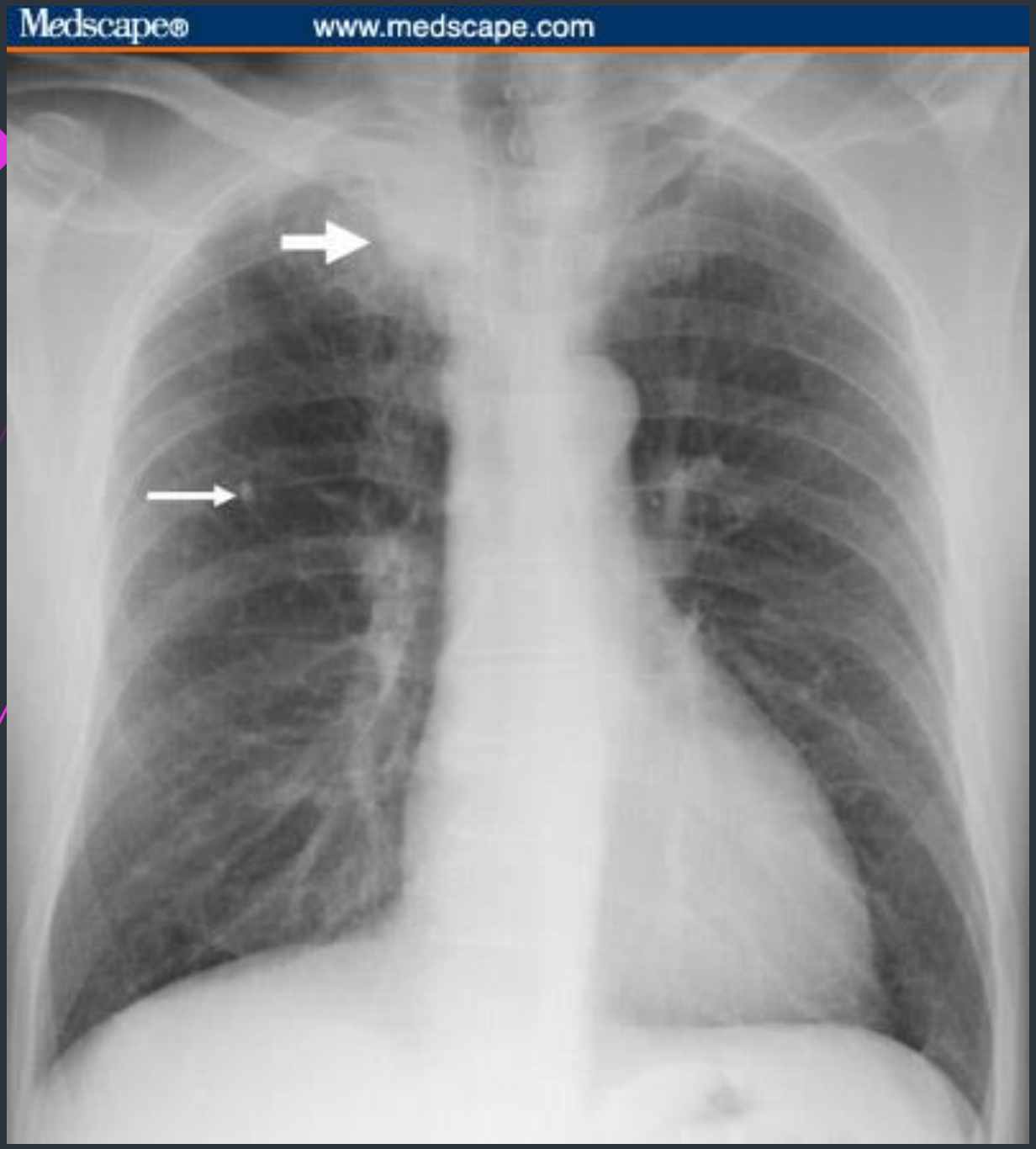
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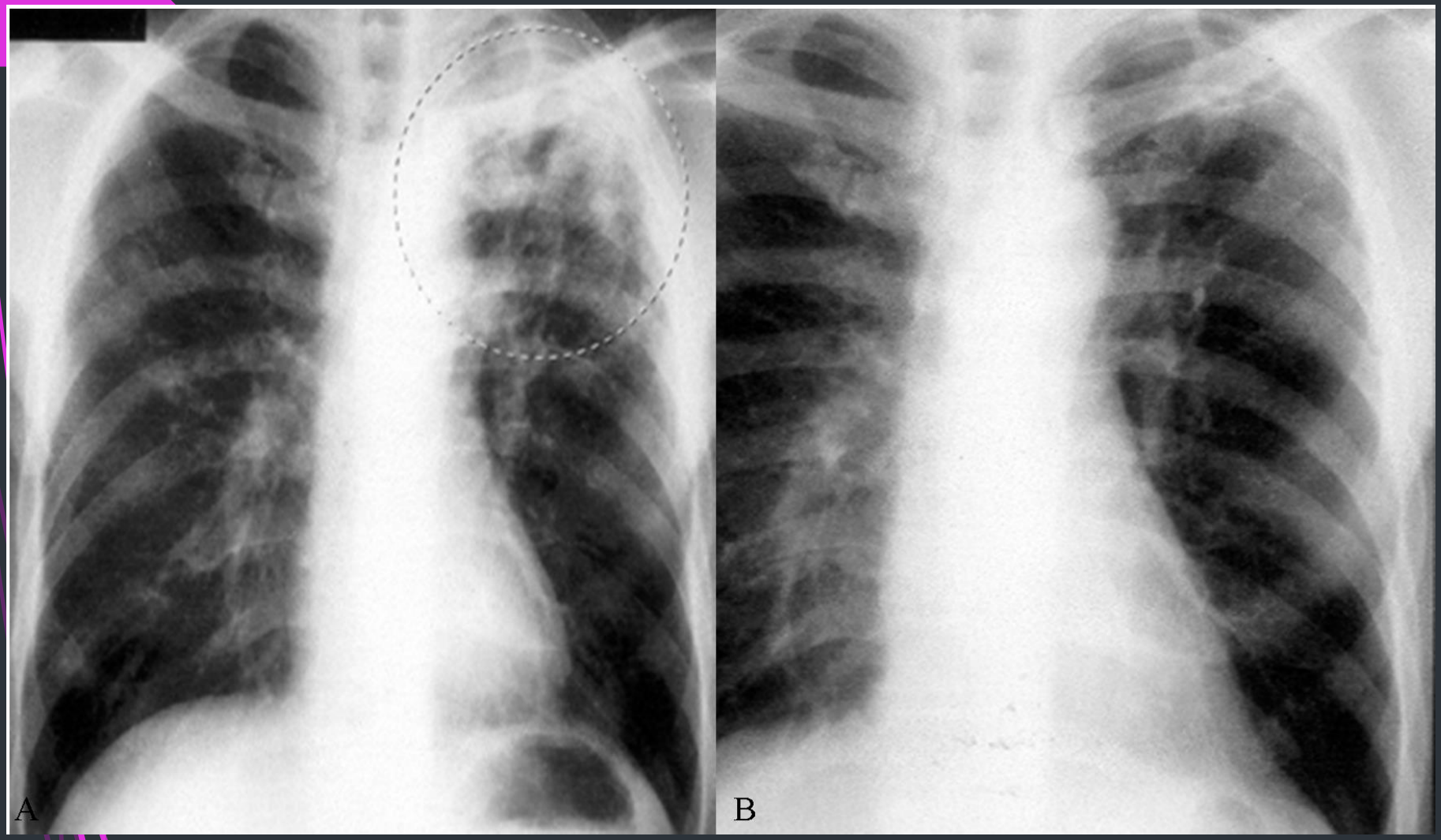
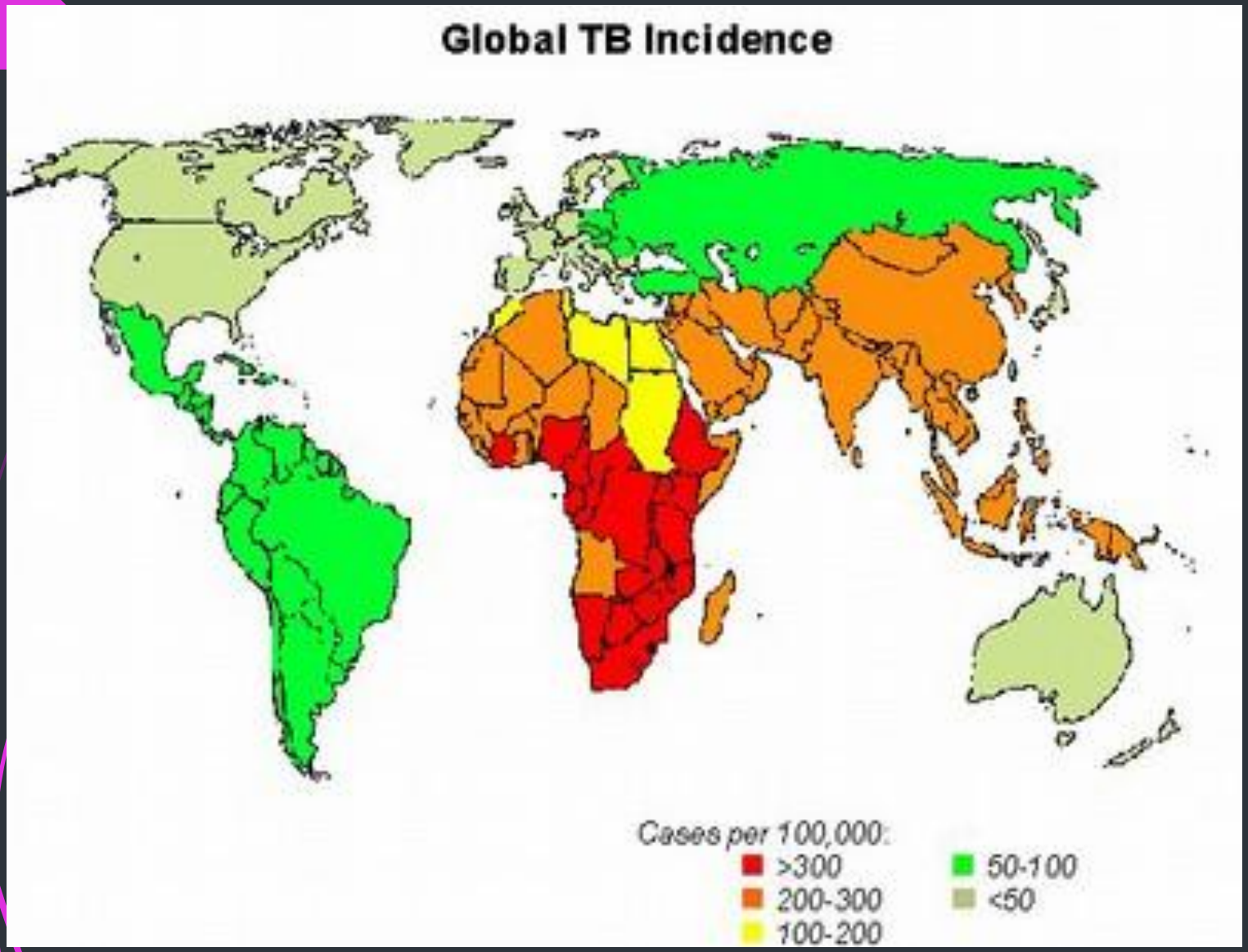

A
B


Global TB Incidence
Cases per 100,000:
>300
200-300
100-200
50-100
<50

World Health Organization

TUBERCULOSIS

Global Tuberculosis Report 2016

49 million lives saved between 2000-2015

TB deaths fell by 22% in the same period

1.8 MILLION TB DEATHS

INCLUDING 0.4 MILLION TB DEATHS AMONG PEOPLE WITH HIV*

TB was one of the top ten causes of death worldwide

TB was responsible for more deaths than HIV and malaria

MDR-TB crisis with gaps in detection and treatment

Only 1 in 5 needing MDR-TB treatment were enrolled on it

US$ 2 BILLION GAP

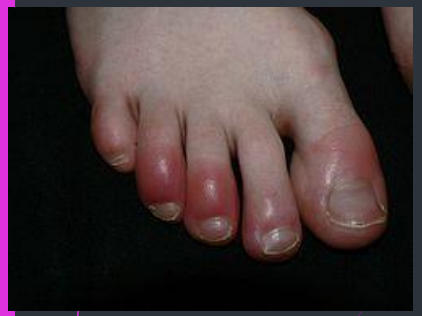
Funding shortfall for TB implementation

Gap of over US$1 billion per year for TB research

OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT

Upon completion of this lecture, the student should:

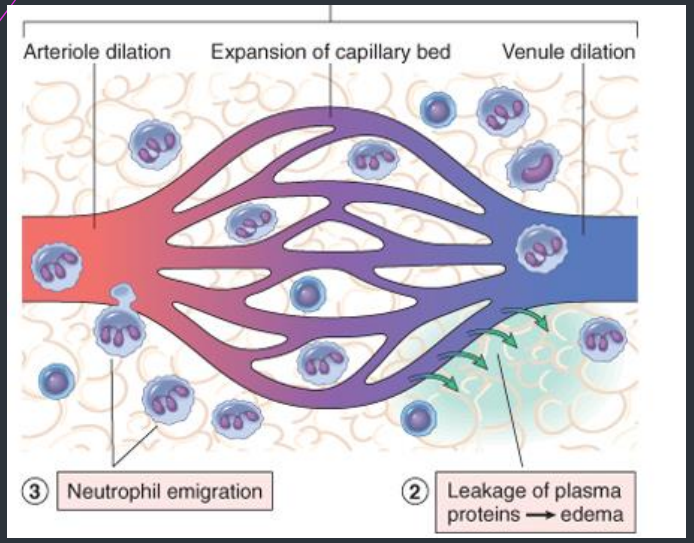
1. Define granulomatous inflammation.
2. Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance.
3. Identify the two types of granulomas, which differ in their pathogenesis.
    a) Foreign body granulomas
    b) Immune granulomas
4. List the common causes of Granulomatous Inflammation.
5. Understands the pathogenesis of granuloma formation.



Inflammation

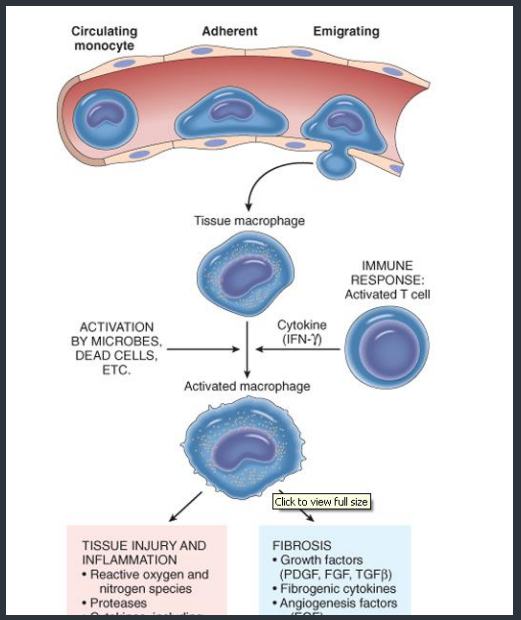
Acute *inflammation*

Neutrophils



Chronic *inflammation*

Macrophage
Lymphocytes
Plasma cells



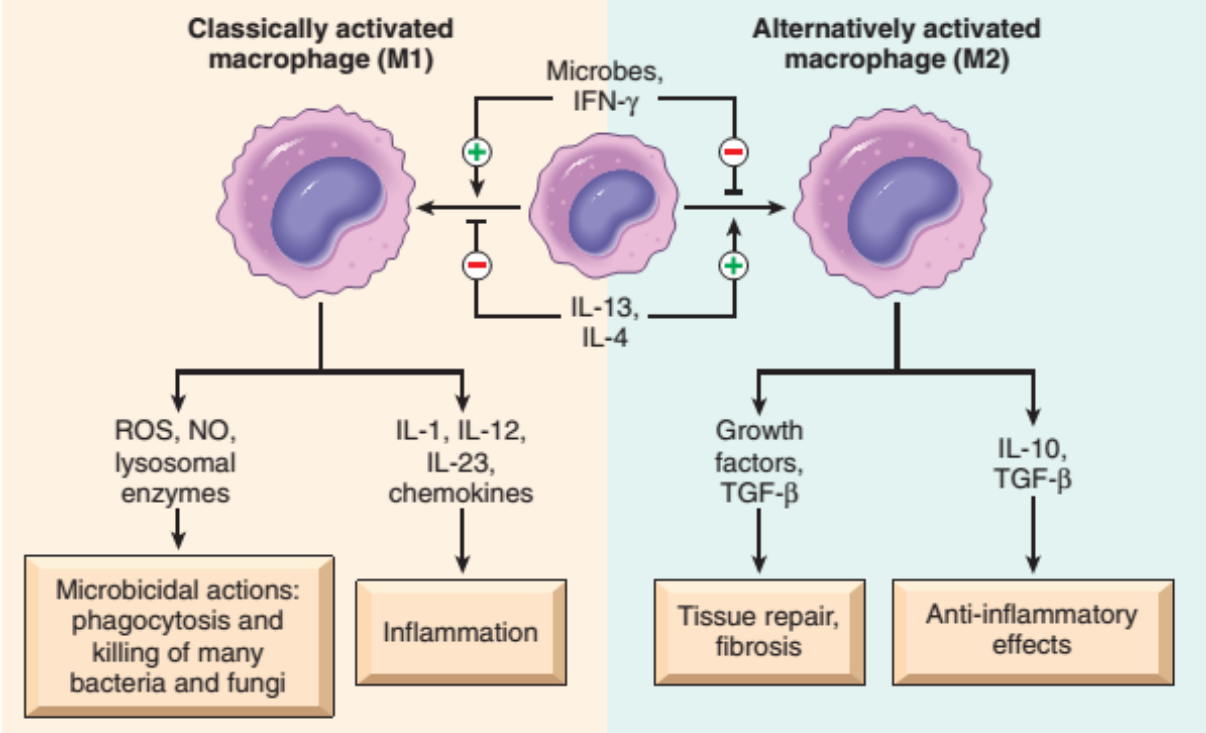


Figure 2–21 Pathways of macrophage activation. Different stimuli activate monocytes/macrophages to develop into functionally distinct populations. Classically activated macrophages are induced by microbial products and cytokines, particularly IFN-γ, and are microbicidal and involved in potentially harmful inflammation. Alternatively activated macrophages are induced by IL-4 and IL-13, produced by T_H2 cells (a helper T cell subset) and other leukocytes, and are important in tissue repair and fibrosis. IFN-γ, interferon-γ; IL-4, IL-13, interkeukin-4, -13.

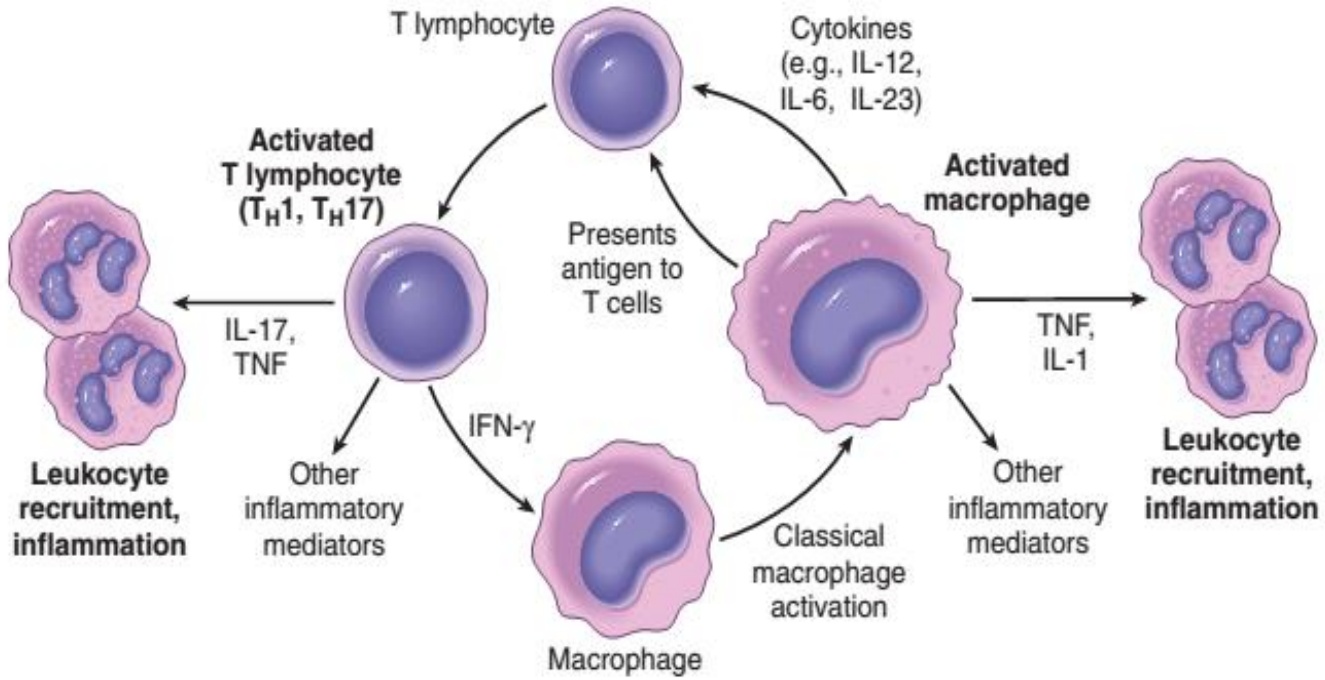


Figure 2–22 Macrophage–lymphocyte interactions in chronic inflammation. Activated lymphocytes and macrophages stimulate each other, and both cell types release inflammatory mediators that affect other cells. IFN-γ, interferon-γ; IL-1, interleukin-1; TNF, tumor necrosis factor.

Granulomatous inflammation

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

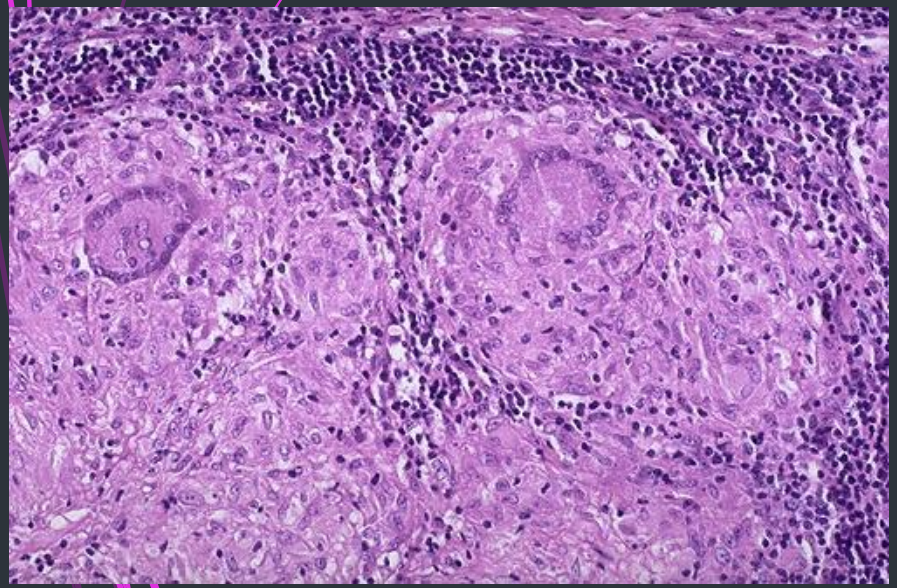
Why is it important?

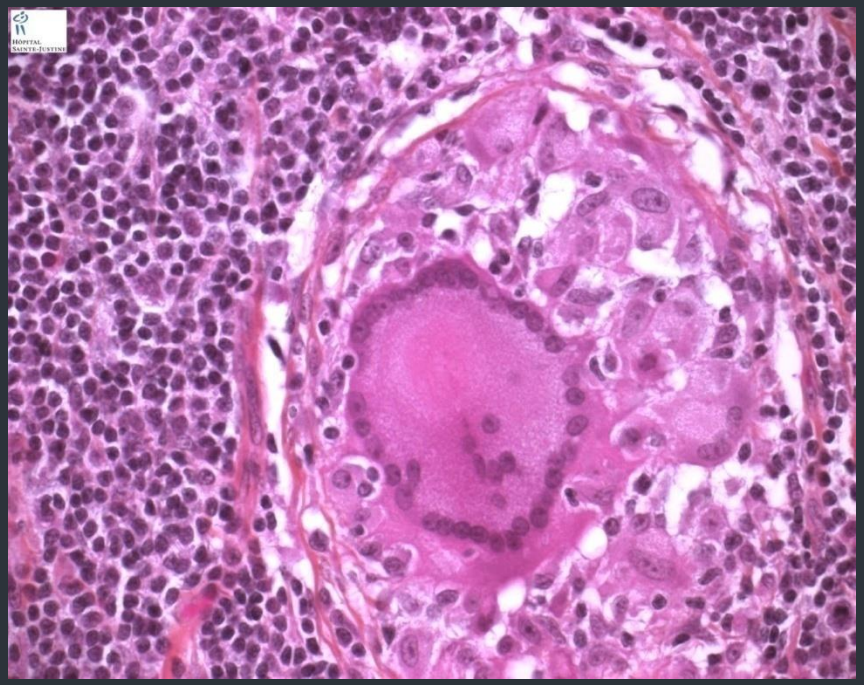
- Granulomas are encountered in certain specific pathologic states.
- Recognition of the granulomatous pattern is important because of the limited number of conditions (some life-threatening) that cause it.

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 chronic inflammation.

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



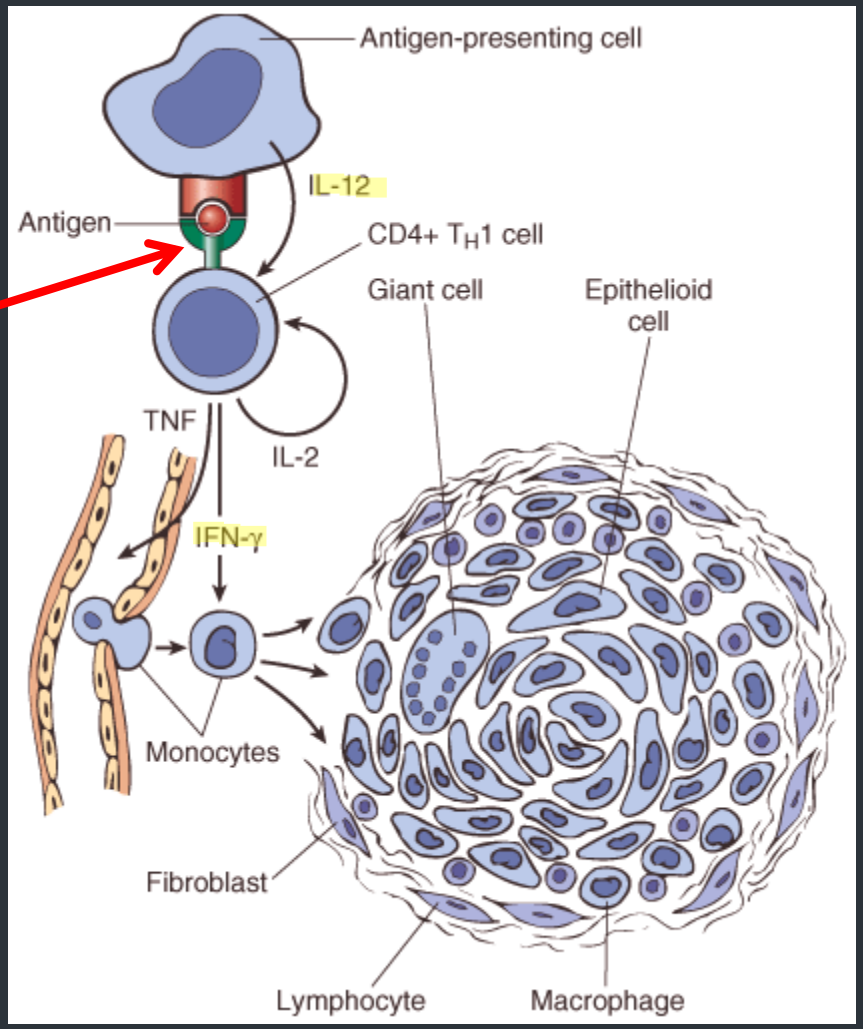


Granulomatous Inflammation mechanism

- **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

Epithelioid Cell granulomas

1. When **macrophages** have successfully phagocytosed the injurious agent but it survives inside them.

2. Then, 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.

Table 2–8 Examples of Diseases with Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease	Immune reaction against intestinal bacteria, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

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**.

Granulomatous Inflammation

Causes

Non-immune Granuloma

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

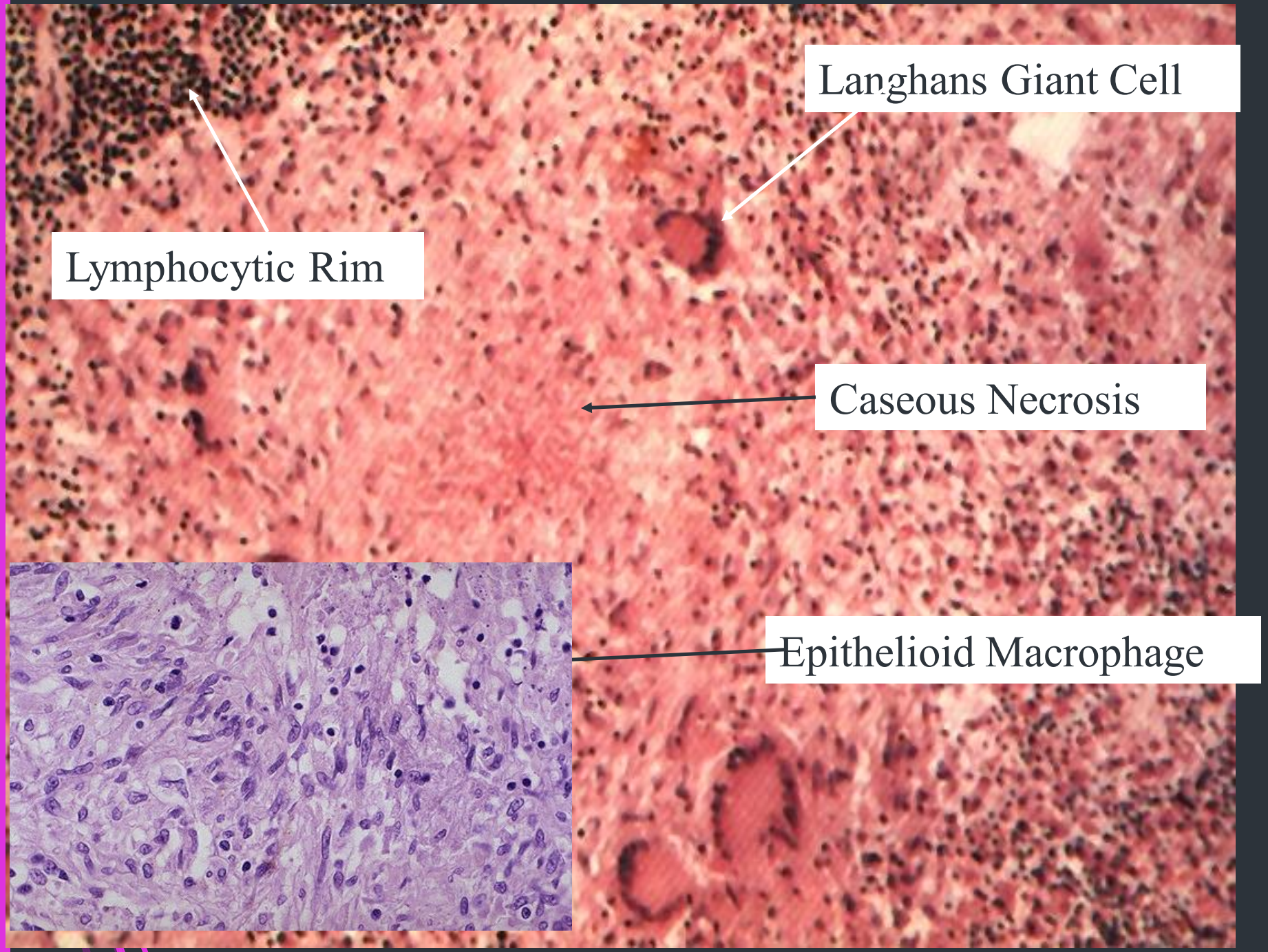
Immune Granuloma:

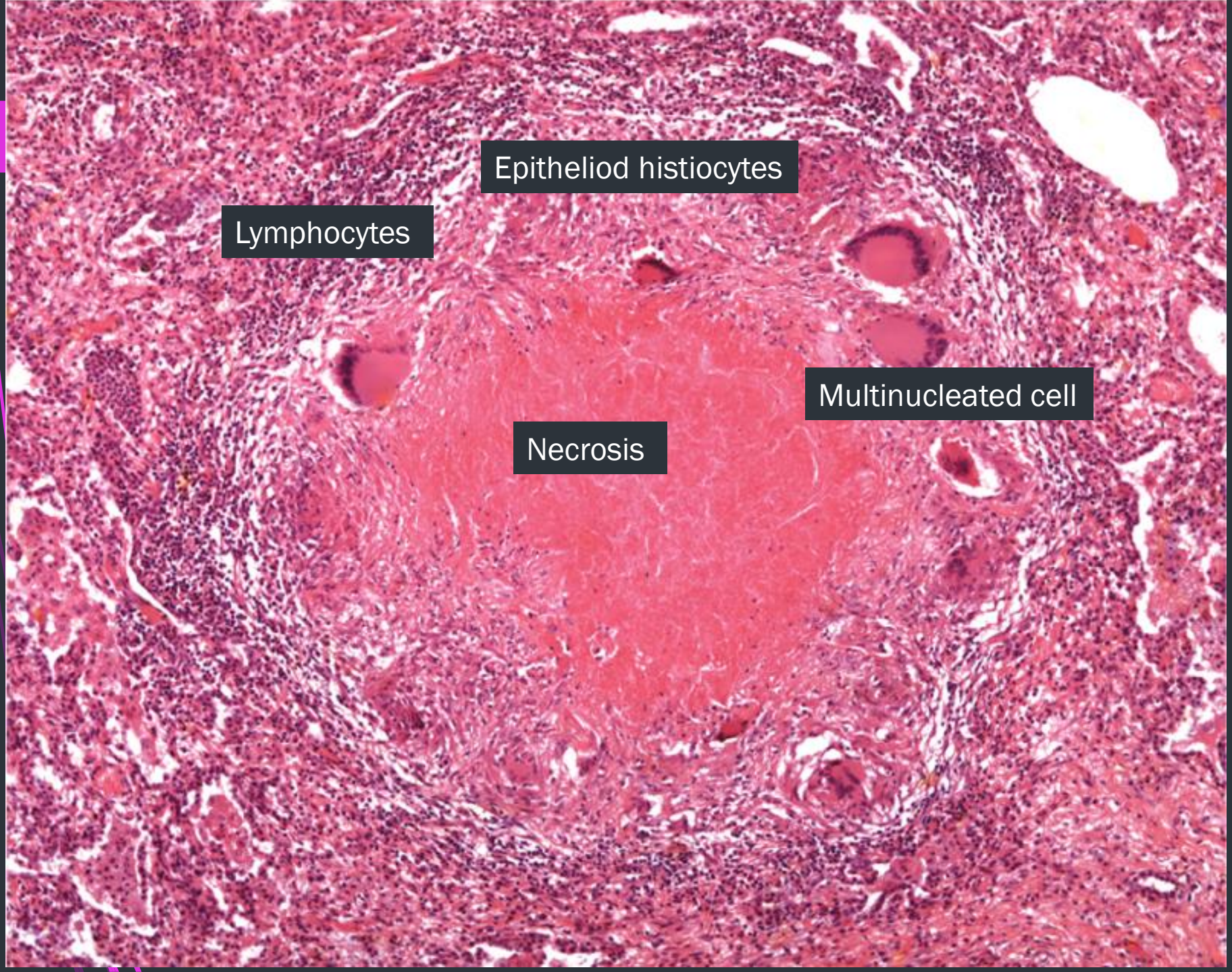
- **Bacteria**
  - Tuberculosis
  - Leprosy
  - Actinomycosis
  - Cat-scratch disease
- **Parasites**
  - Schistosomiasis
  - Leishmaniasis
- **Fungi**
  - Histoplasmosis
  - Blastomycosis
- **Metal/Dust**
  - Berylliosis

unknown

Sarcoidosis

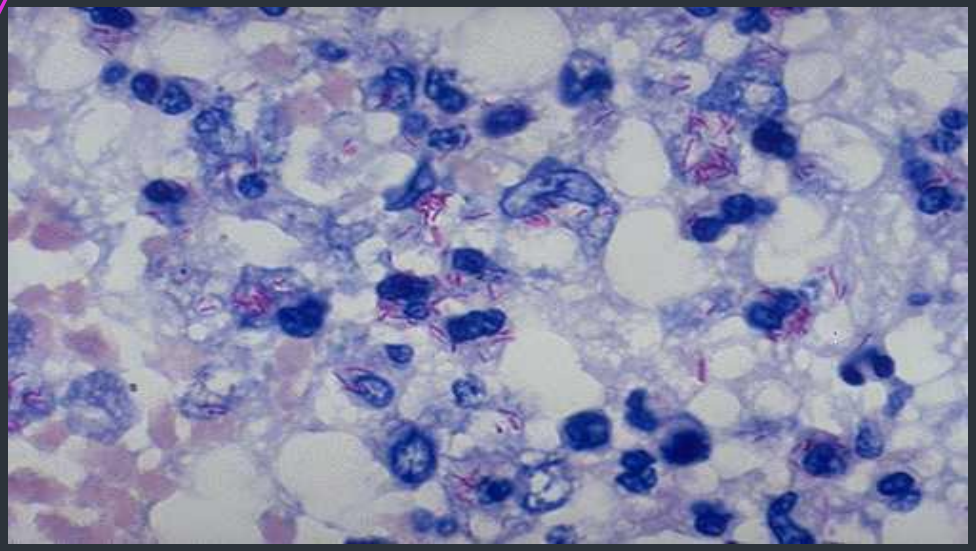
Crohn's disease

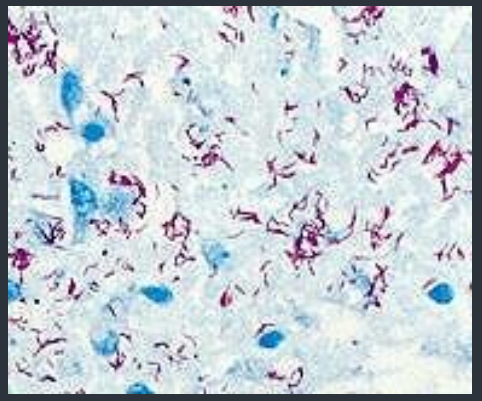

Langhans Giant Cell
Lymphocytic Rim
Caseous Necrosis
Epithelioid Macrophage


Epitheliod histiocytes
Lymphocytes
Multinucleated cell
Necrosis

Tuberculosis (TB)
M. 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).

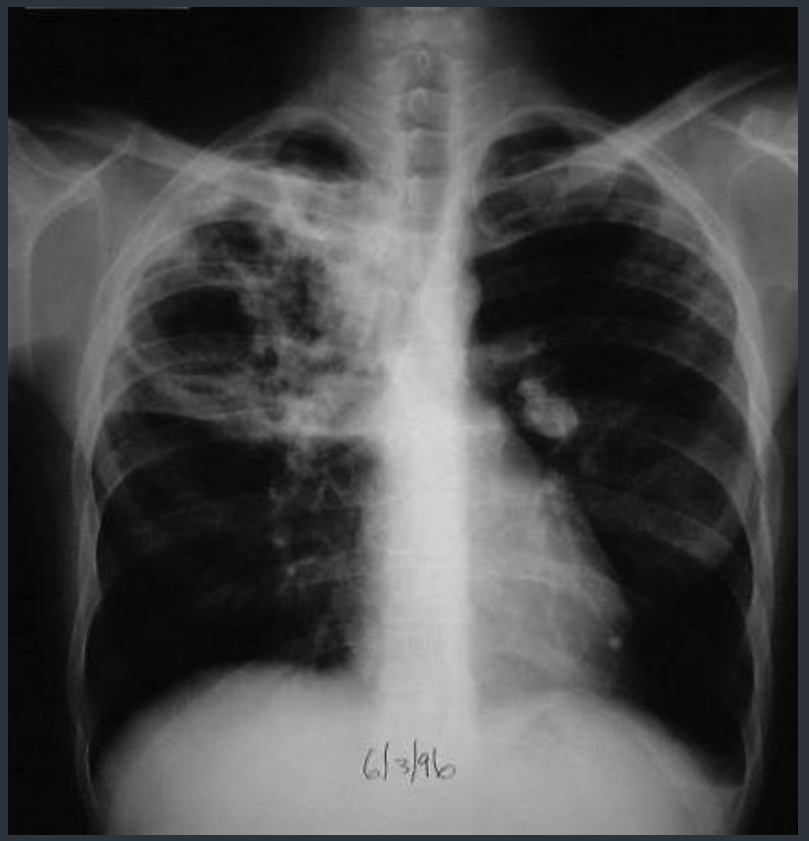




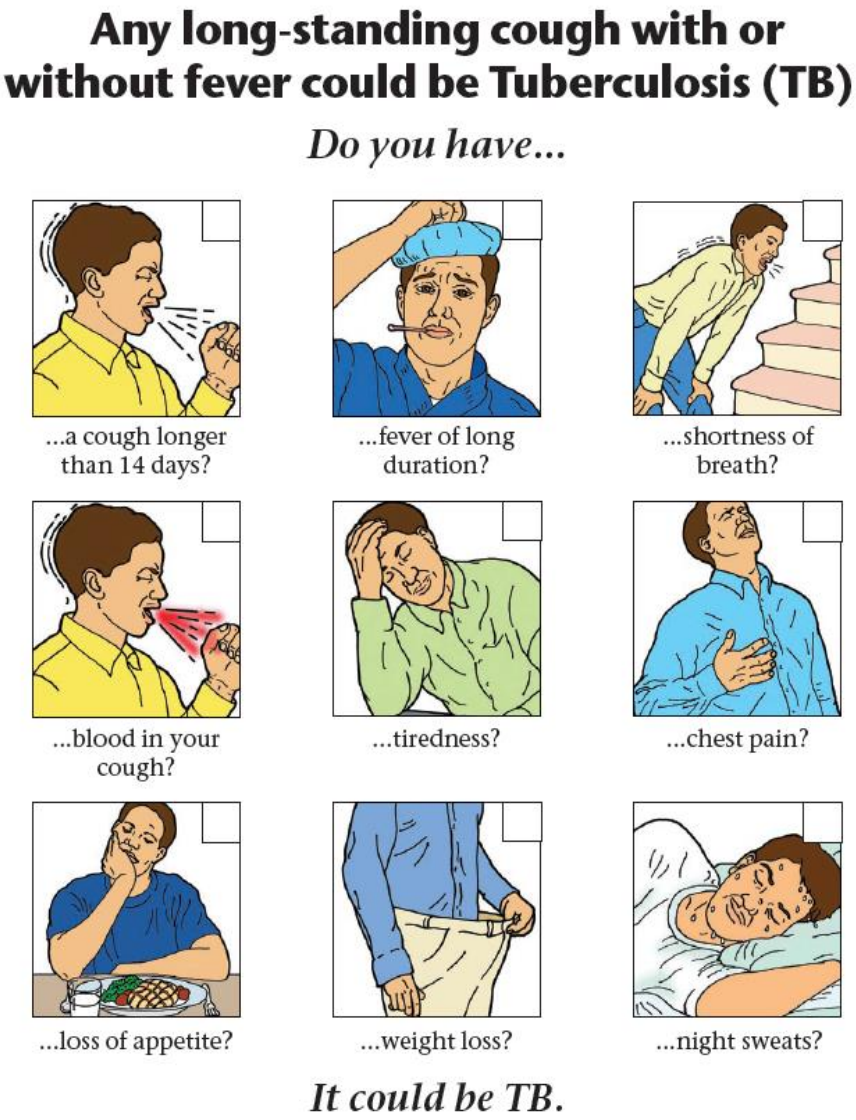
Pathogenesis of TB

- **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
- Cord factor presence increases the production of the **cytokines interleukin-12** (IL-12), IL-1β, IL-6 and TNF which are all pro-inflammatory cytokines important for granuloma formation

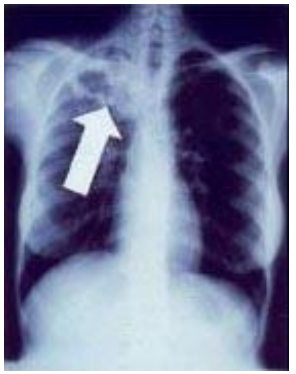
Tuberculosis



Signs, Symptoms and Diagnosis of TB



- X-ray

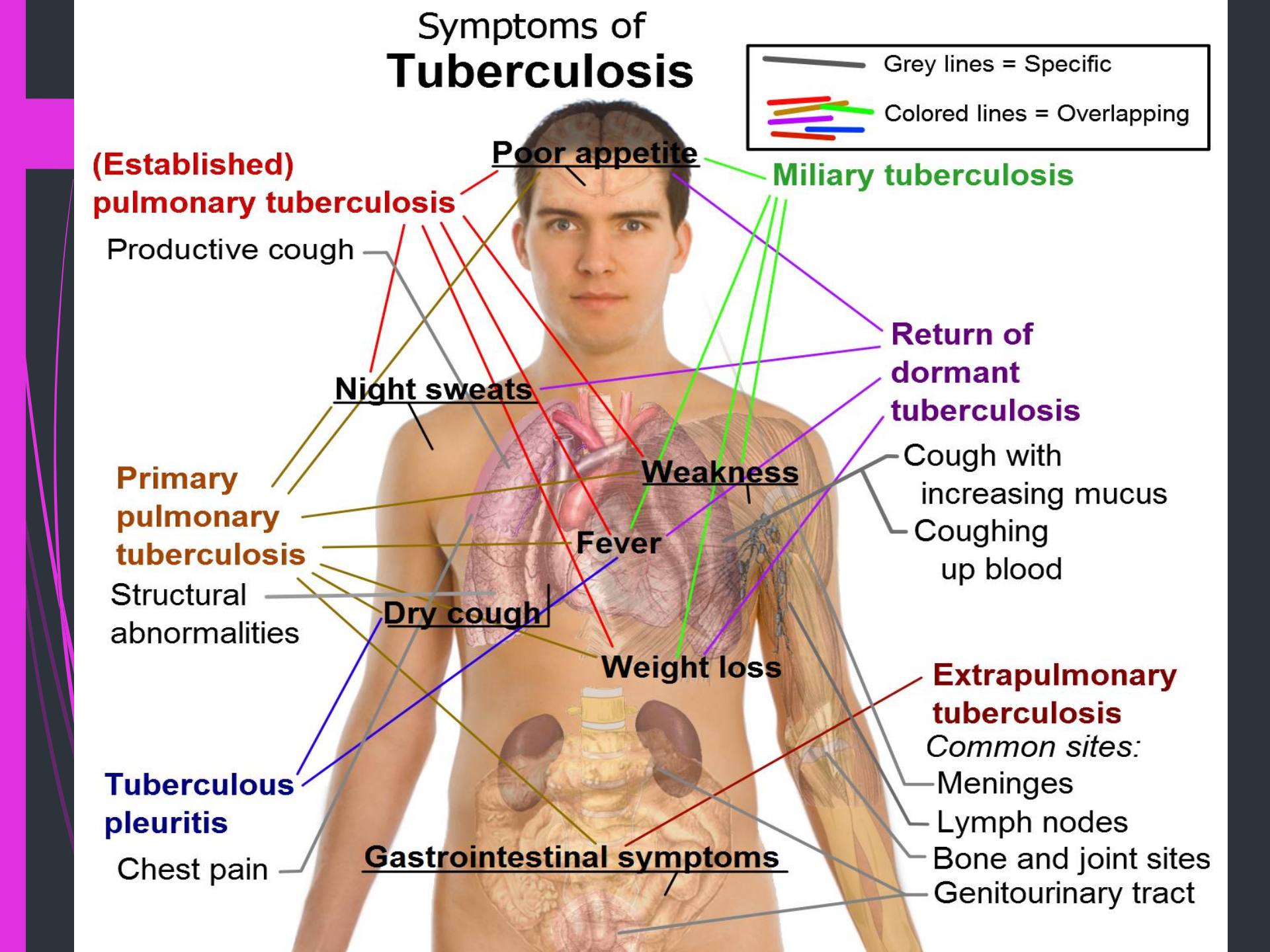


Tuberculin skin testing (TST)

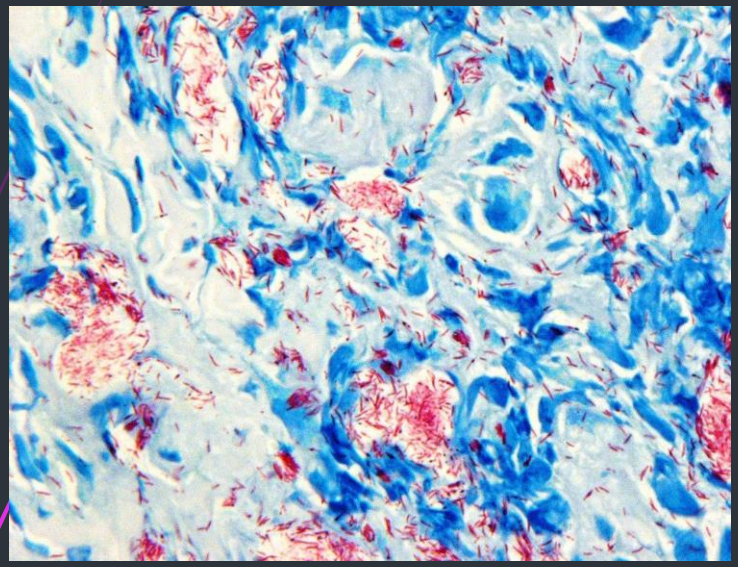
- Sputum smear microscopy

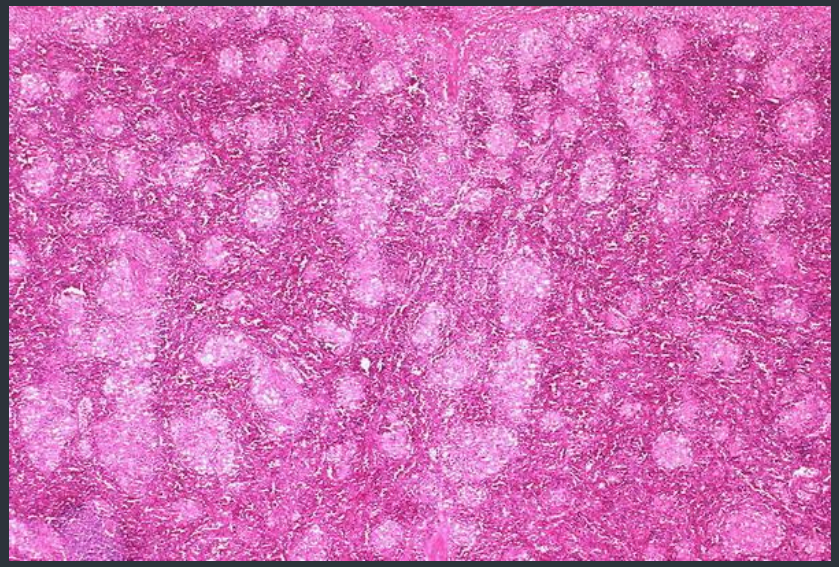
- Culture
- PCR: identification & drug resistance

Symptoms of Tuberculosis



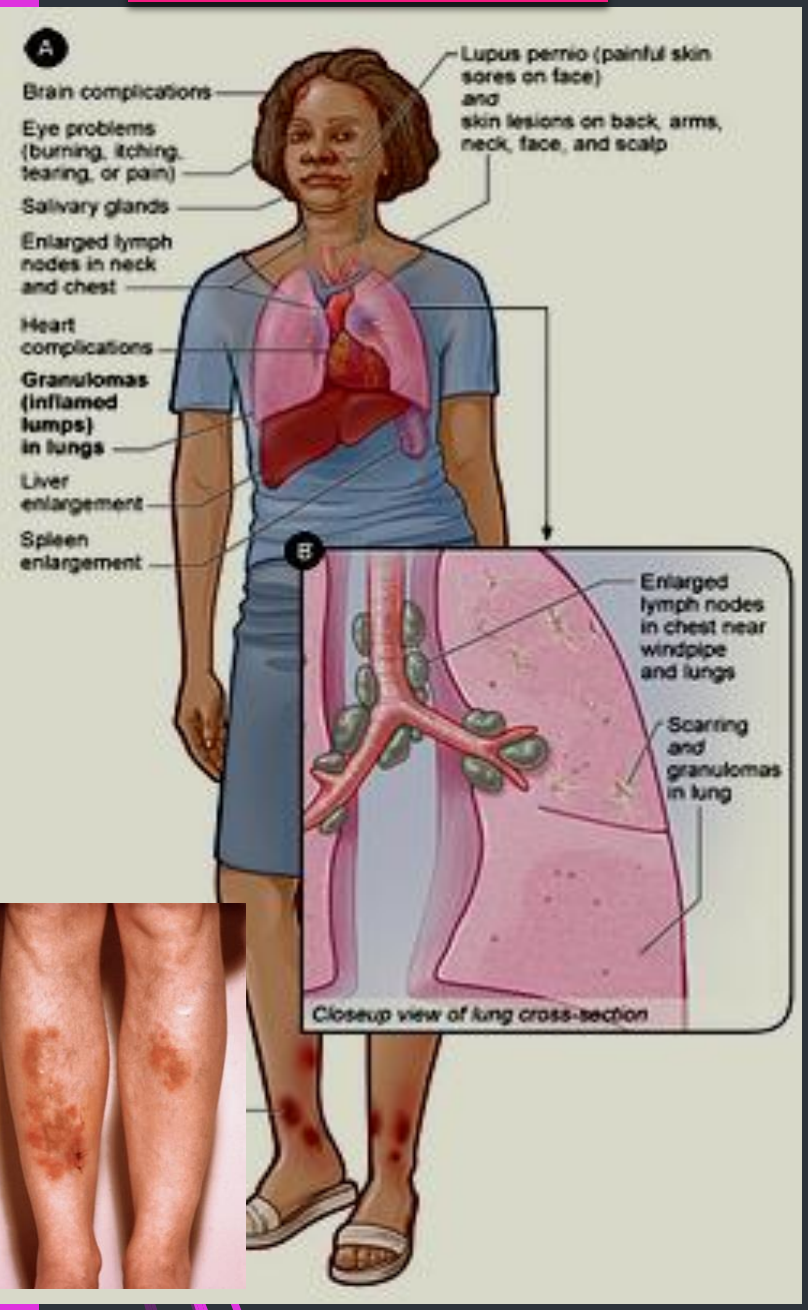
Leprosy

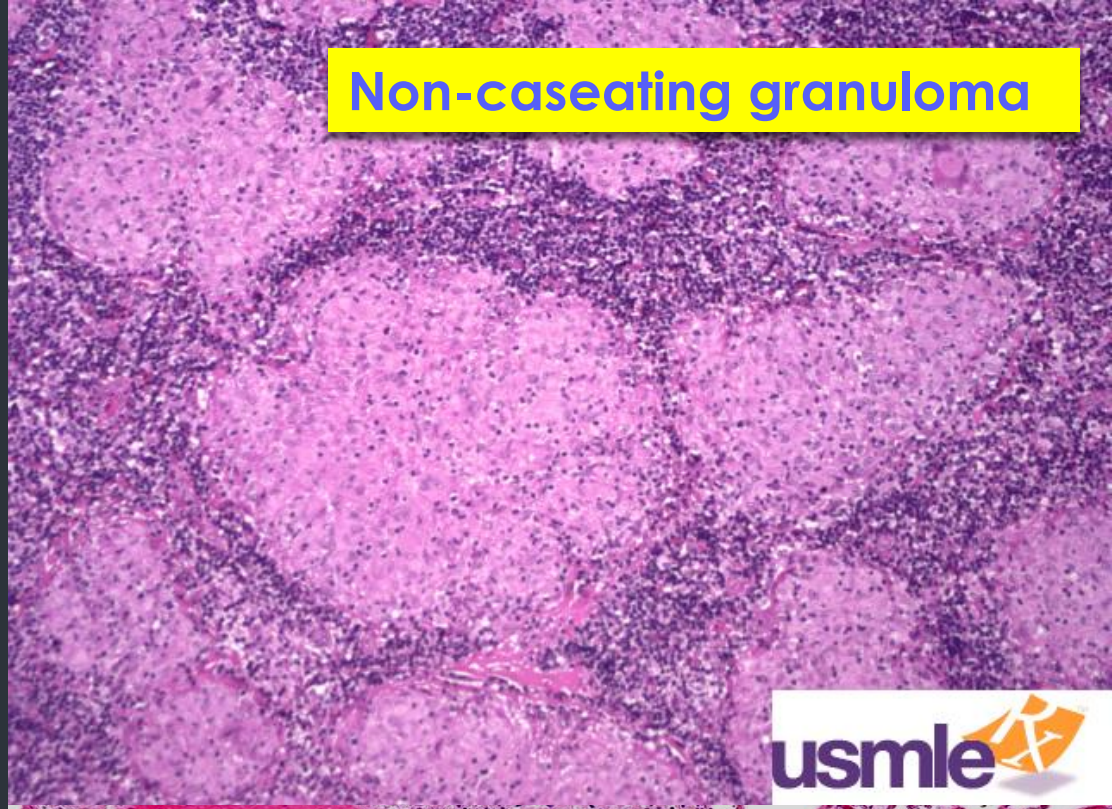


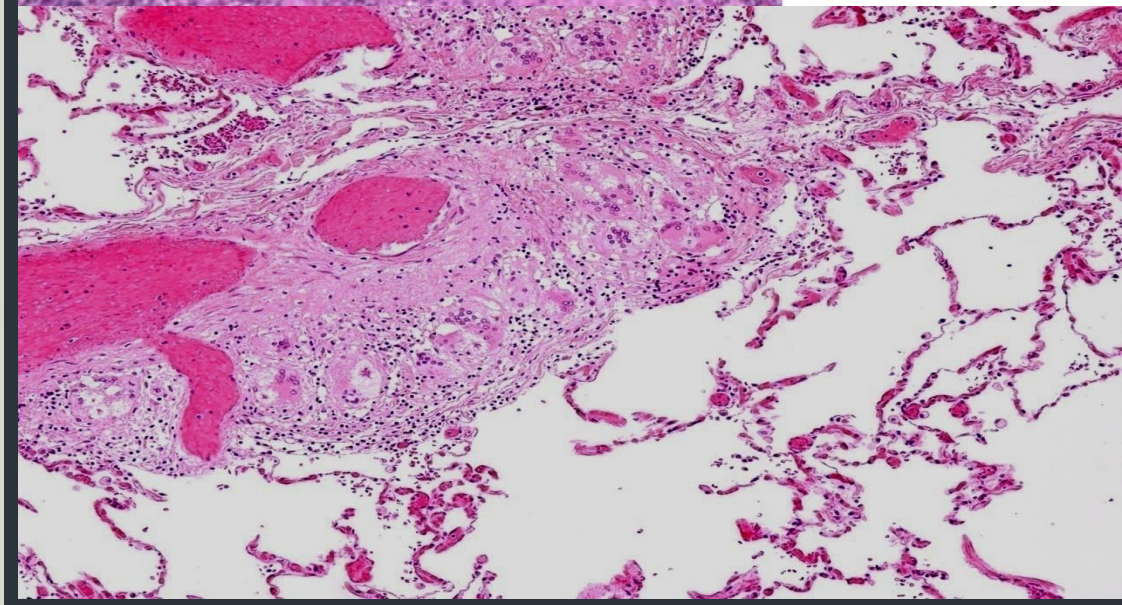


Non-caseating necrosis

Sarcoidosis



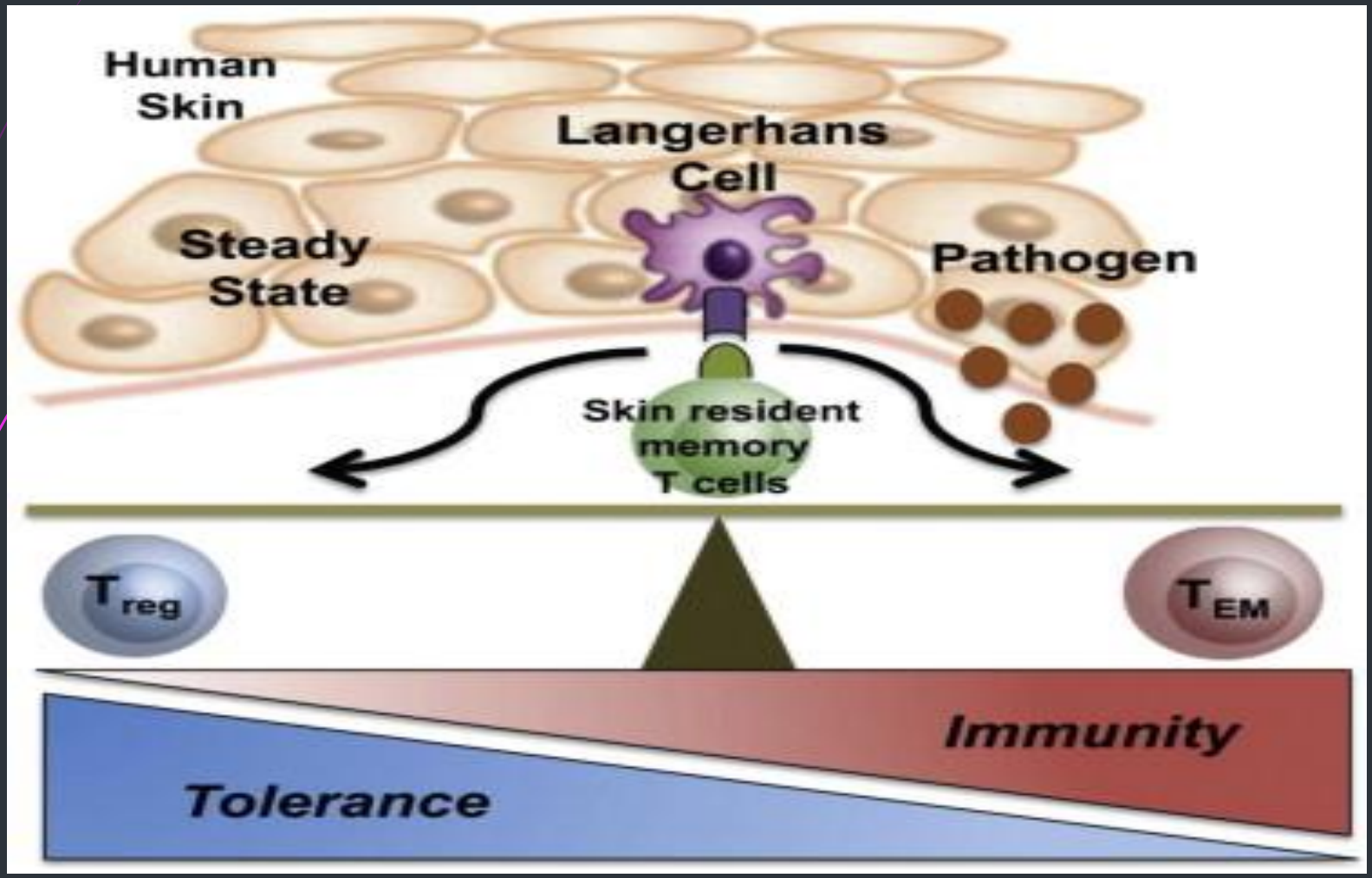




Match A and B

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



- **Which of the following diseases does not cause granulomatous inflammation**

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

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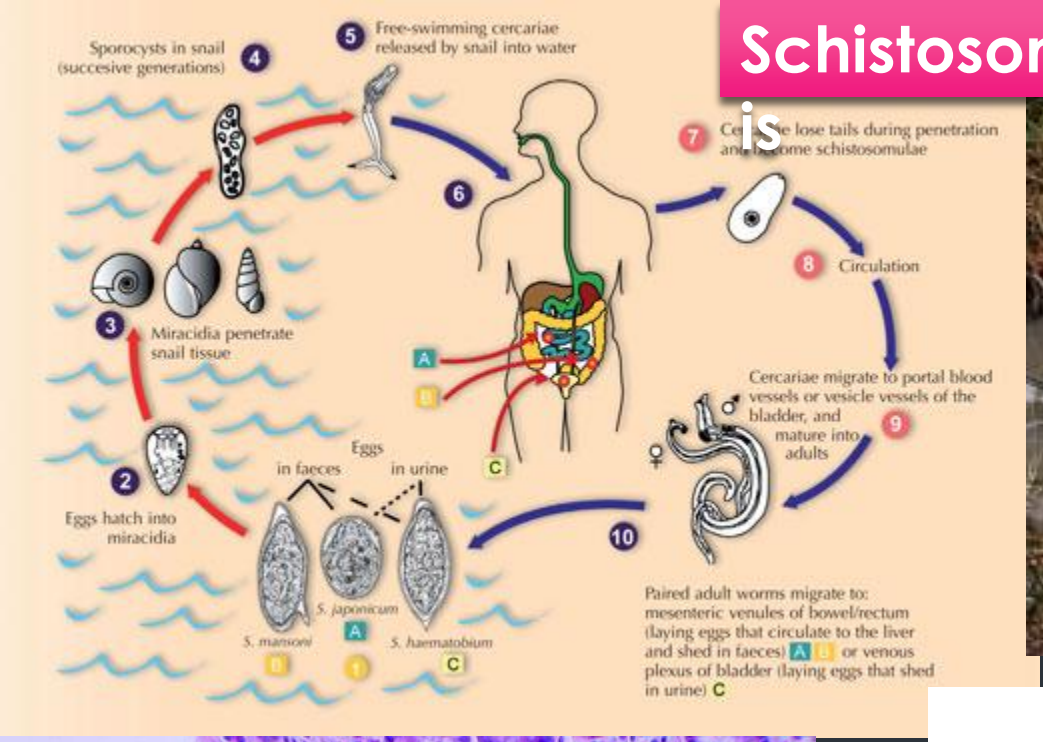
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against intestinal bacteria, possibly self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

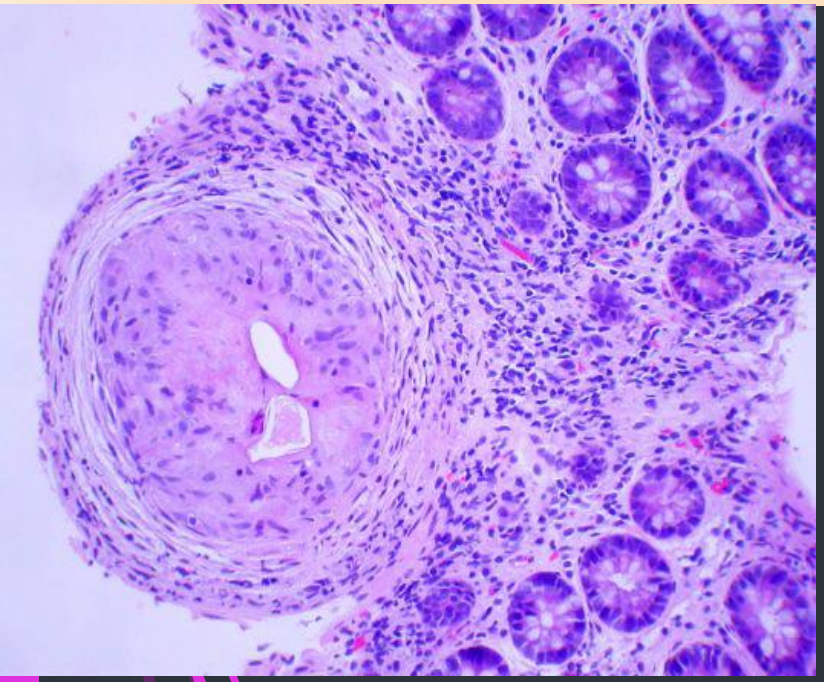
TAKE HOME MESSAGES:

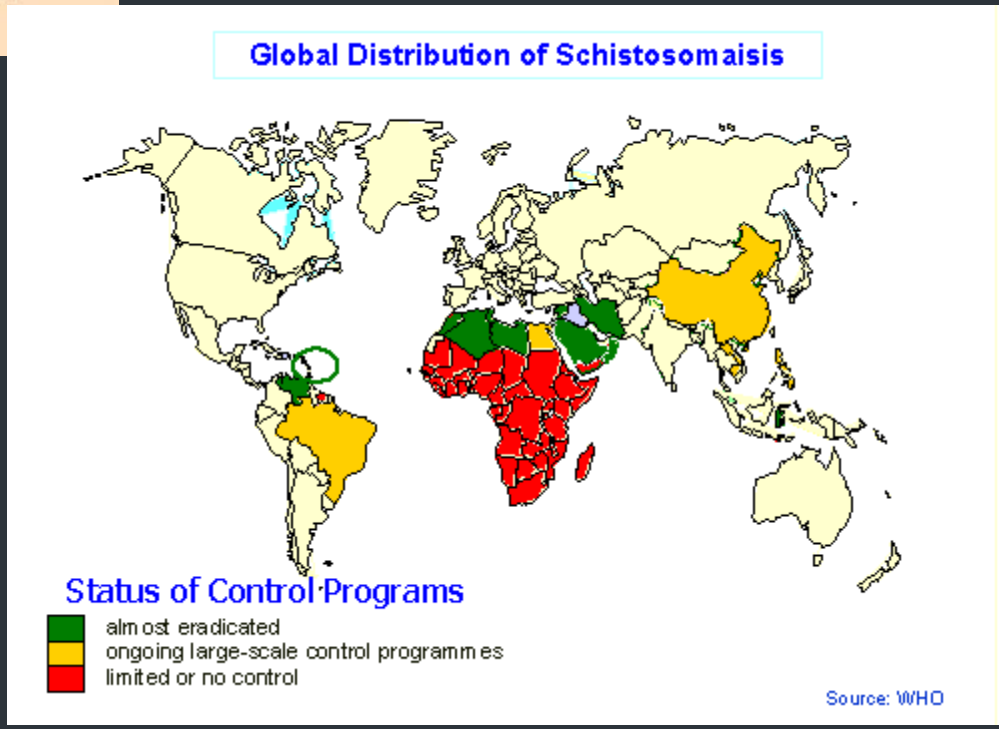
- Granulomatous inflammation is a distinctive pattern of **chronic inflammation** characterized by aggregates **epithelioid macrophages**.
- Damaging stimuli which provoke a granulomatous inflammatory response include; **microorganisms** which are of low inherent pathogenicity but which excite an **immune response**.
- Granulomata are also produced in response to:
  - Parasitic infection: e.g. Schistosoma infection.
  - Certain fungi cannot be dealt with adequately by neutrophils.
  - 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.

THANK YOU

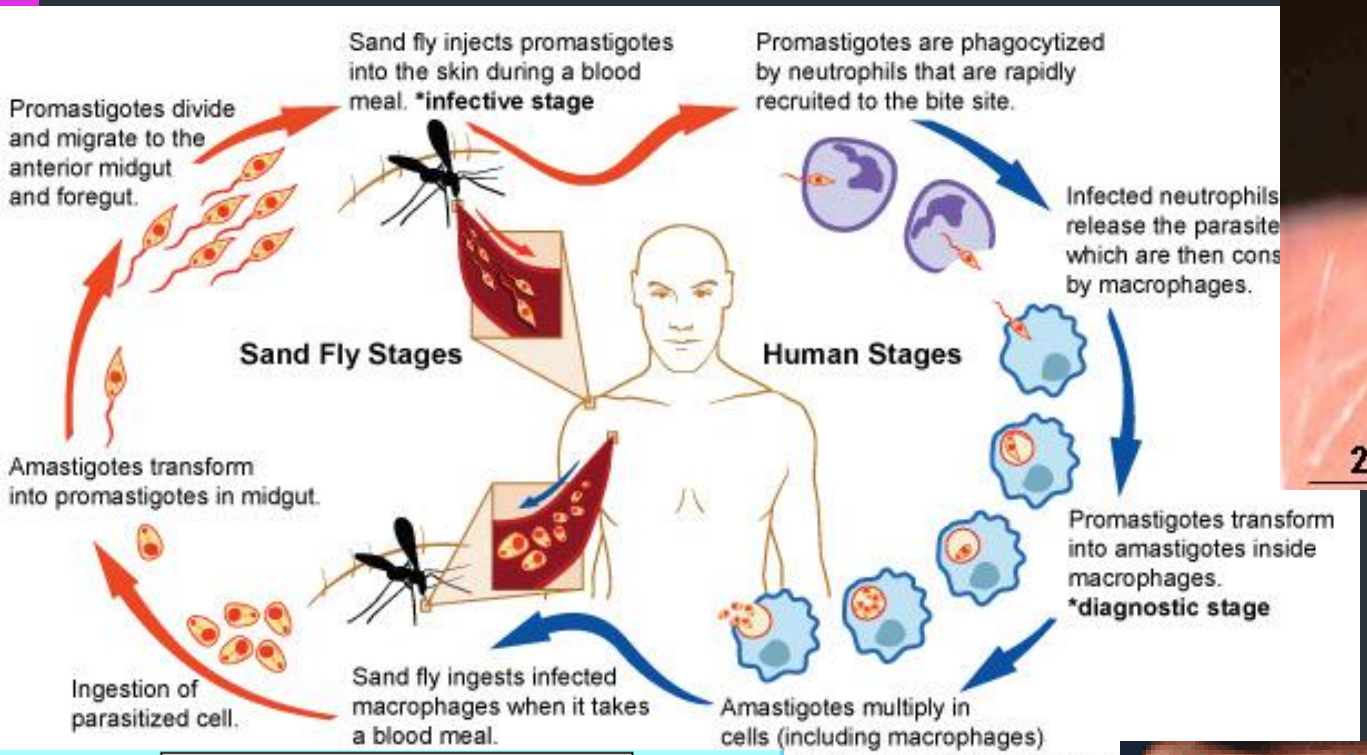
Schistosomias is

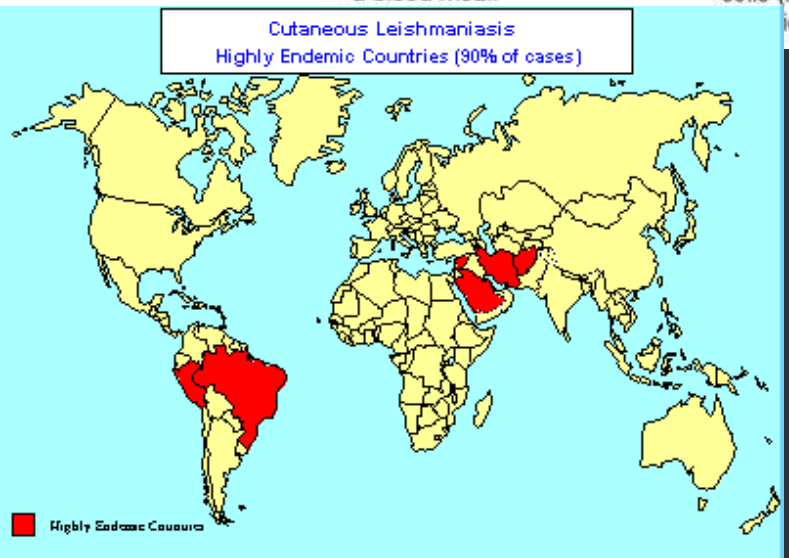


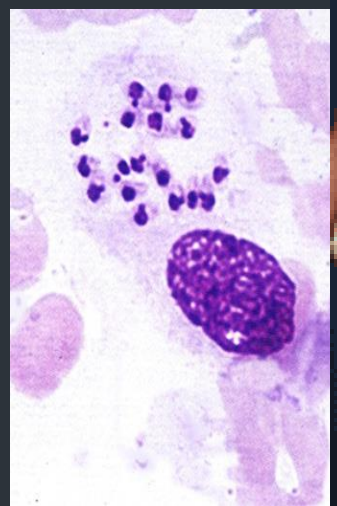


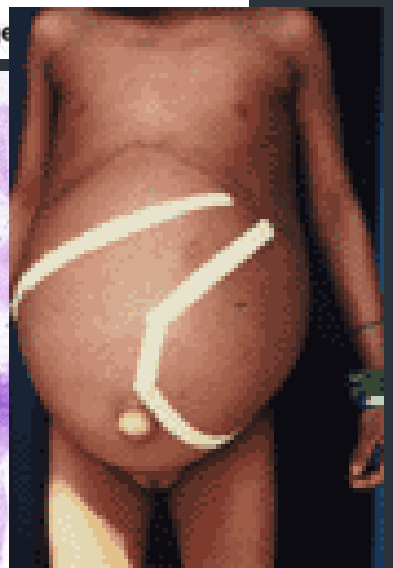


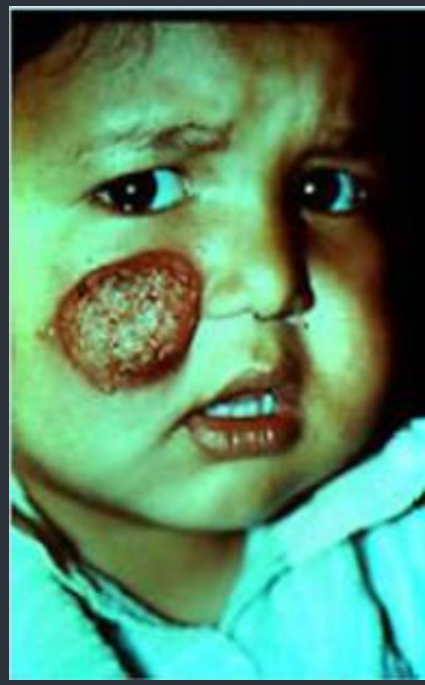
Leishmaniasis



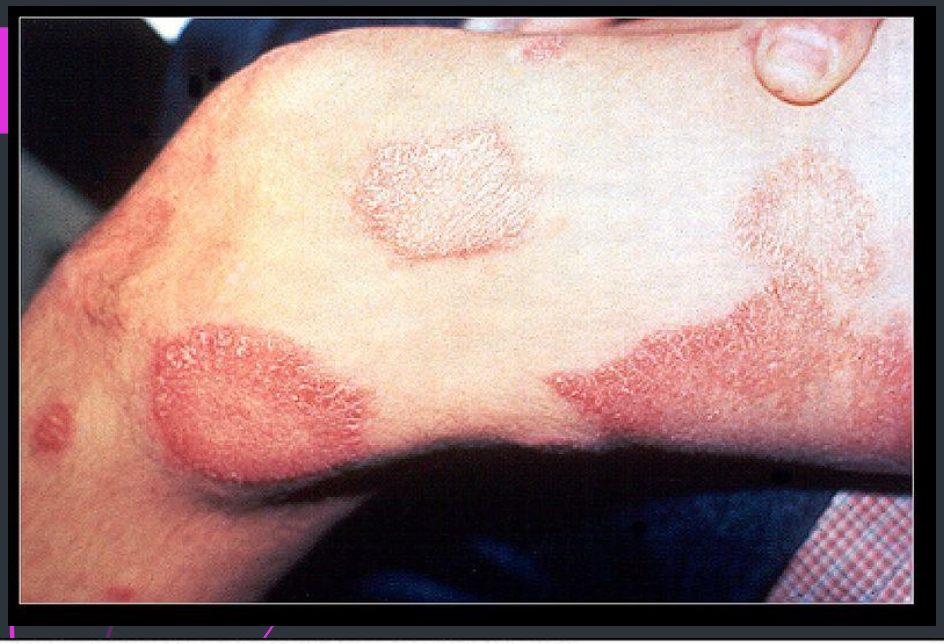


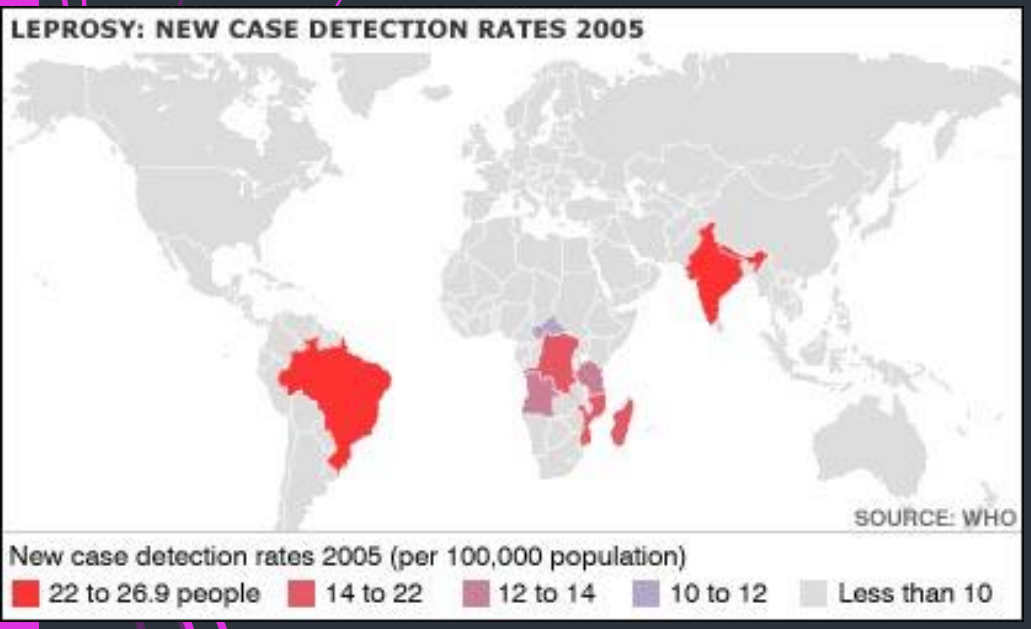






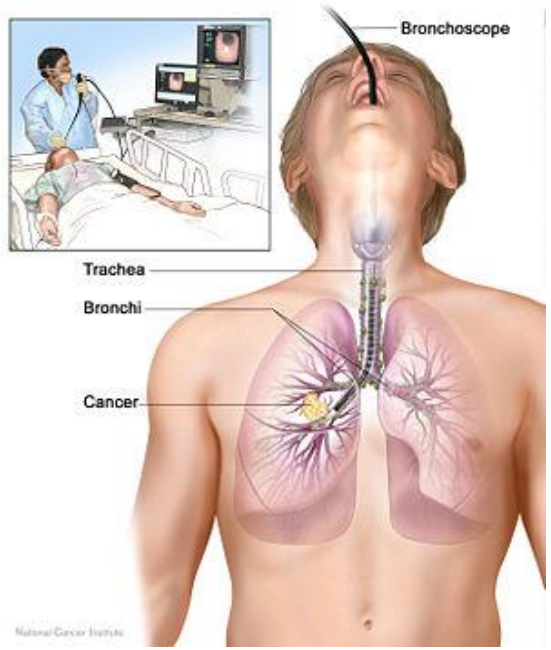
Leprosy

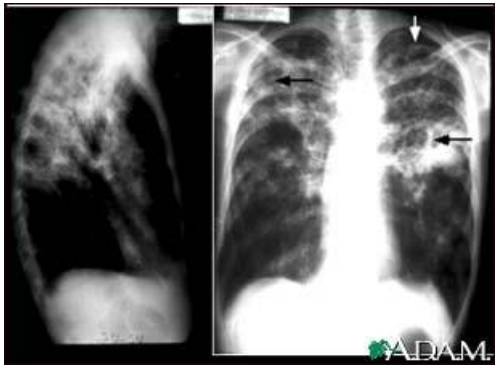



LEPROSY: NEW CASE DETECTION RATES 2005
SOURCE: WHO
New case detection rates 2005 (per 100,000 population)
22 to 26.9 people
14 to 22
12 to 14
10 to 12
Less than 10

Diagnosis of pulmonary TB

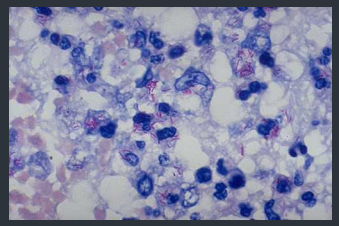
- Sputum smear
  - Acid fast stain (>10,000 CFU/ml)
- Bronchoscopy
- Chest X-Ray
- Tuberculin skin testing (TST)





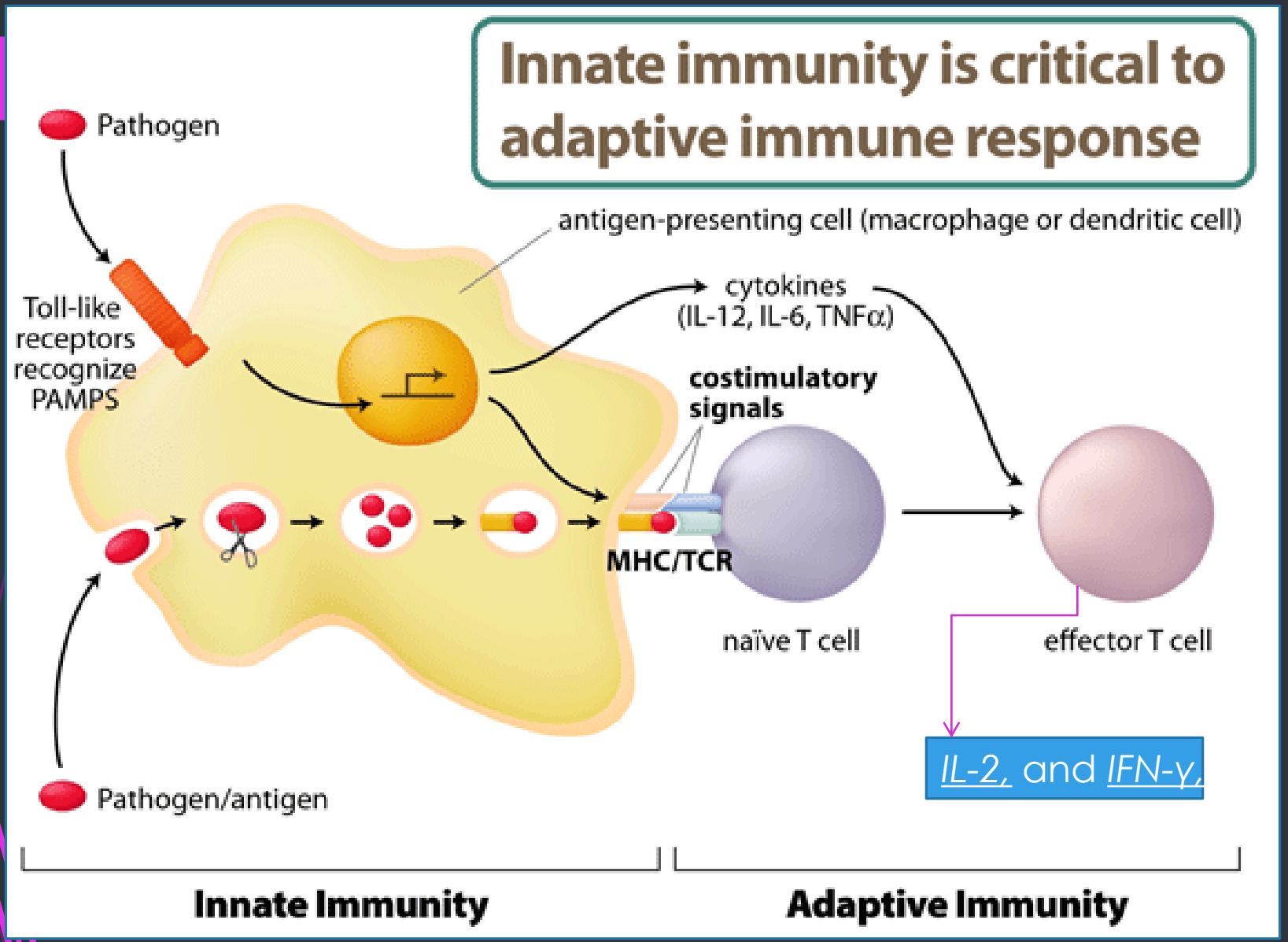
National Cancer Institute. 2006
http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/1607.jpg

Sputum , TB bacilli



- Sputum smear
  - Acid fast stain (>10,000 CFU/ml)
- Bronchoscopy
- Chest X-Ray
- Tuberculin skin testing (TST)

Innate immunity is critical to adaptive immune response



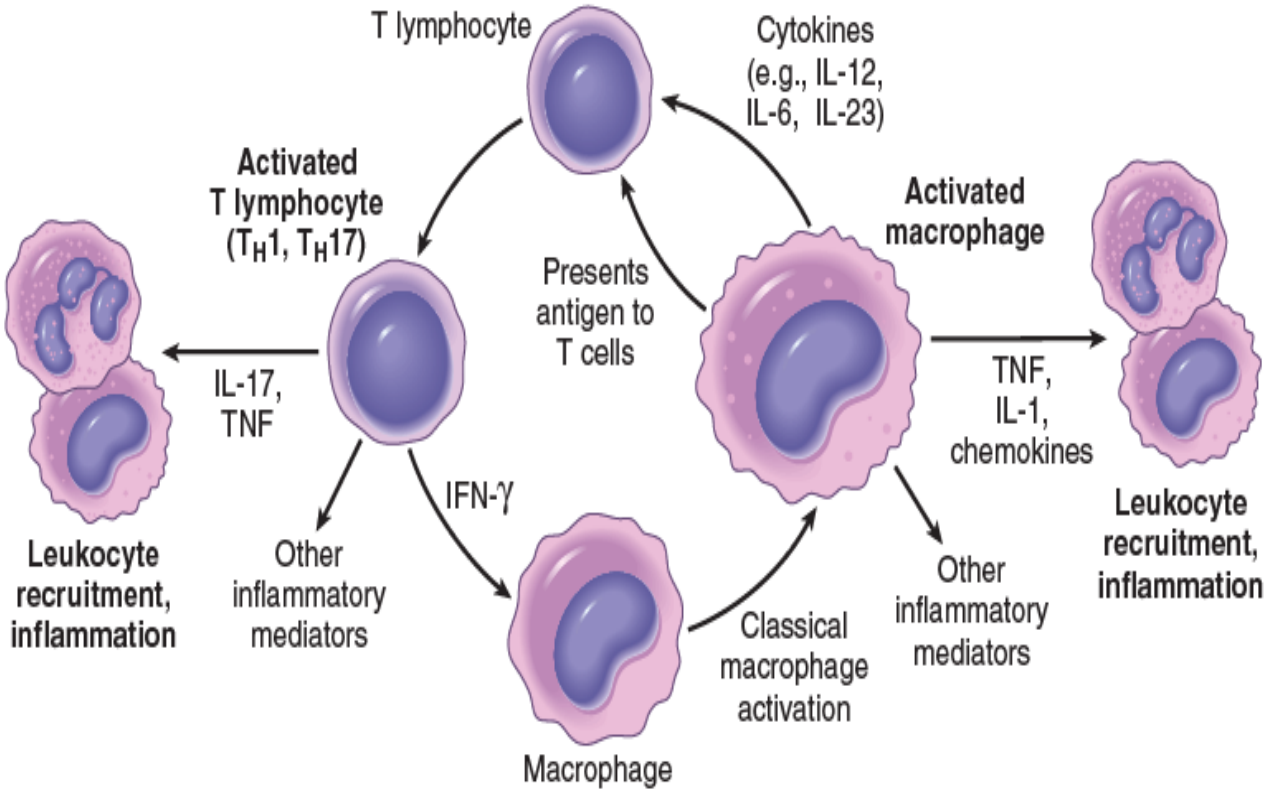


Figure 3-21 Macrophage-lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit macrophages (TNF, IL-17, chemokines) and others that activate macrophages (IFN-γ). Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines such as IL-12.