GRANULOMATOUS INFLAMMATION

2015

Slides have been taken from Dr. Maha Arafah.
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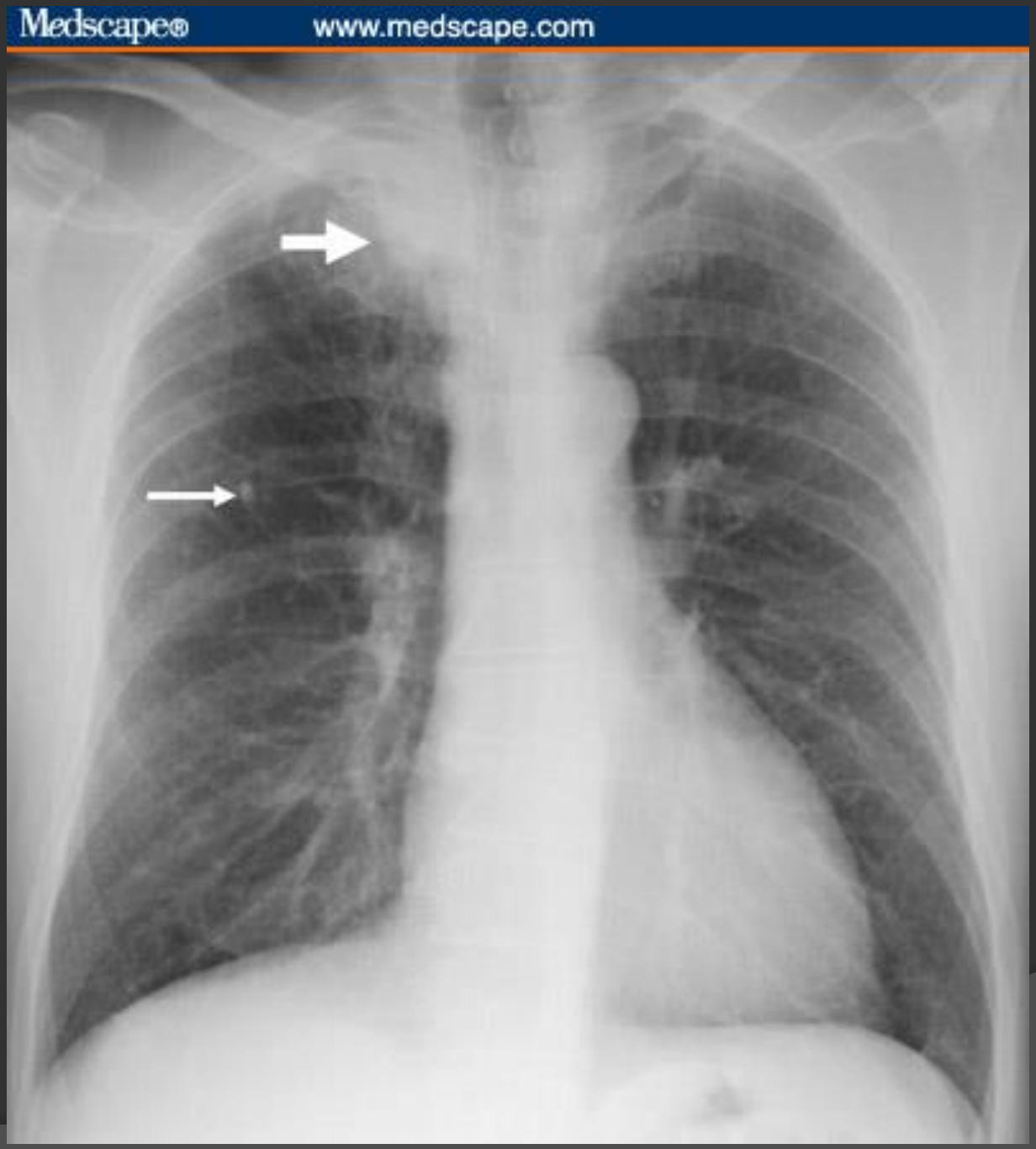
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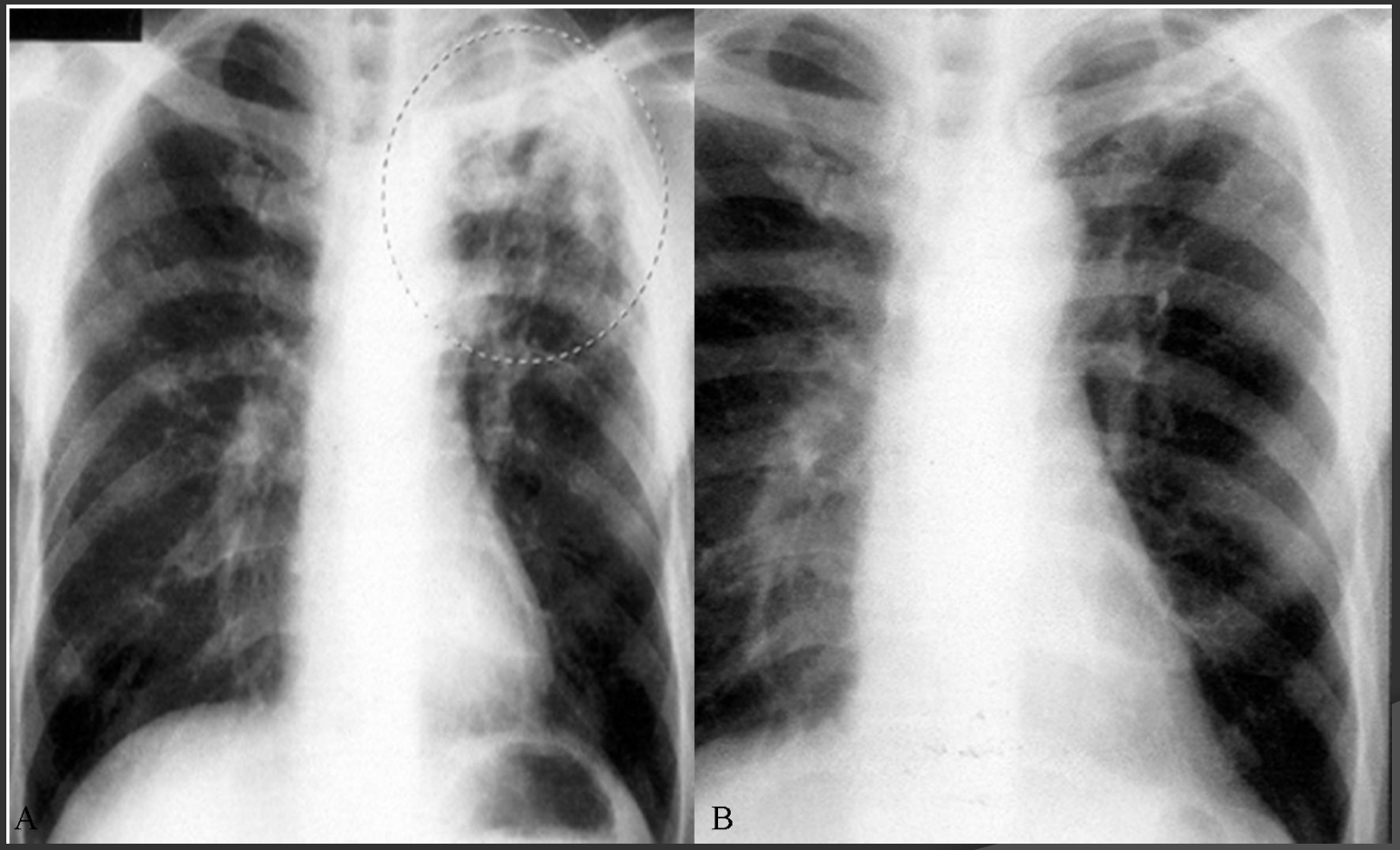
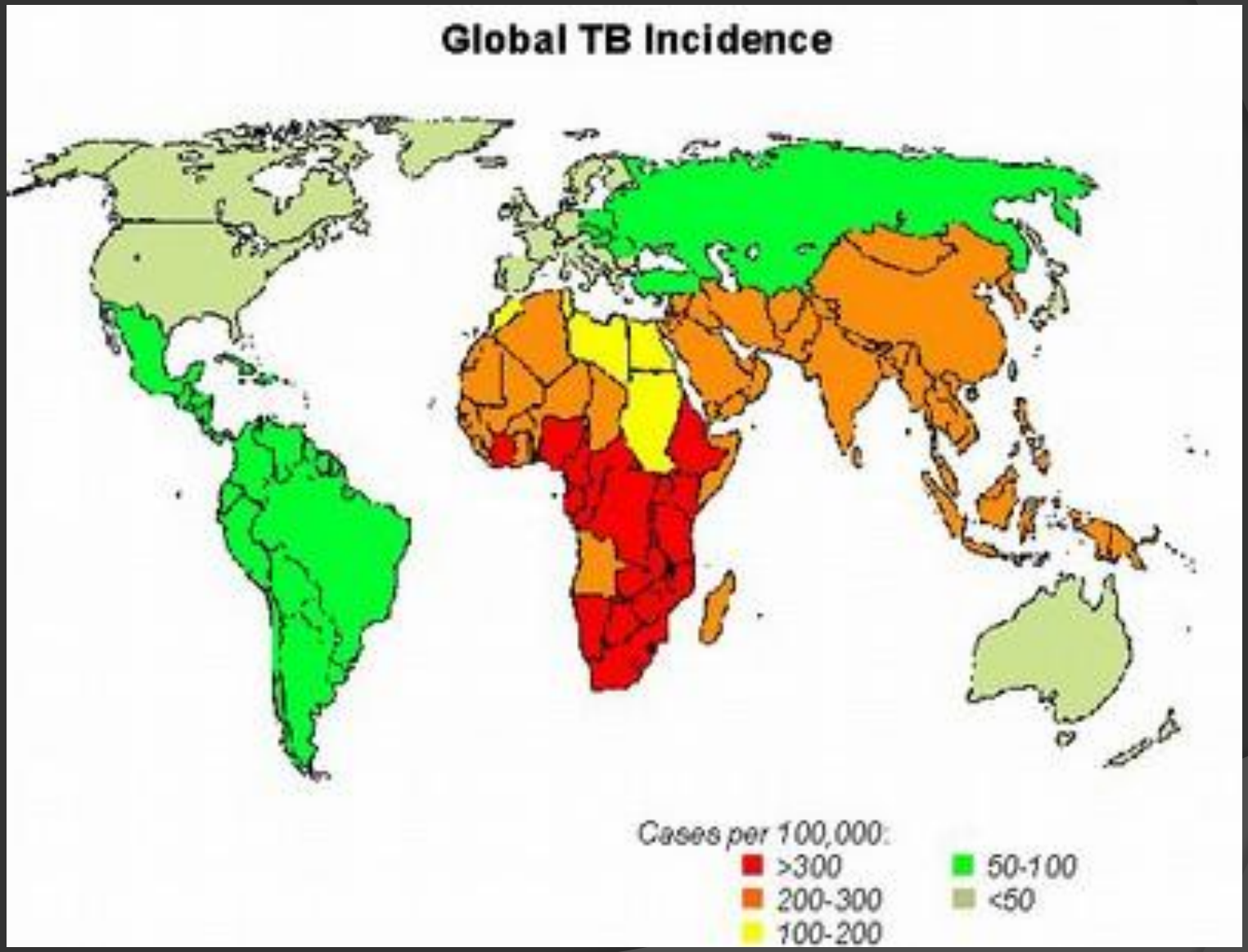
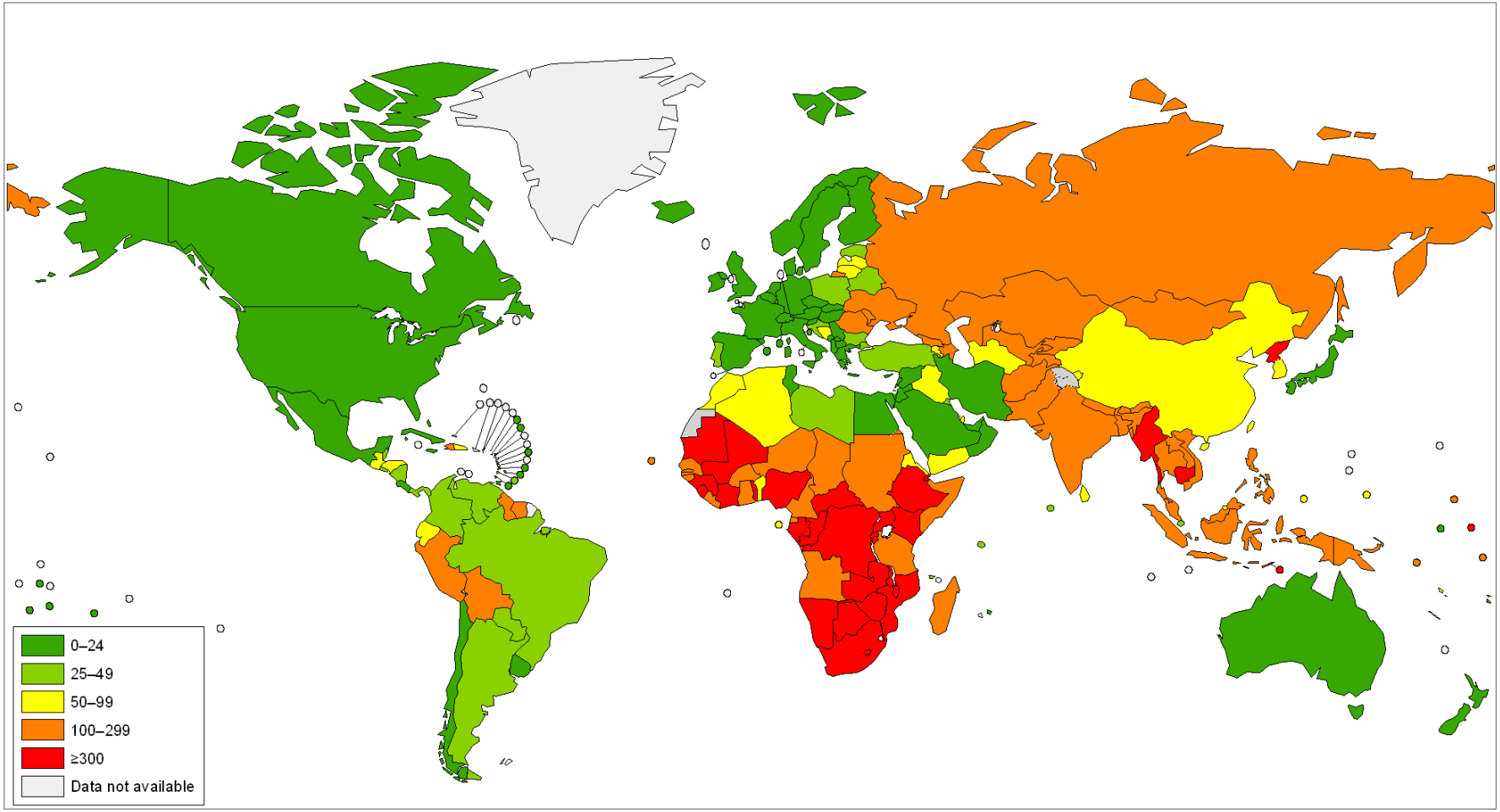

A
B


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

Estimated incidence of tuberculosis (per 100 000 population), 2008



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

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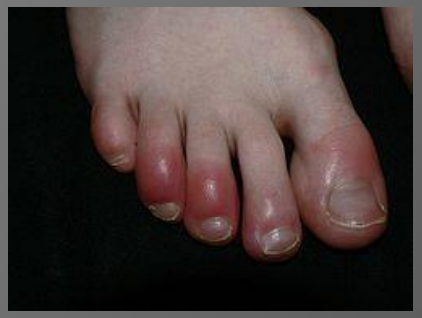
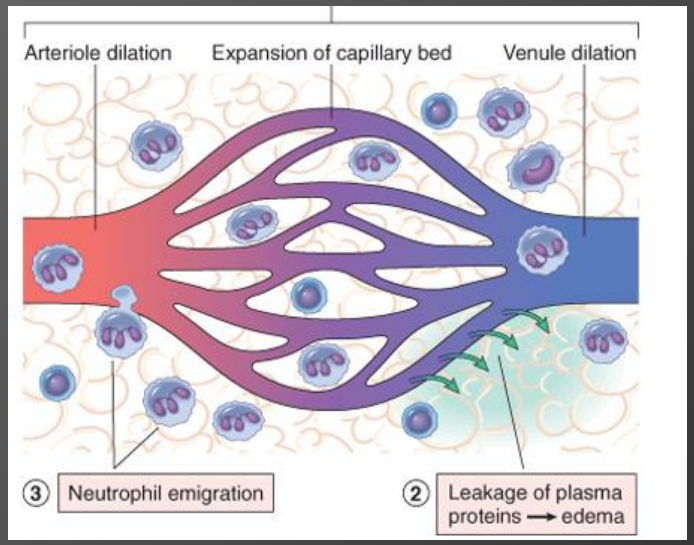


Inflammation

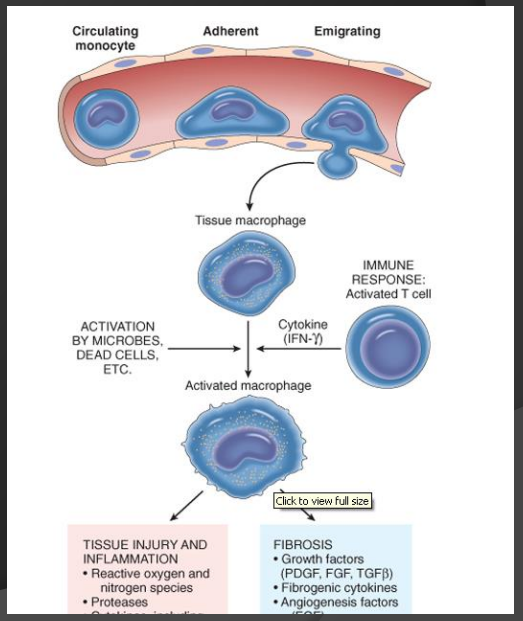
Acute *inflammation*

Neutrophils



Chronic *inflammation*

Macrophage
Lymphocytes
Plasma cells



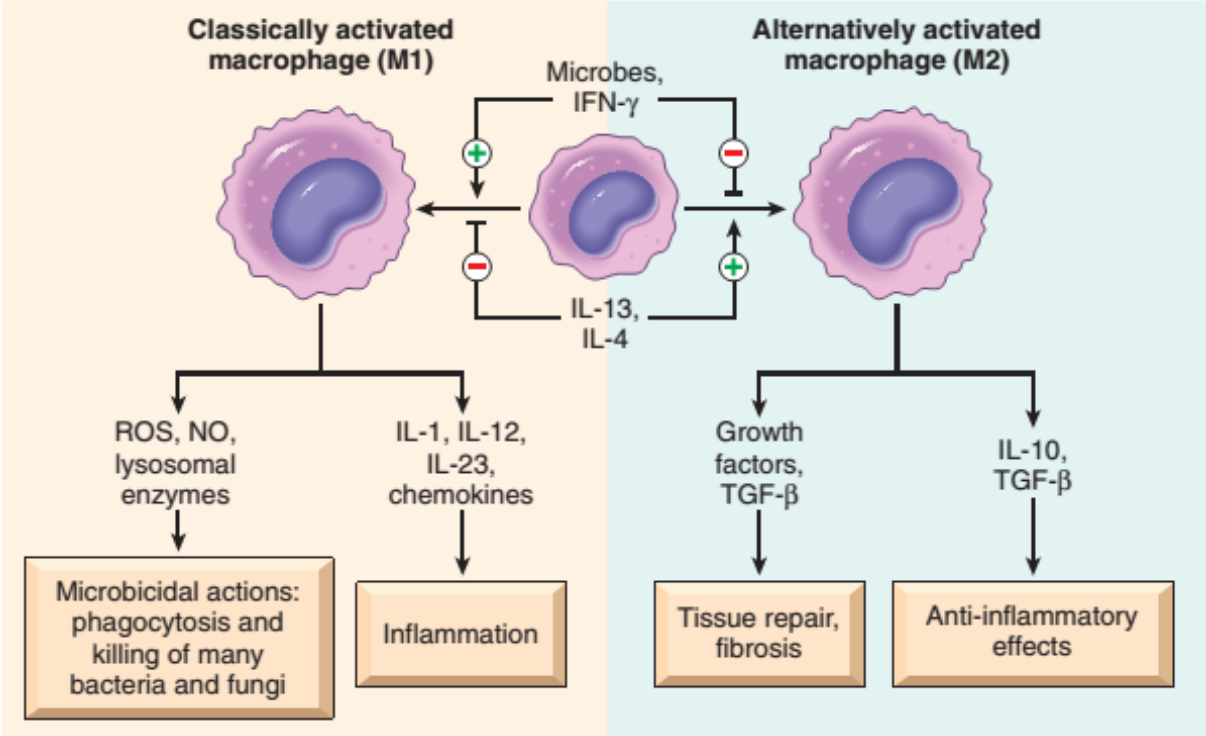


Figure 2–21 Pathways of macrophage activation. Different stimuli activate monocytes/macrophages to develop into functionally distinct populations. Classically activated macrophages are induced by microbial products and cytokines, particularly IFN-γ, and are microbicidal and involved in potentially harmful 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.

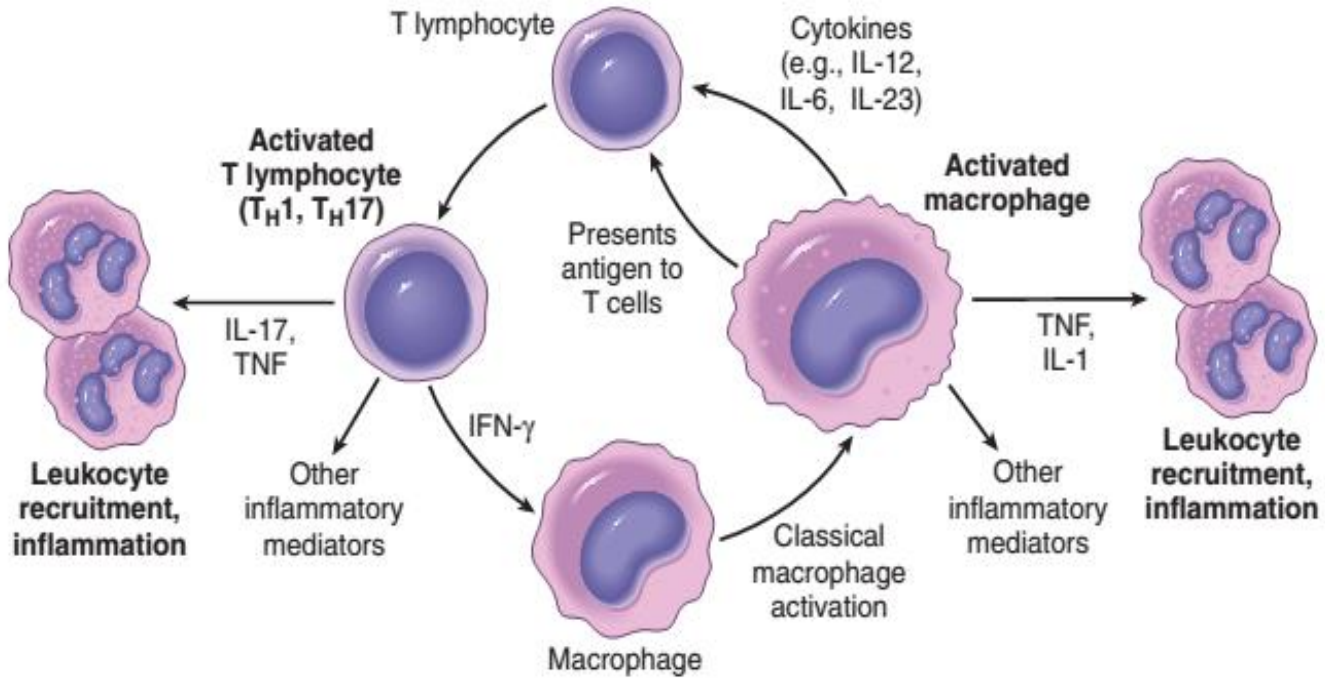


Figure 2–22 Macrophage–lymphocyte interactions in chronic inflammation. Activated lymphocytes and macrophages stimulate each other, and both cell types release inflammatory mediators that affect other cells. IFN-γ, interferon-γ; IL-1, interleukin-1; TNF, tumor necrosis factor.

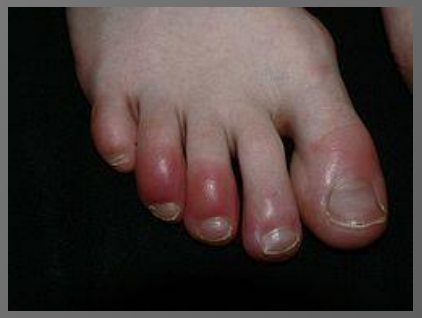
Table 2–8 Examples of Diseases with Granulomatous Inflammation

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

SUMMARY

Features of Chronic Inflammation

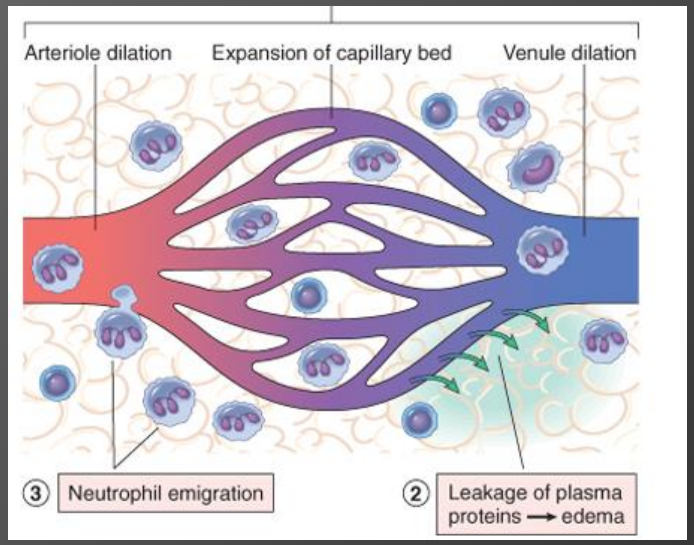
- Prolonged host response to persistent stimulus
- Caused by microbes that resist elimination, immune responses against self and environmental antigens, and some toxic substances (e.g., silica); underlies many important diseases
- Characterized by persistent inflammation, tissue injury, attempted repair by scarring, and immune response
- Cellular infiltrate consisting of activated macrophages, lymphocytes, and plasma cells, often with prominent fibrosis
- Mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes), with a tendency to an amplified and prolonged inflammatory response owing to bidirectional interactions between these cells



Inflammation

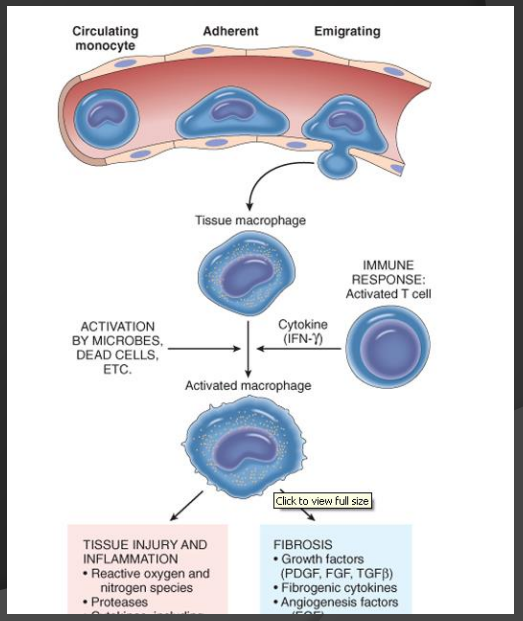
Acute *inflammation*

Neutrophils



Chronic *inflammation*

Macrophage
Lymphocytes
Plasma cells



OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT:

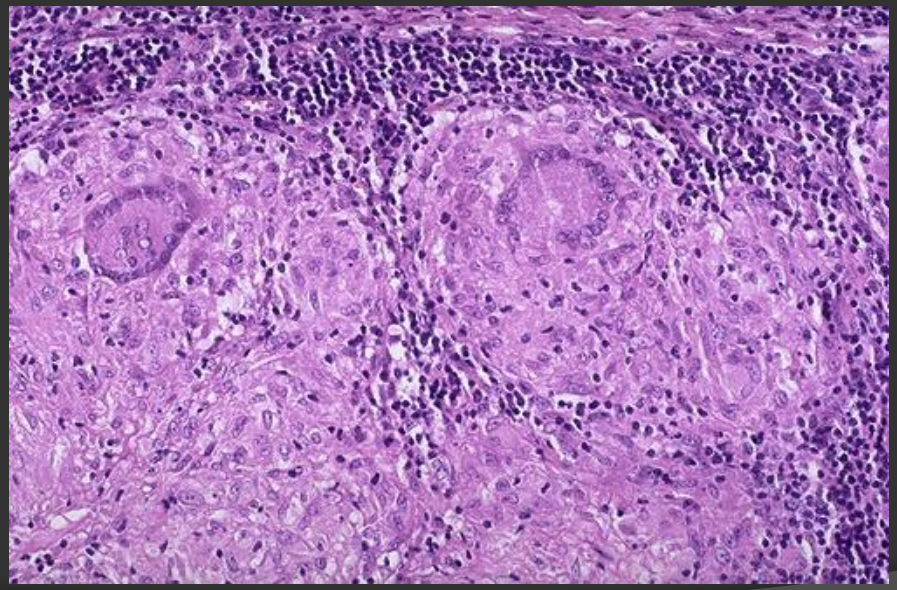
Upon completion of this lecture, the student should:

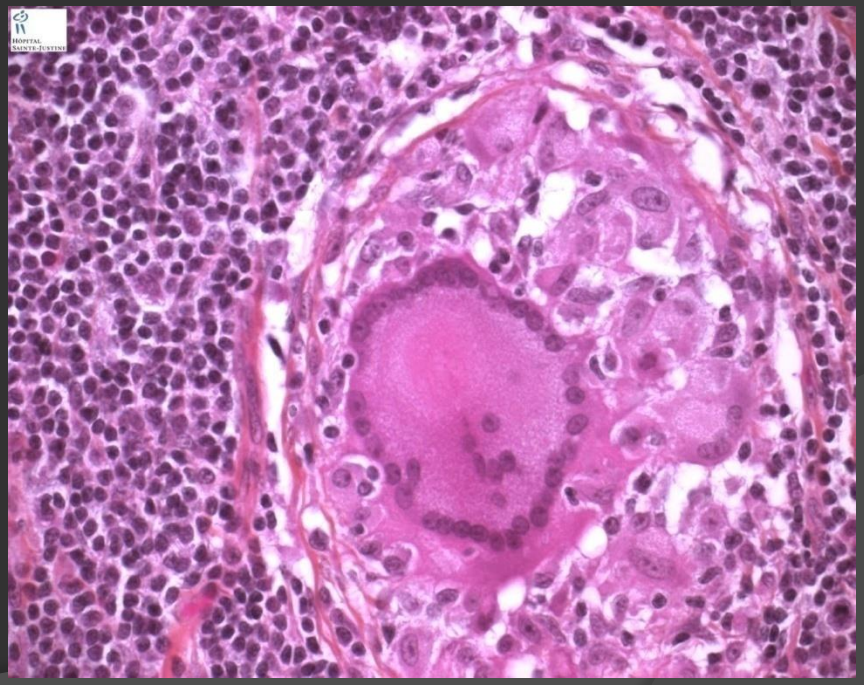
- Define Granulomatous inflammation.
- Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance.
- Identify the two types of granulomas, which differ in their pathogenesis.
  - Foreign body granulomas
  - Immune granulomas
- List the common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

GRANULOMATOUS INFLAMMATION

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

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





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

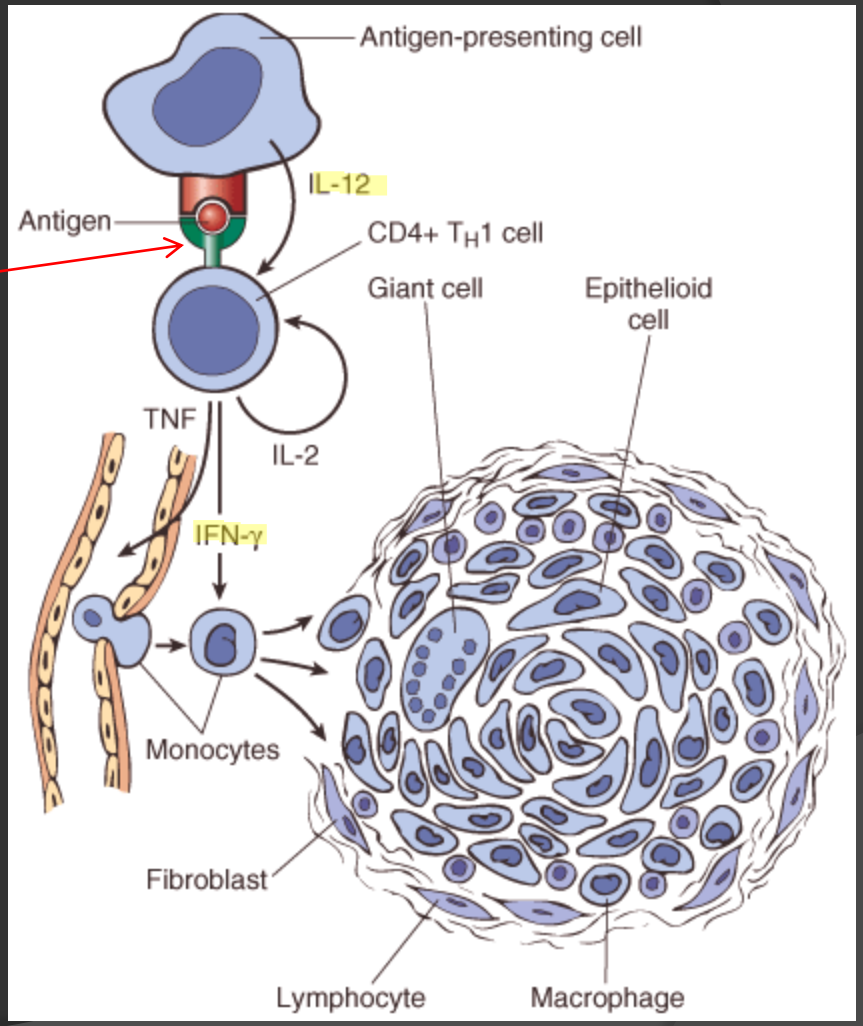
- Neutrophils ordinarily remove agents that incite an acute inflammatory response. However, there are circumstances in which reactive neutrophils ***cannot*** digest the substances that provoke acute inflammation.

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 hypersensitvity

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.

Pathogenesis

There are two types of granulomas

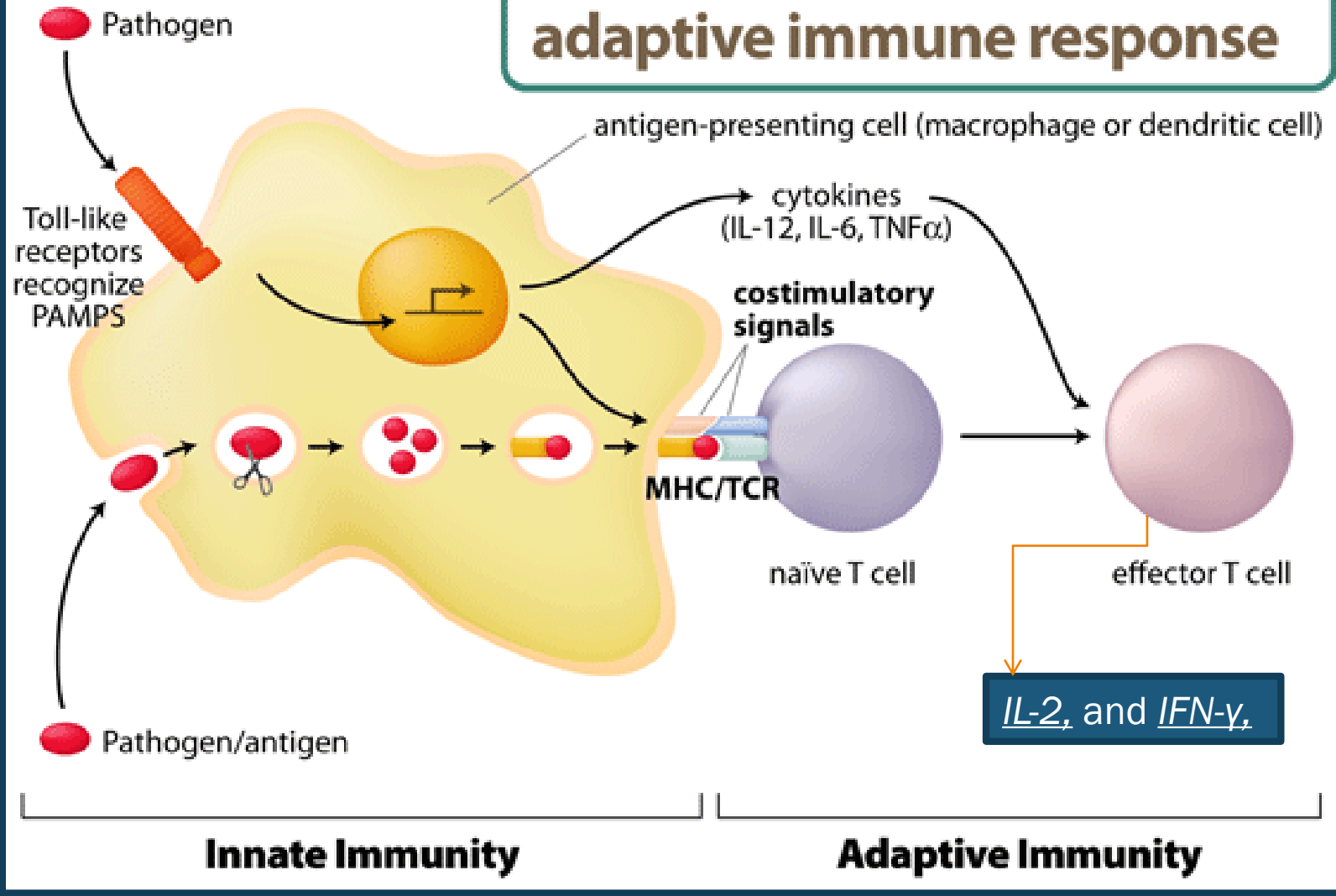
Foreign body granuloma

- 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).

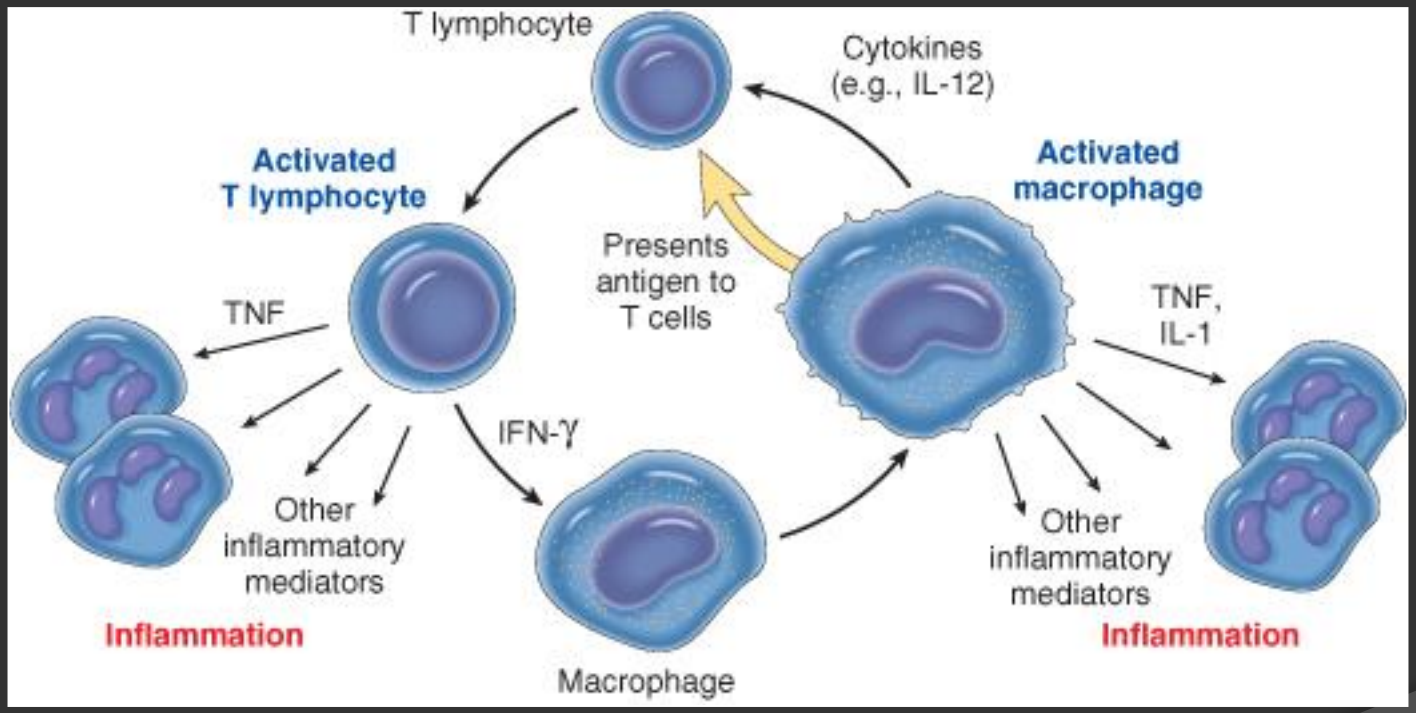
Immune granuloma

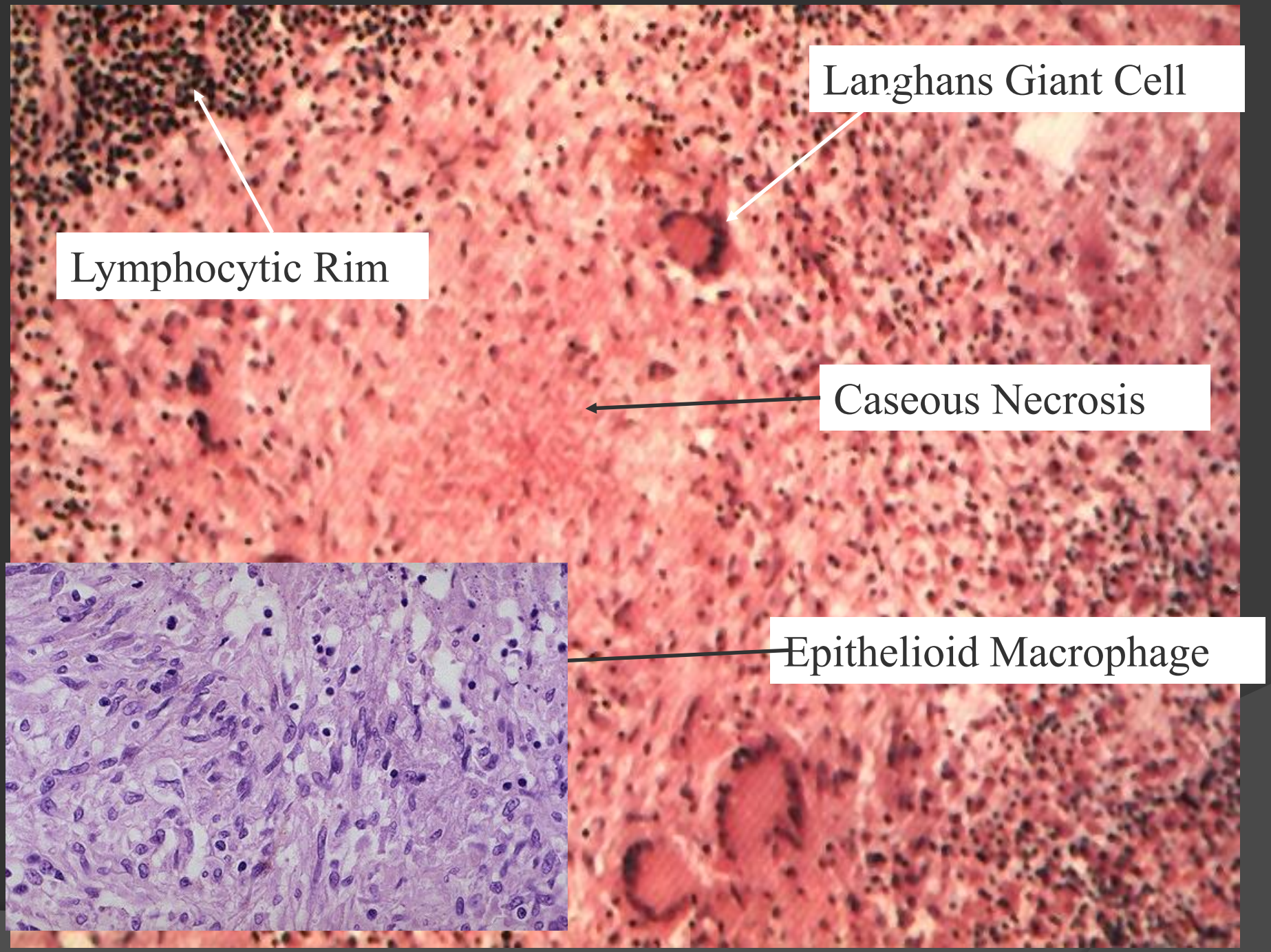
- are caused by insoluble particles, typically microbes, that are capable of inducing a **cell-mediated immune response.**

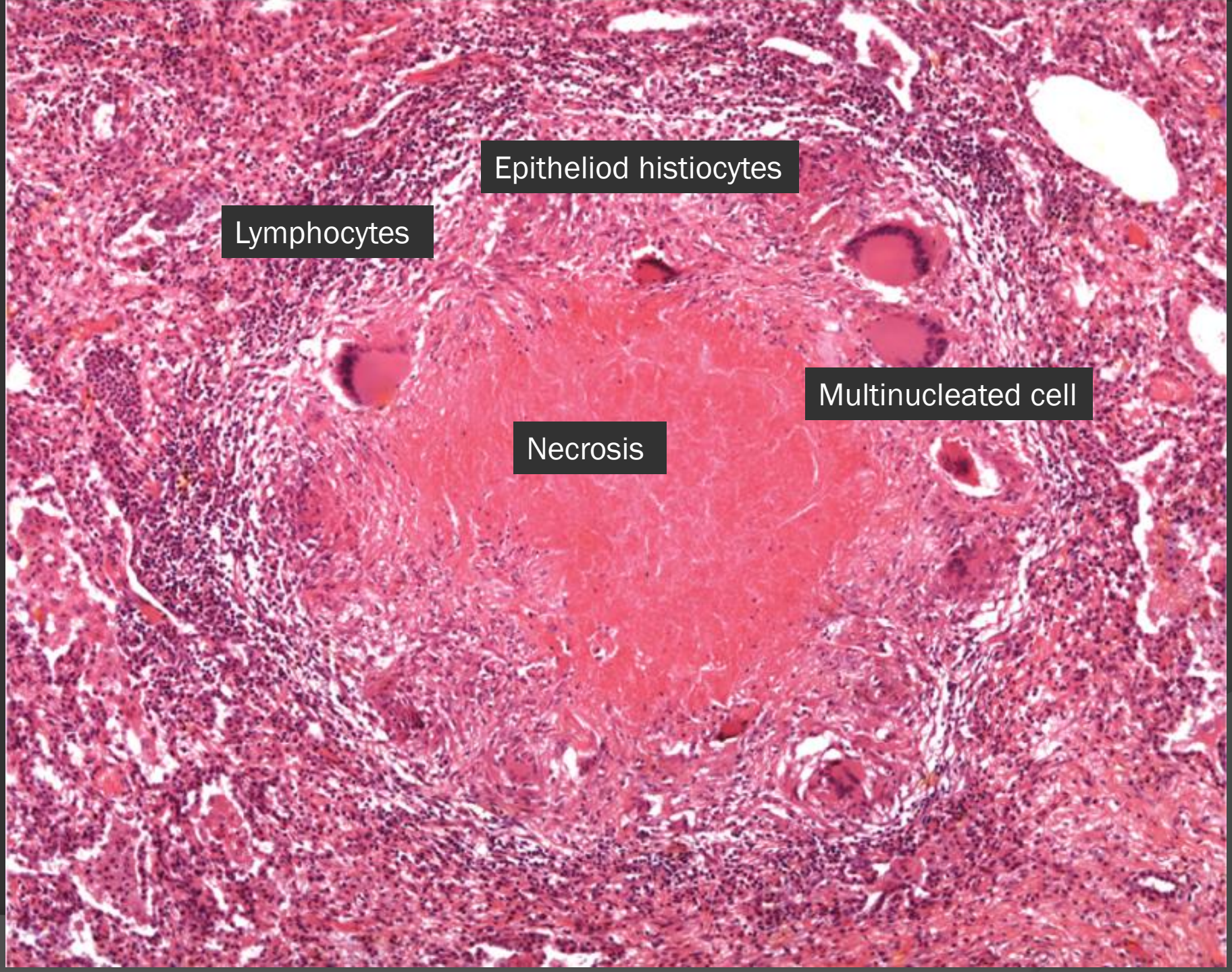
Innate immunity is critical to adaptive immune response



IL-2, and *IFN-γ,*


T lymphocyte
Cytokines
(e.g., IL-12)
Activated
T lymphocyte
Activated
macrophage
Presents
antigen to
T cells
TNF
TNF,
IL-1
IFN-γ
Other
inflammatory
mediators
Other
inflammatory
mediators
Inflammation
Inflammation
Macrophage


Langhans Giant Cell
Lymphocytic Rim
Caseous Necrosis
Epithelioid Macrophage


Epitheliod histiocytes
Lymphocytes
Multinucleated cell
Necrosis

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

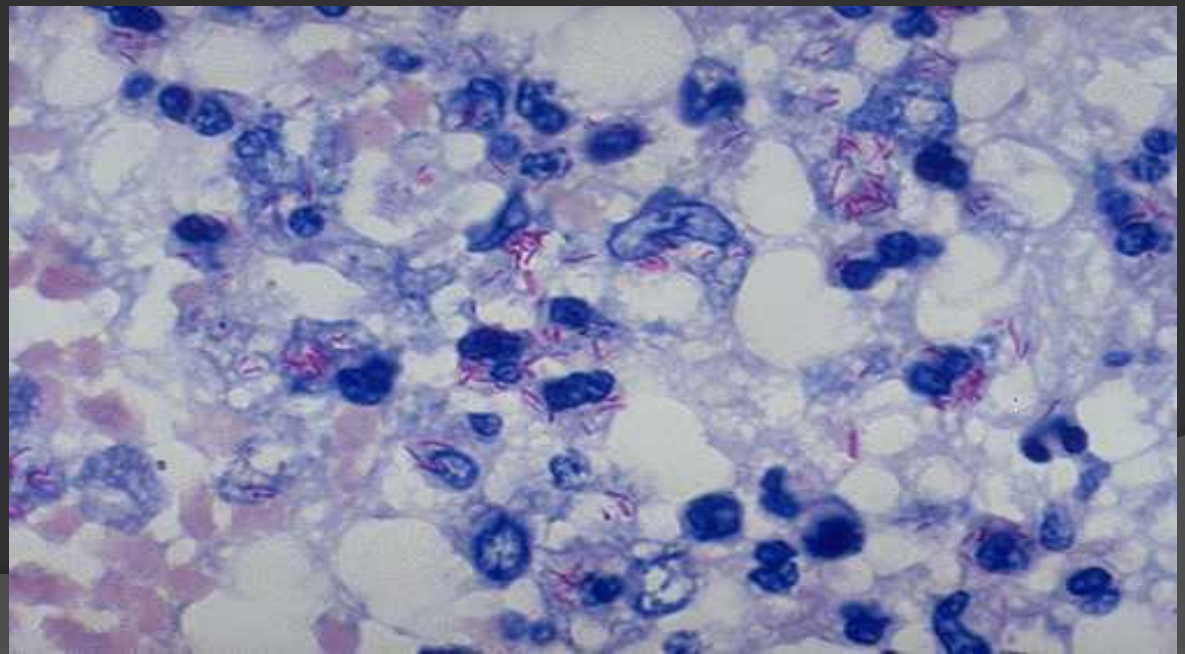
Sarcoidosis

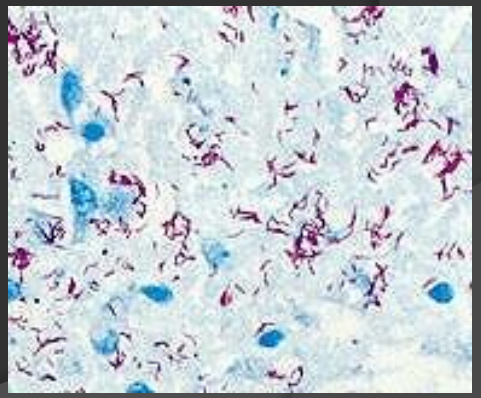
Crohn's disease

Tuberculosis

Mycobacterum 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).

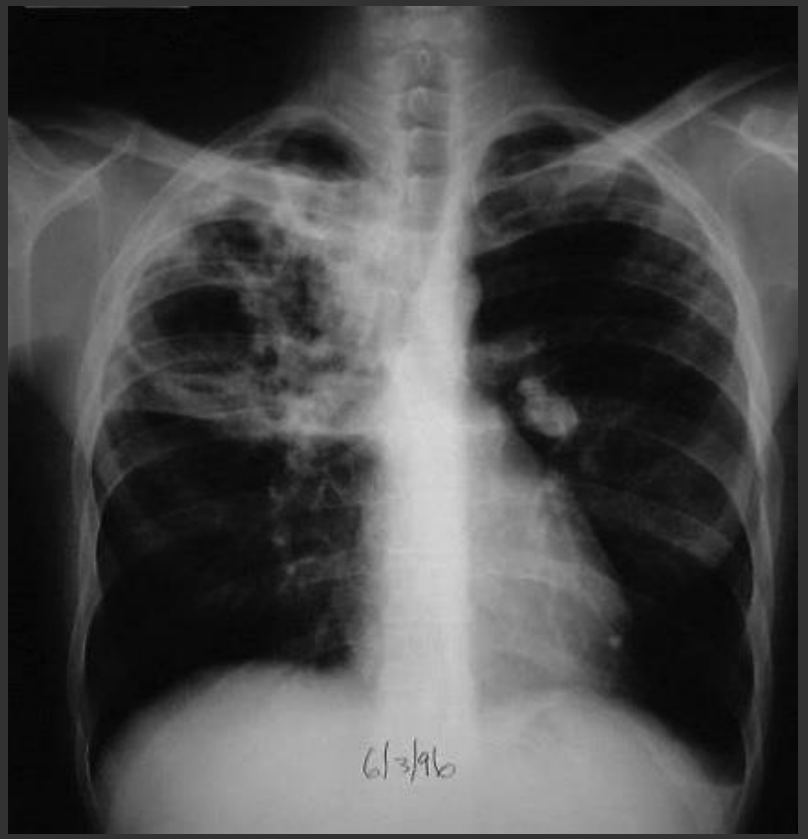




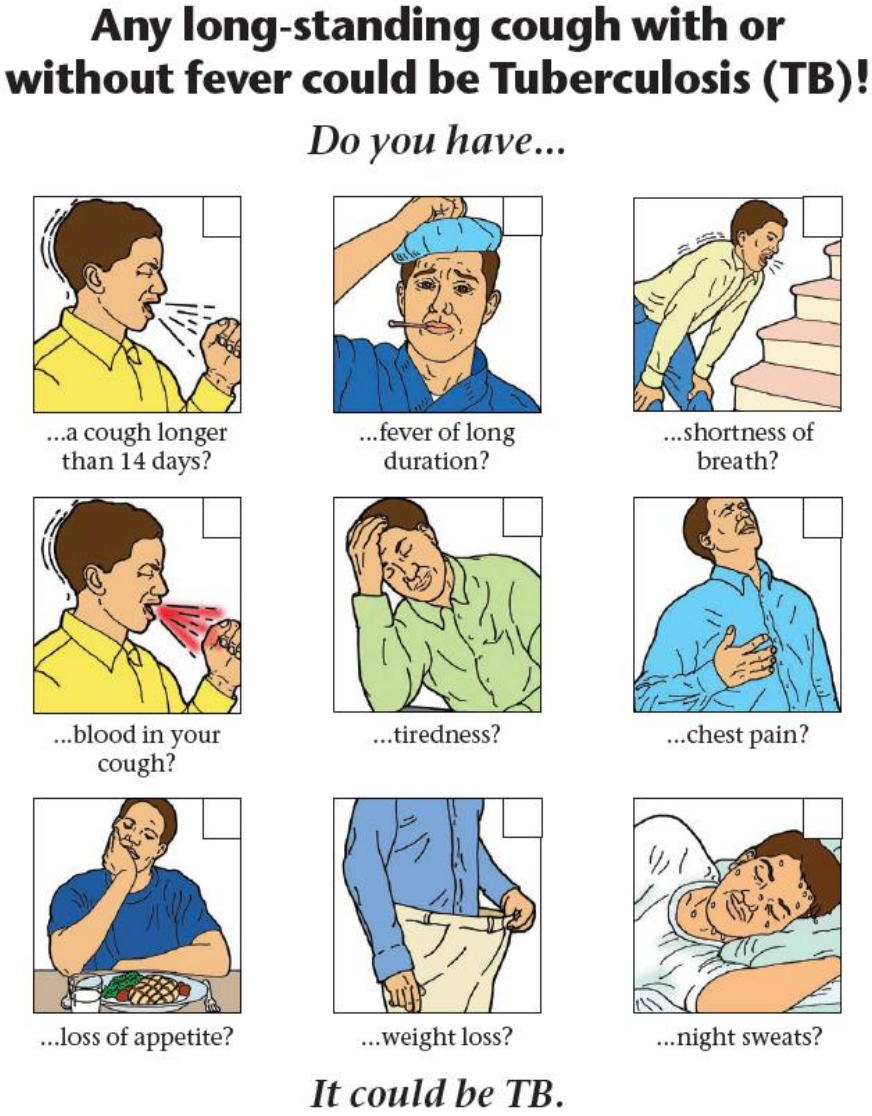
Pathogenesis of TB

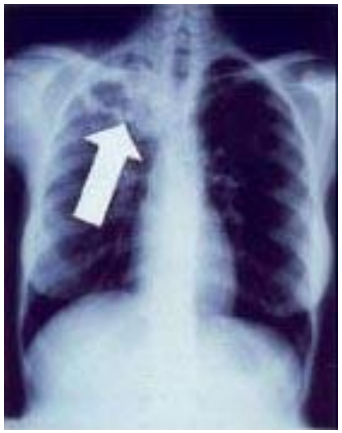
- Cord factor is a glycolipid molecule found in the cell wall of Mycobacterium tuberculosis and similar species.
- It protects *M. tuberculosis* from the defenses of the host
- Cord factor presence increases the production of the cytokines interleukin-12 (IL-12), IL-1β, IL-6 and TNF which are all pro-inflammatory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

Tuberculosis

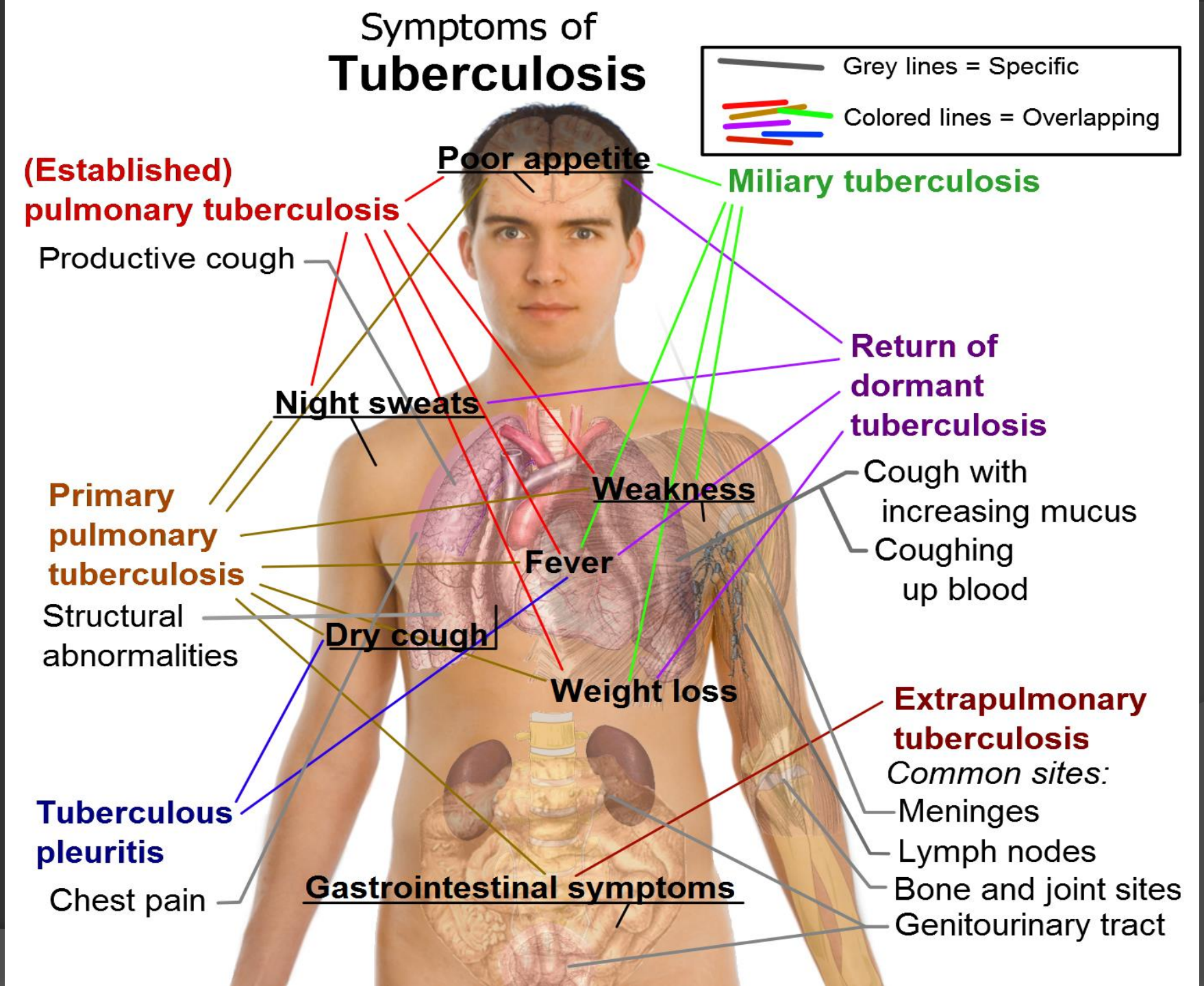


Signs, Symptoms and Diagnosis of TB



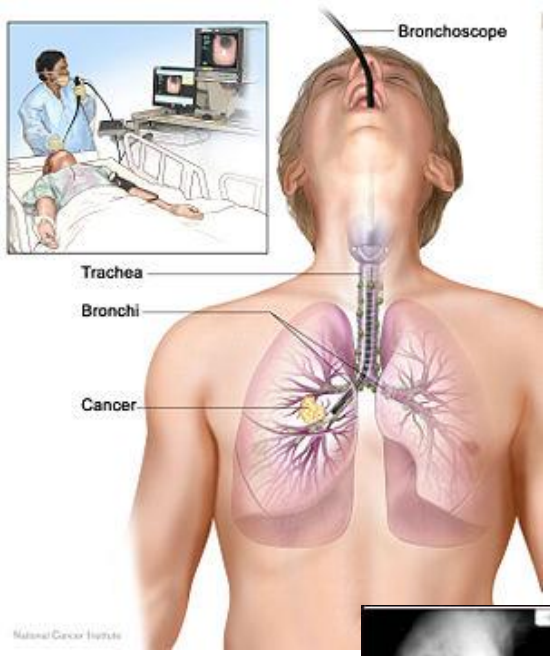


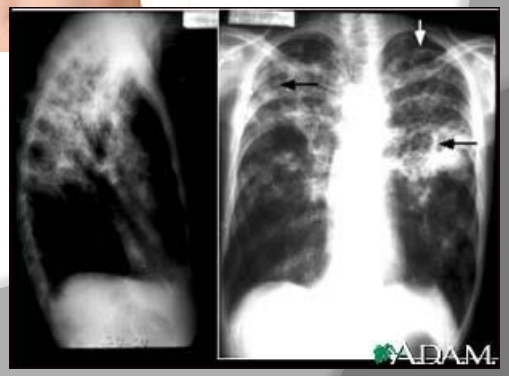
- X-ray
- Sputum smear microscopy
- Culture


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

Diagnosis of pulmonary TB

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

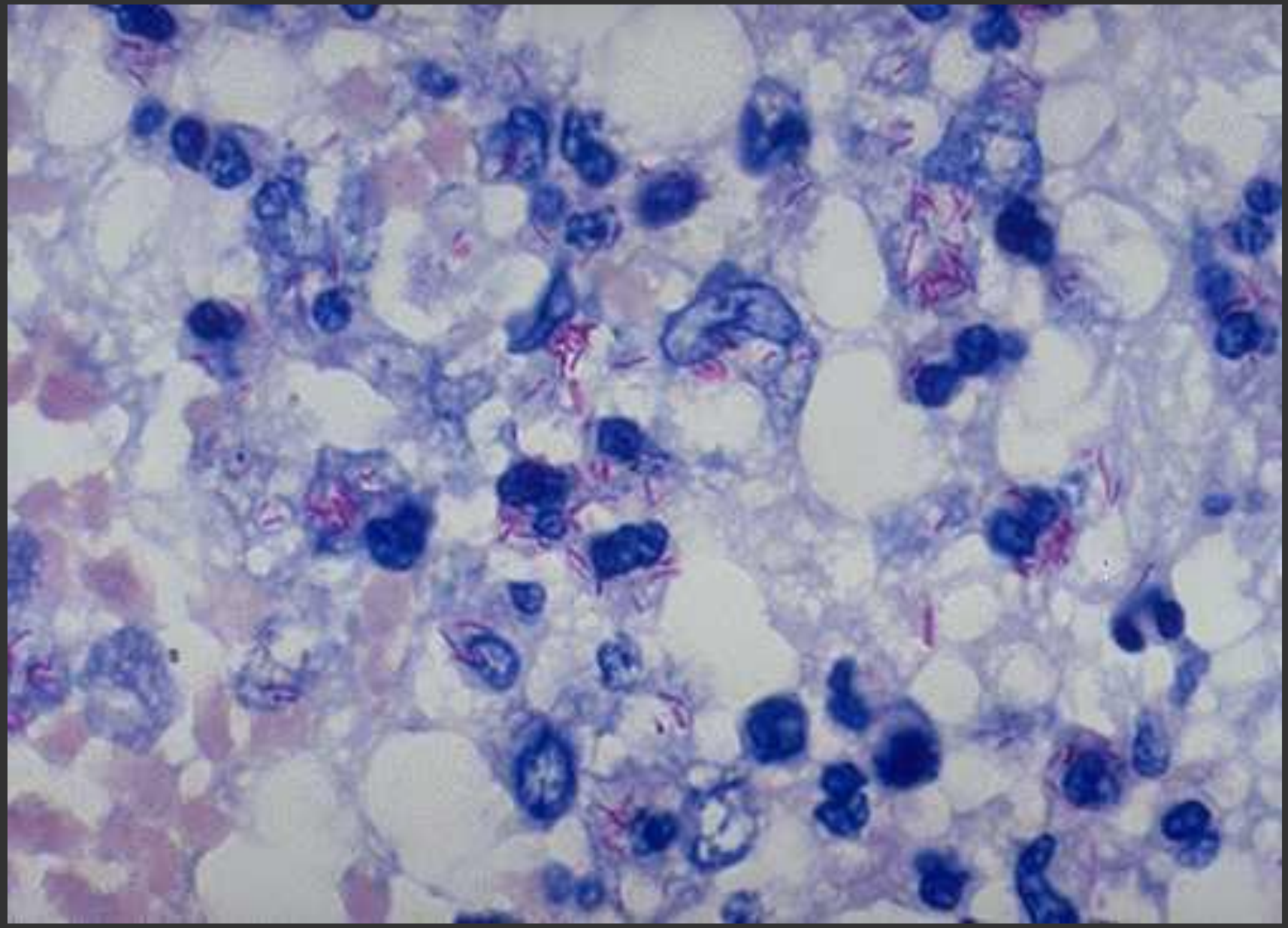




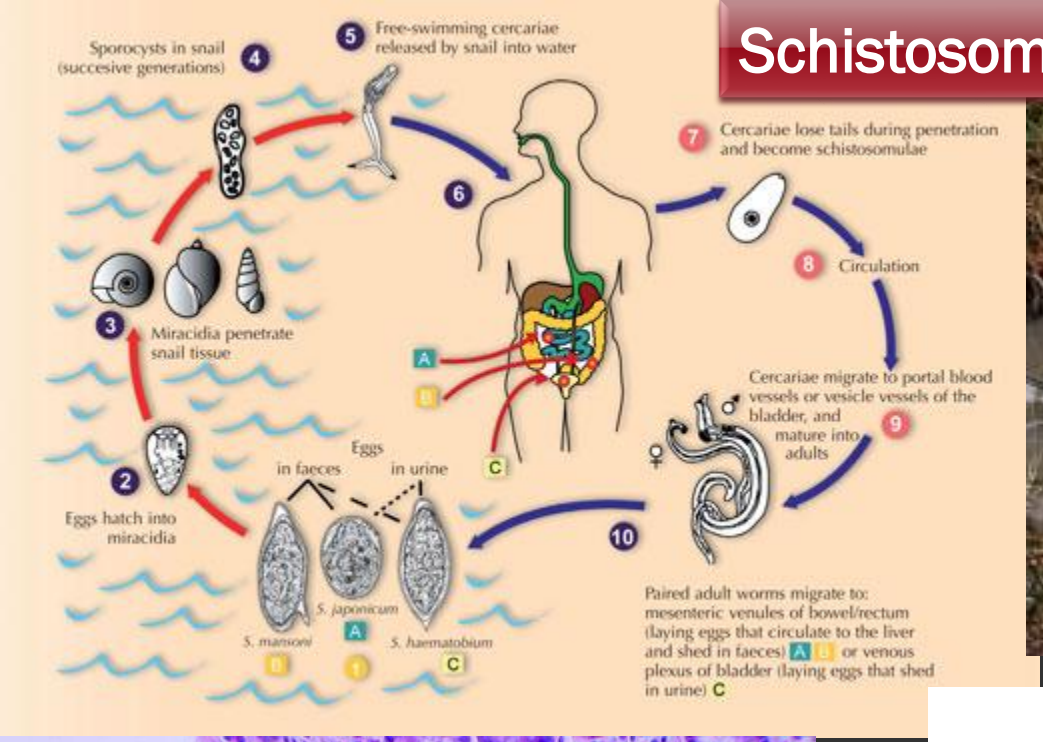
National Cancer Institute. 2006

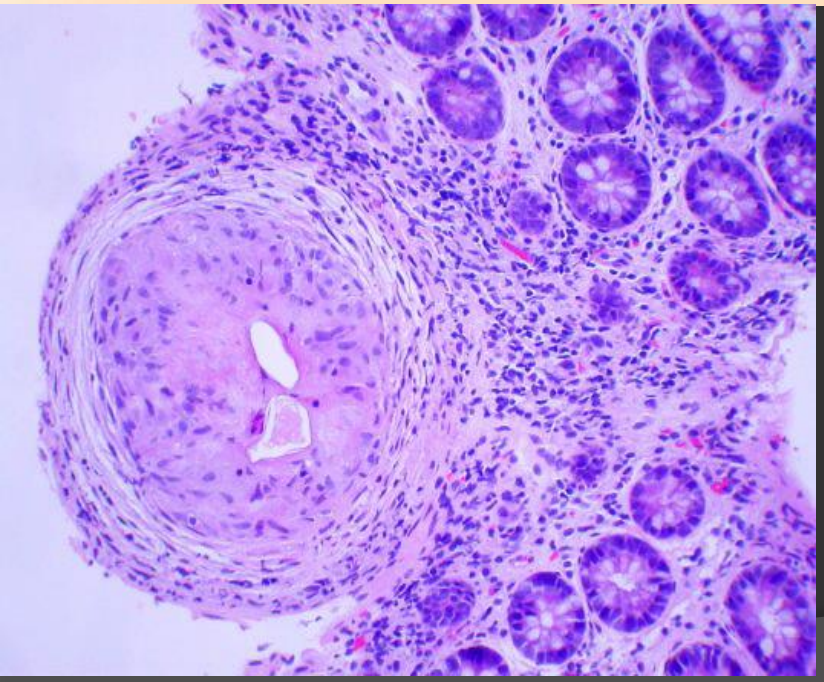
http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/1607.jpg

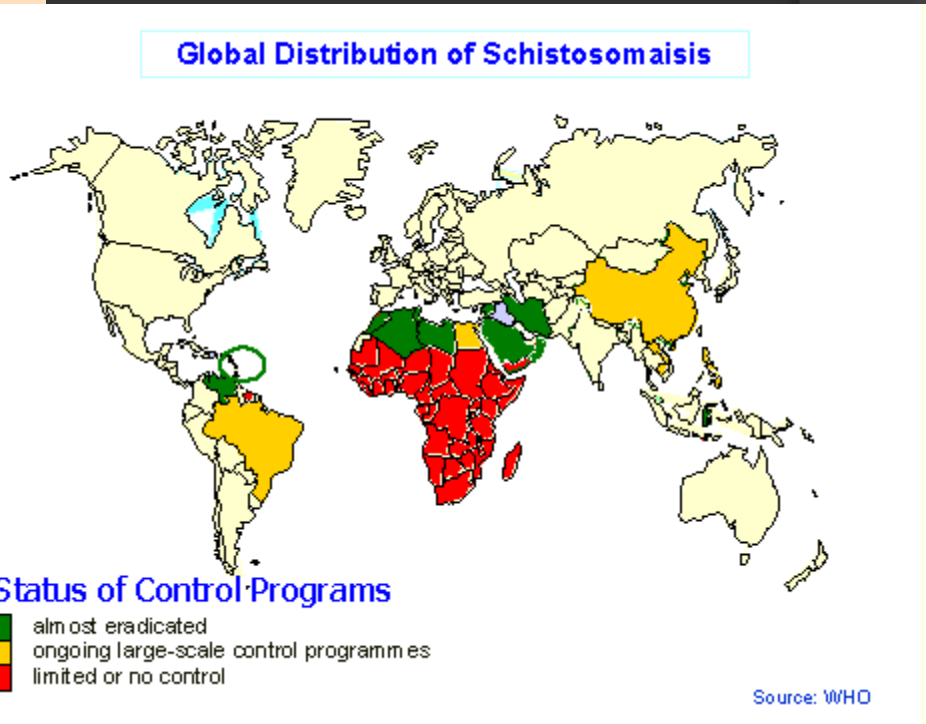
Sputum , TB bacilli



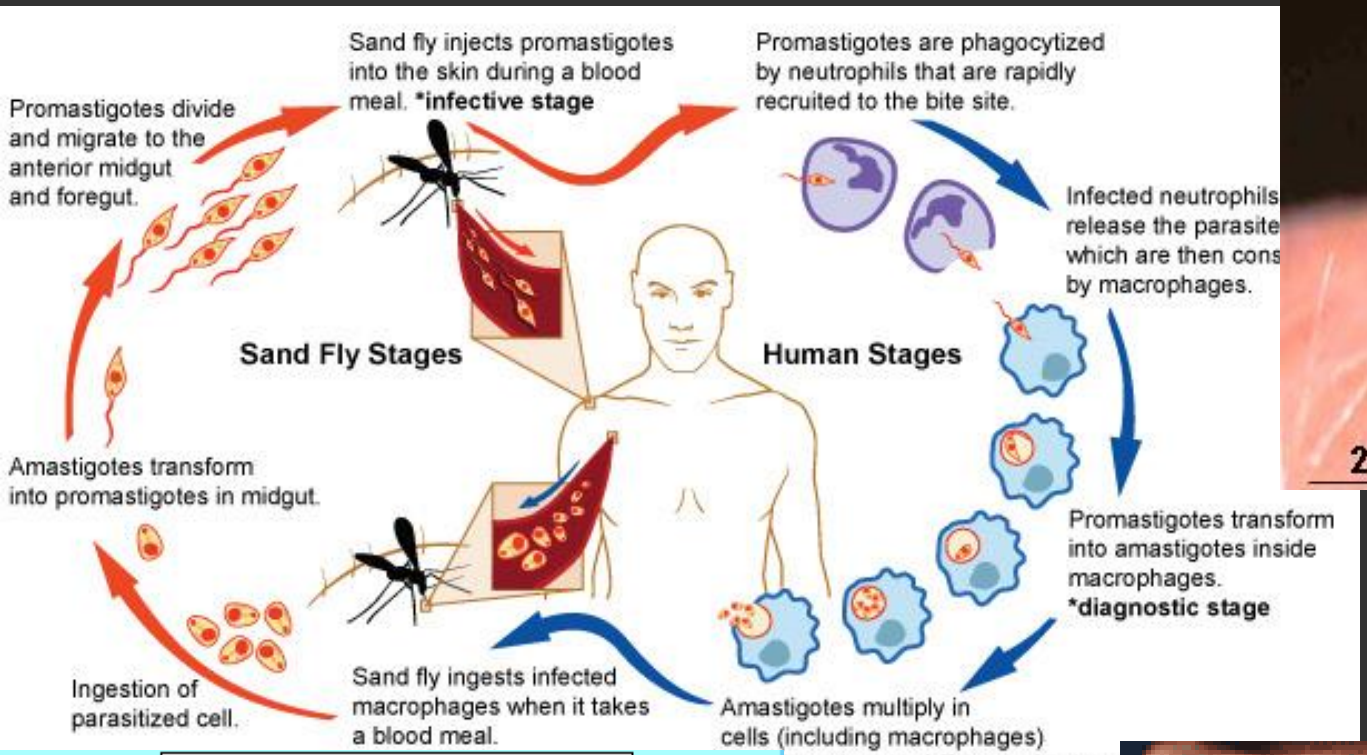
Schistosomiasis

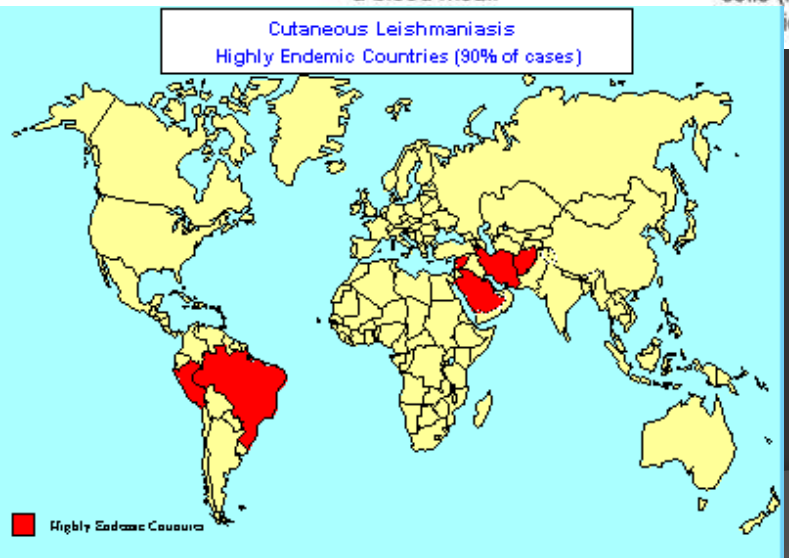


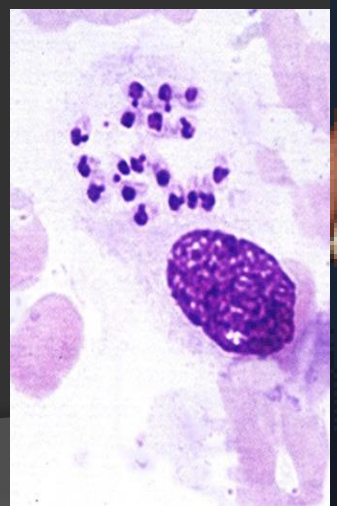


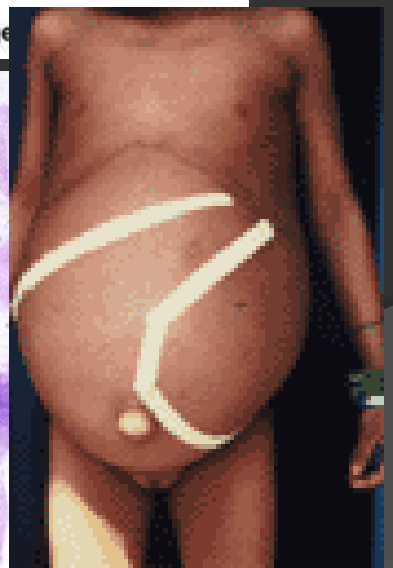


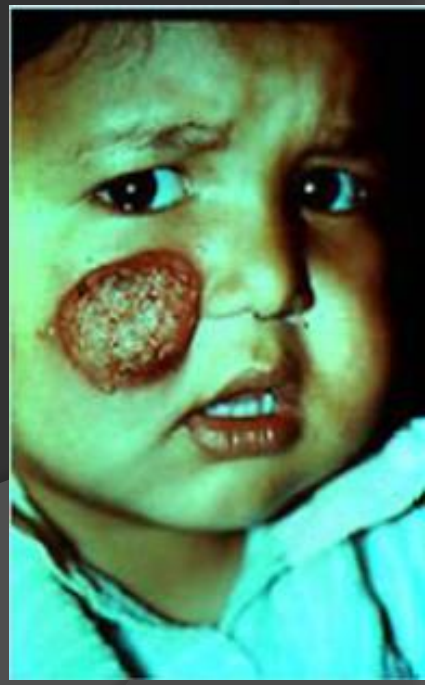
Leishmaniasis



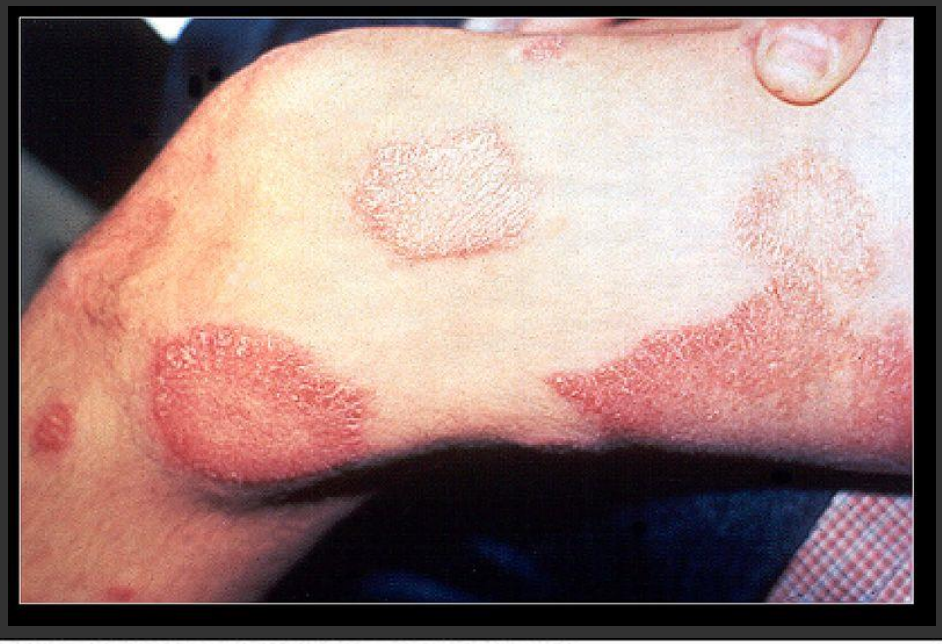


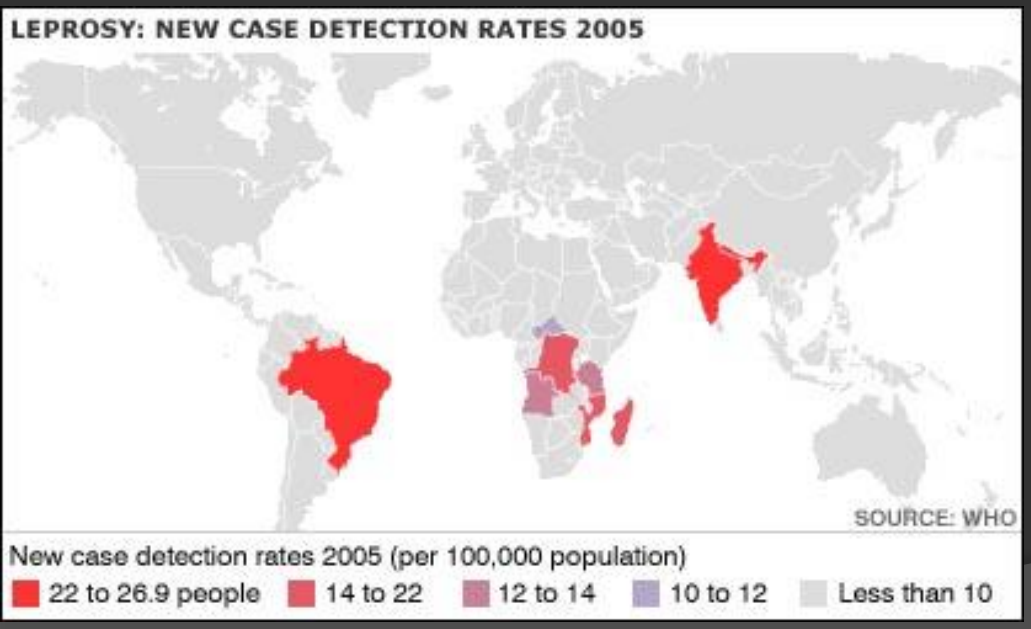




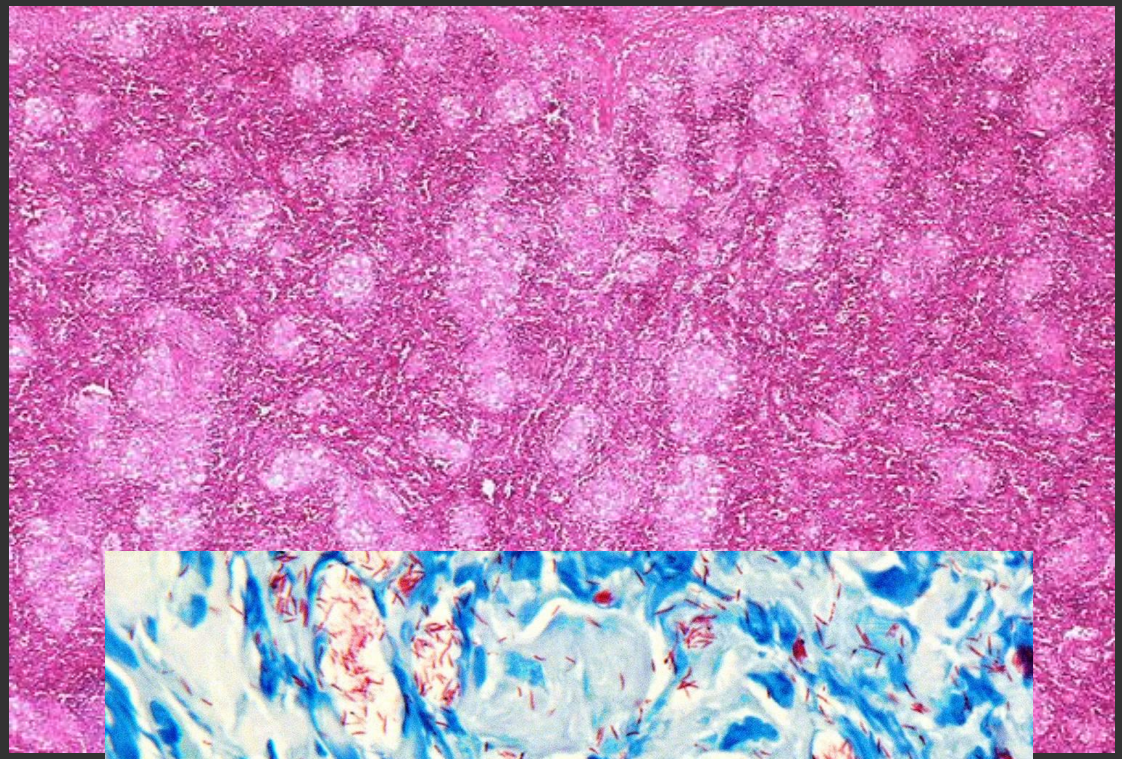


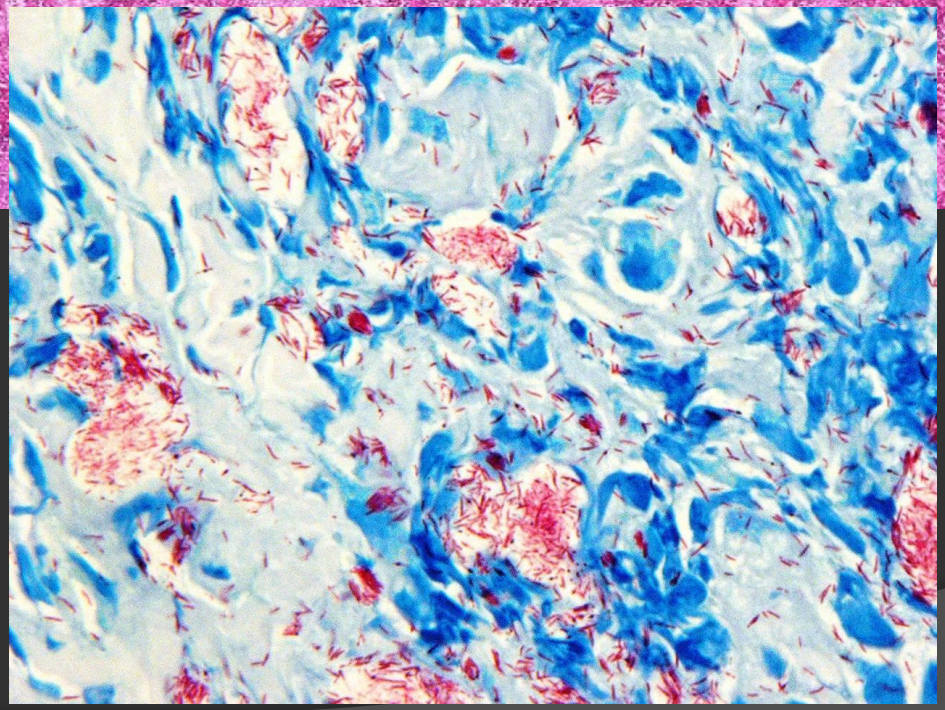
Leprosy



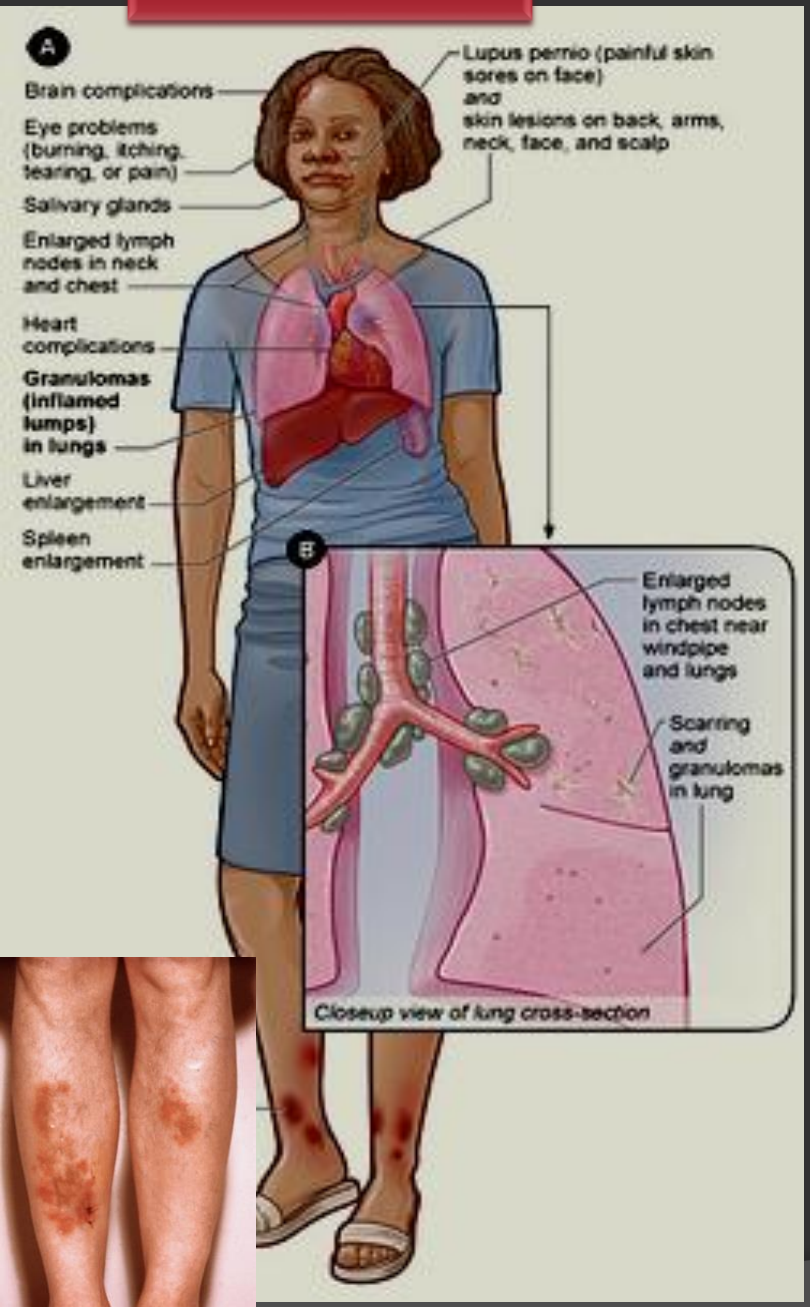

LEPROSY: NEW CASE DETECTION RATES 2005
SOURCE: WHO
New case detection rates 2005 (per 100,000 population)
22 to 26.9 people
14 to 22
12 to 14
10 to 12
Less than 10

Leprosy

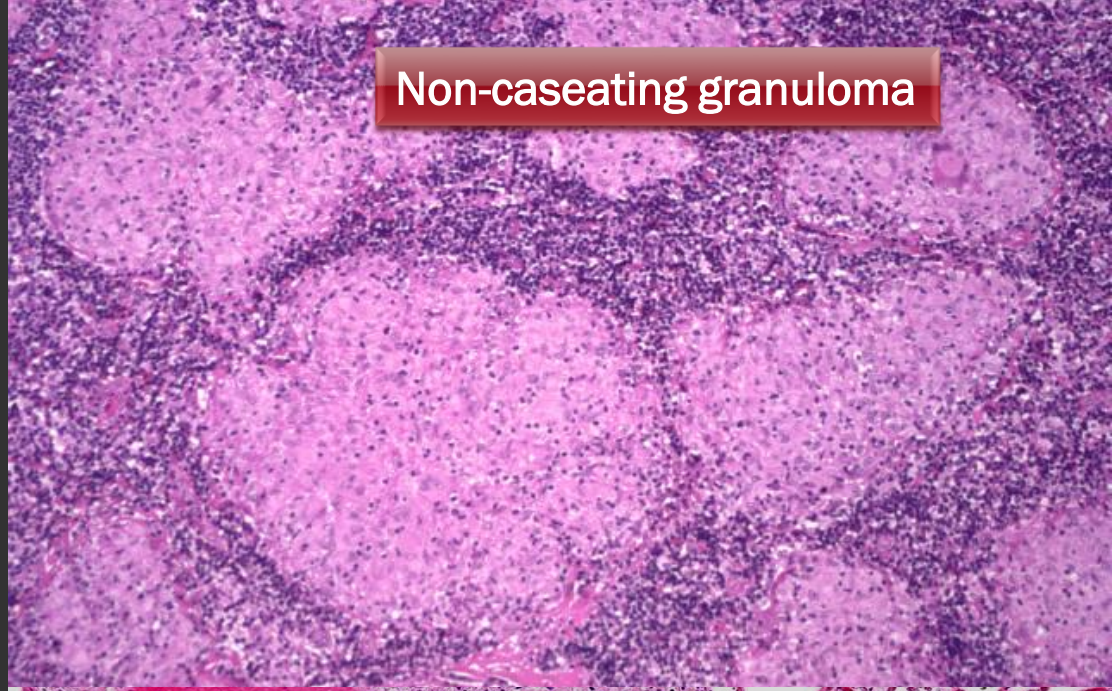


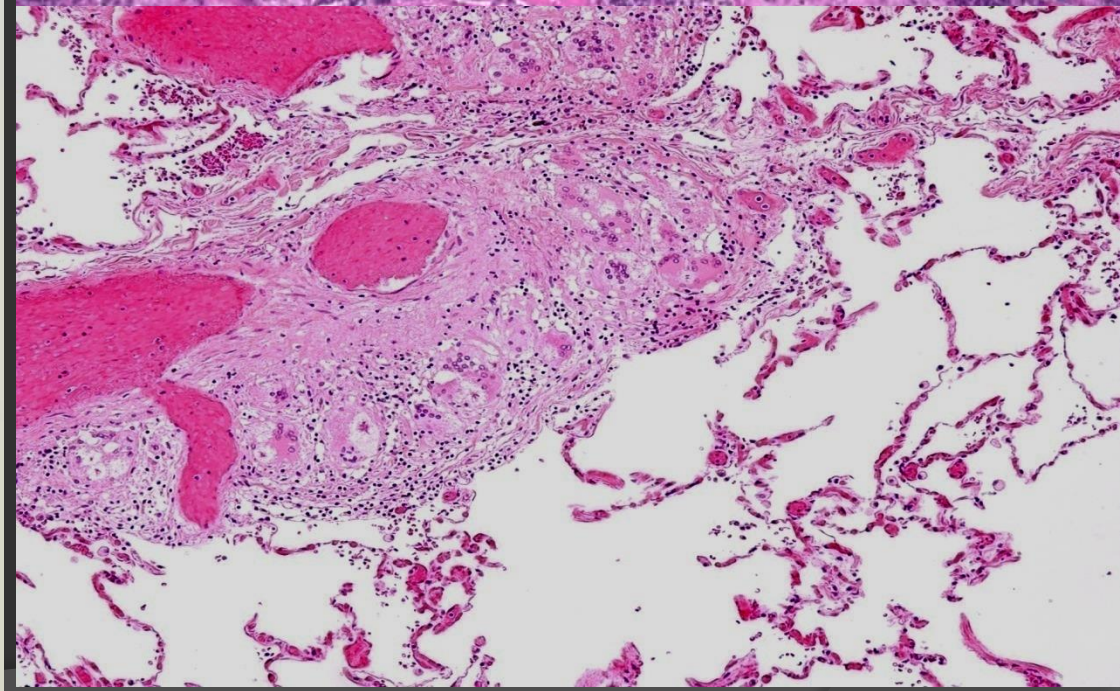


Sarcoidosis



Non-caseating granuloma



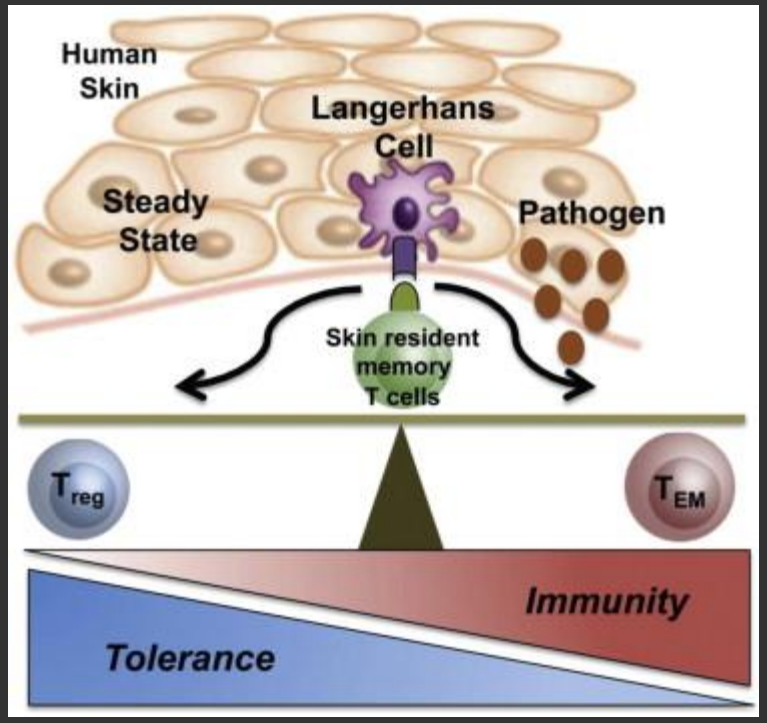


Match A and B

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

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 diseas