

GRANULOMATOUS INFLAMMATION

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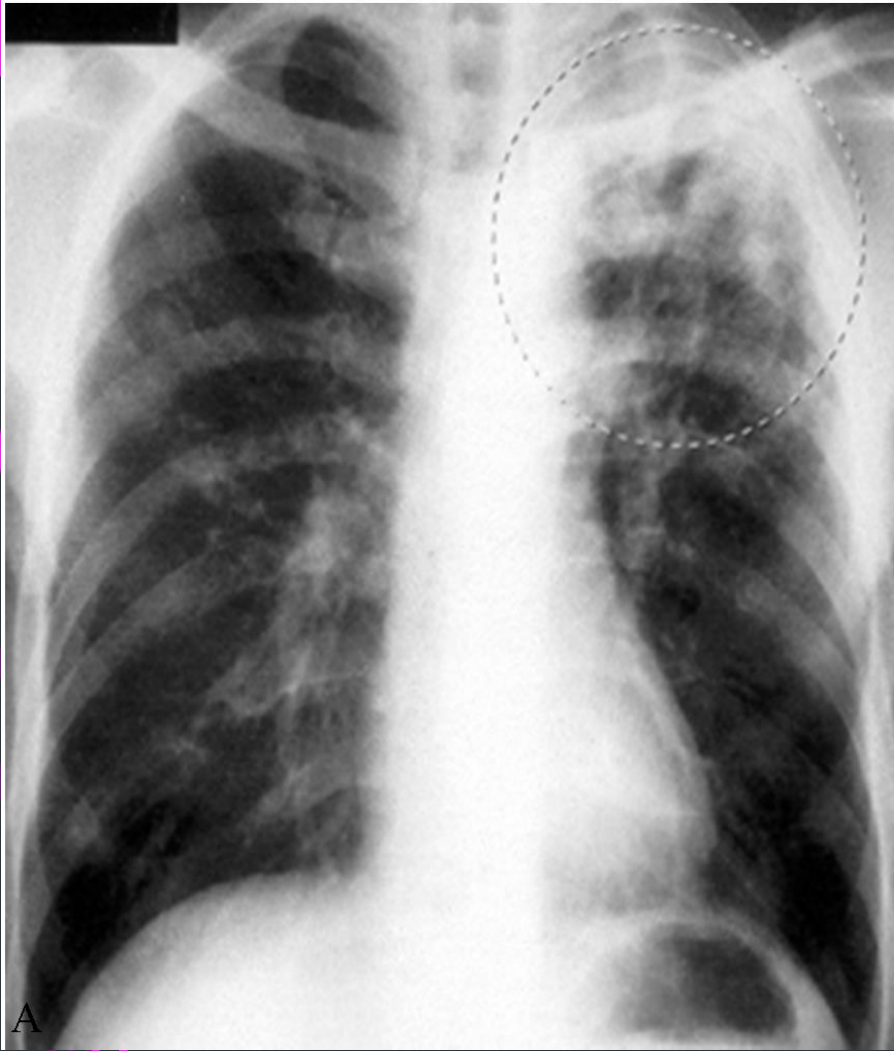
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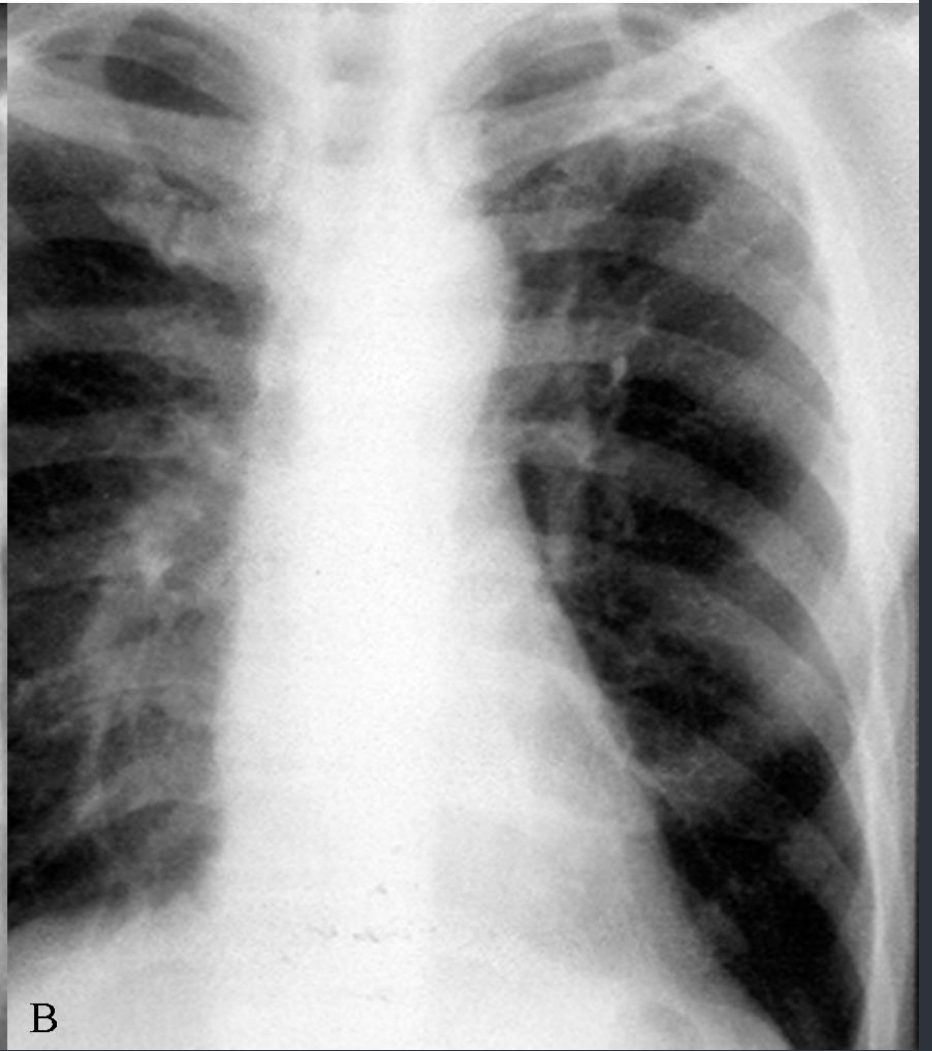
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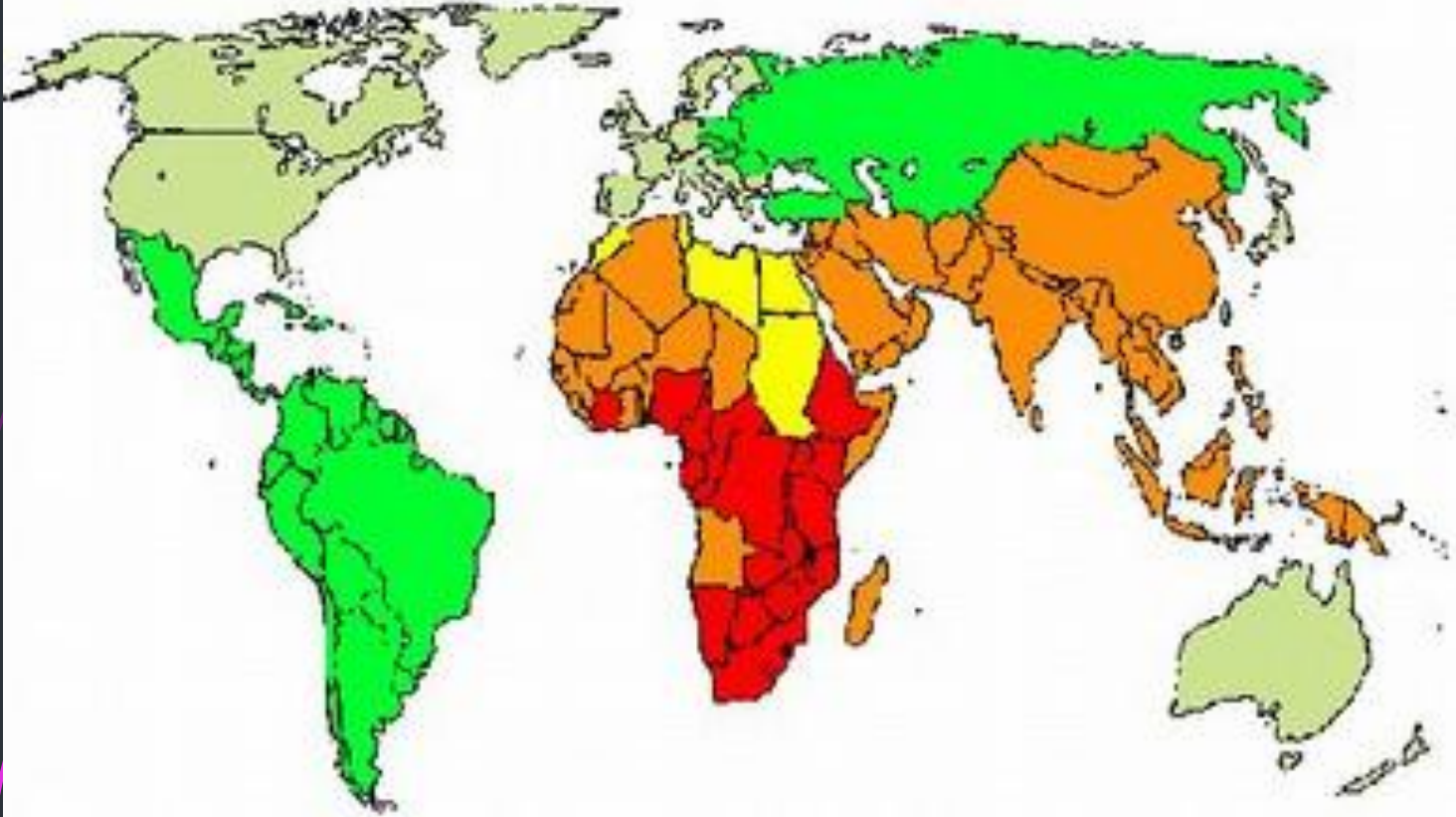


A



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:

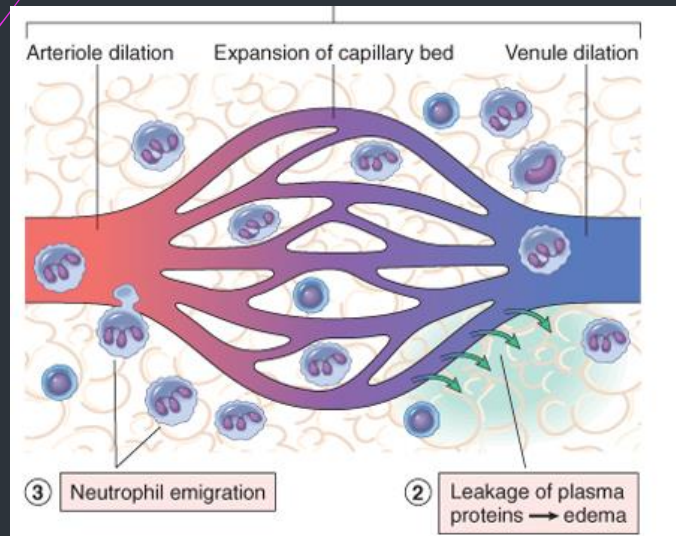
1. Define granulomatous inflammation.
2. Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance.
3. Identify the two types of granulomas, which differ in their pathogenesis.
 - a) Foreign body granulomas
 - b) Immune granulomas
4. List the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



Inflammation

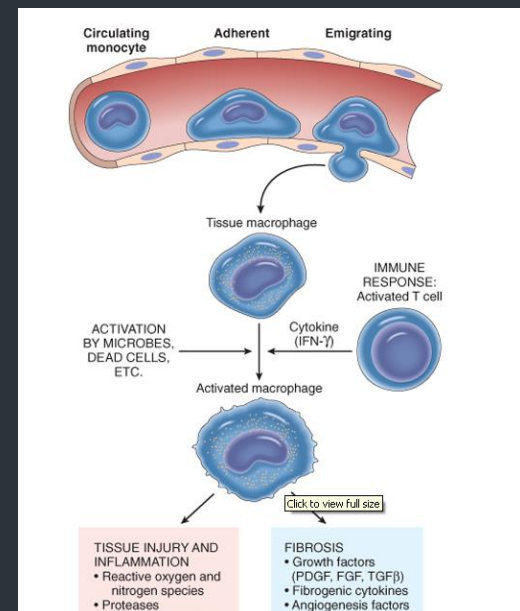
Acute inflammation

Neutrophils



Chronic inflammation

Macrophage
Lymphocytes
Plasma cells



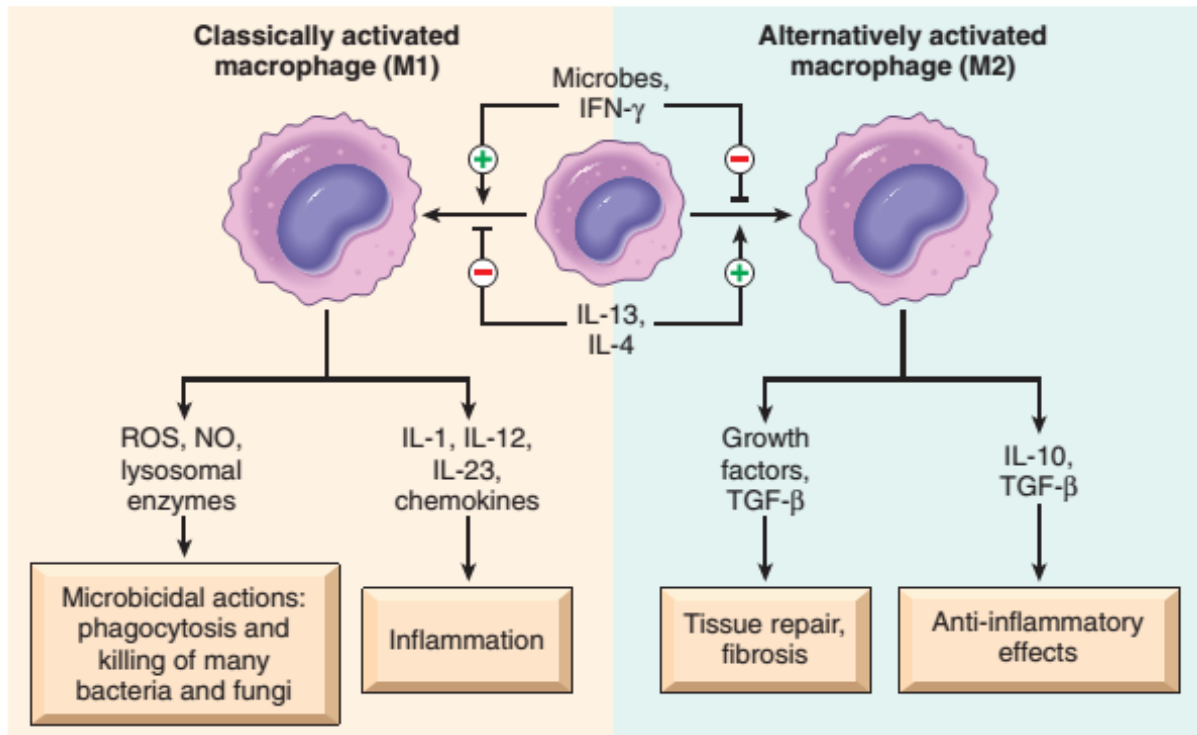


Figure 2–21 Pathways of macrophage activation. Different stimuli activate monocytes/macrophages to develop into functionally distinct populations. Classically activated macrophages are induced by microbial products and cytokines, particularly IFN- γ , and are microbicidal and involved in potentially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

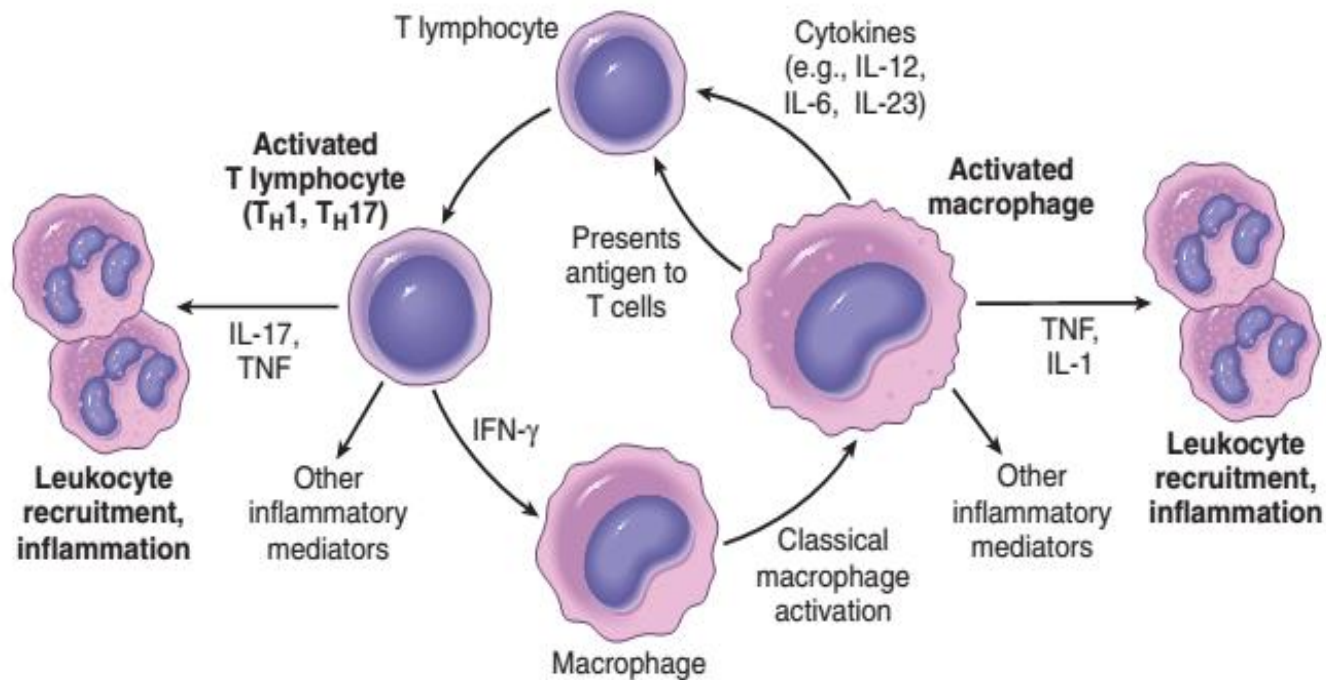


Figure 2–22 Macrophage–lymphocyte interactions in chronic inflammation. Activated lymphocytes and macrophages stimulate each other, and both cell types release inflammatory mediators that affect other cells. IFN- γ , interferon- γ ; IL-1, interleukin-1; TNF, tumor necrosis factor.

Granulomatous inflammation

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



Why is it important?

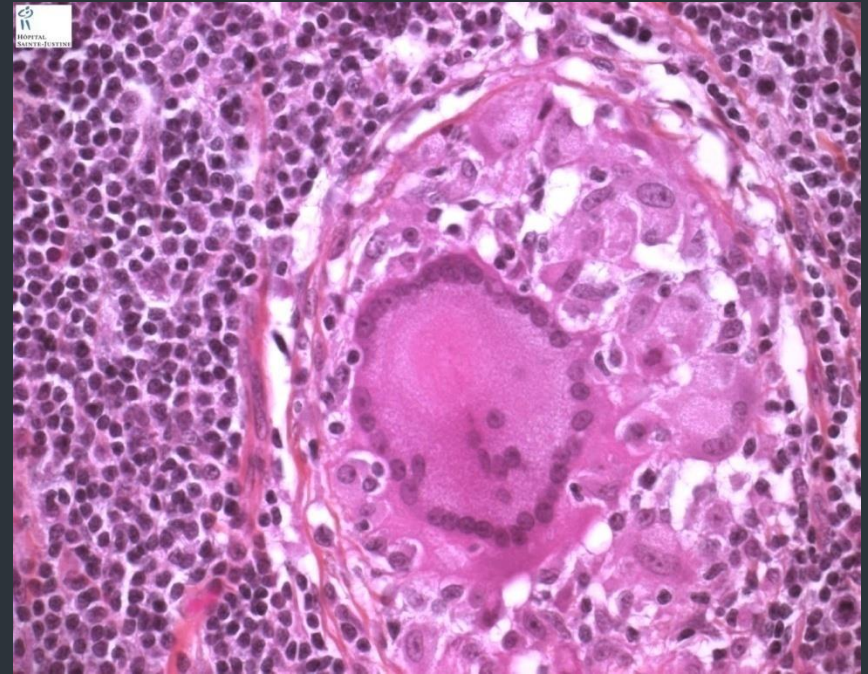
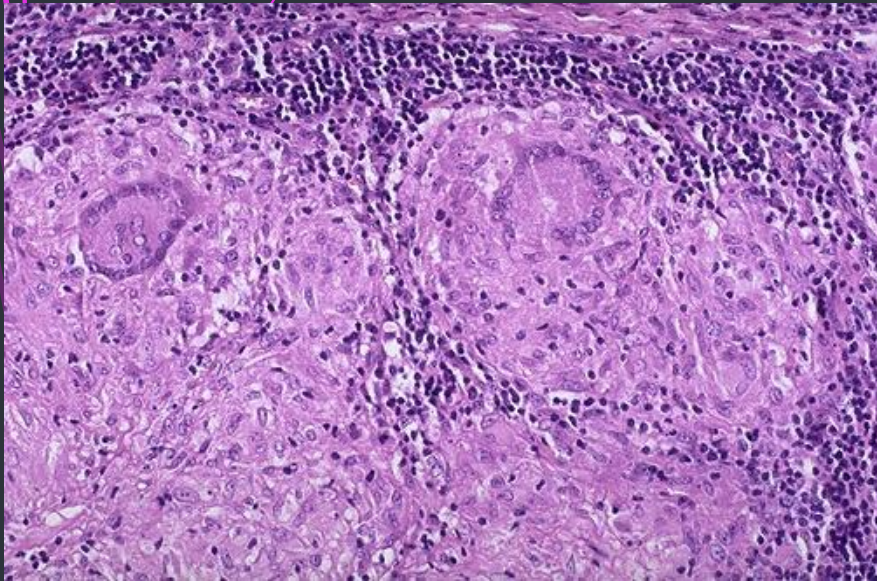
- Granulomas are encountered in certain **specific** pathologic states.
- Recognition of the granulomatous pattern is important because of the **limited number of conditions** (some life-threatening) that cause it.



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.
- ▶ Epithelioid macrophages: squamous cell-like appearance.

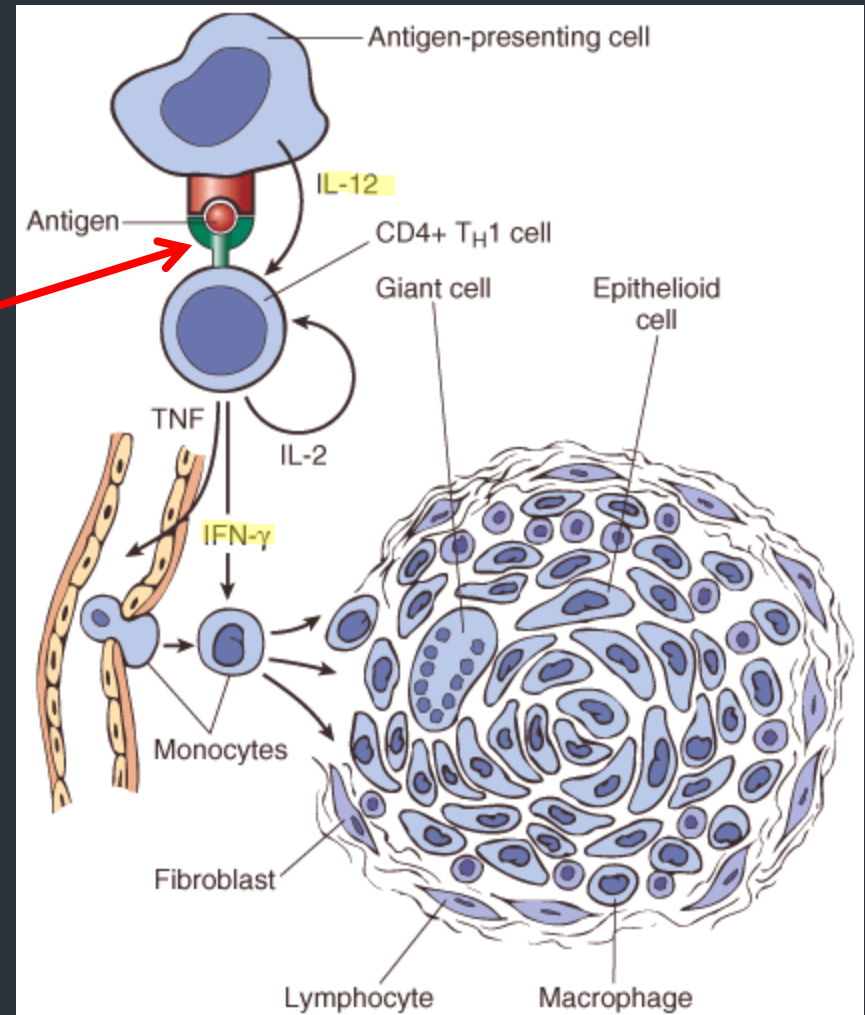


Granulomatous Inflammation mechanism

► **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	<i>Mycobacterium tuberculosis</i>	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	<i>Mycobacterium leprae</i>	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	<i>Treponema pallidum</i>	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 as 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

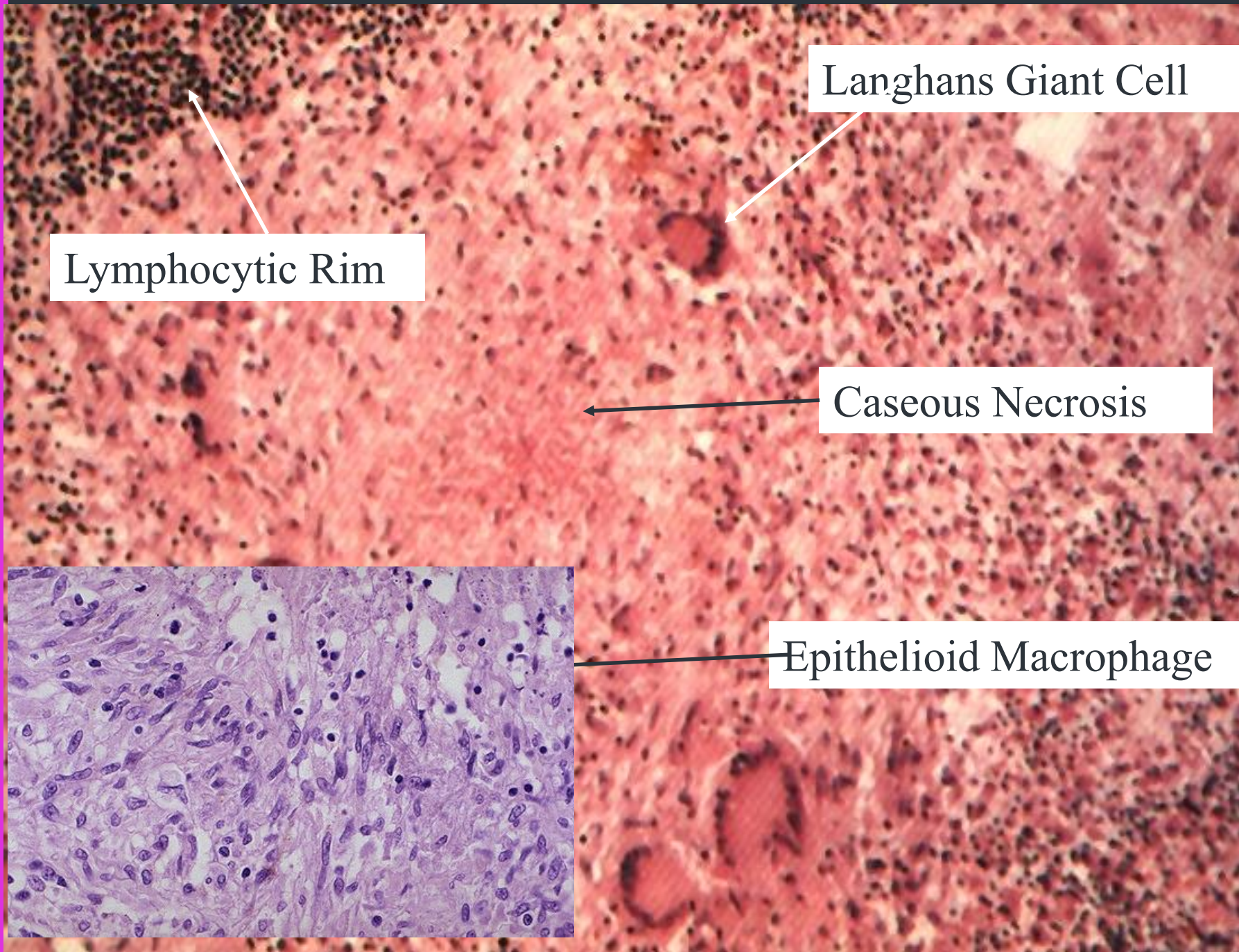
Fungi

- Histoplasmosis
- Blastomycosis

Metal/Dust

- Berylliosis

unknown
Sarcoidosis
Crohn's disease



Langhans Giant Cell

Lymphocytic Rim

Caseous Necrosis

Epithelioid Macrophage



Epithelioid histiocytes

Lymphocytes

Multinucleated cell

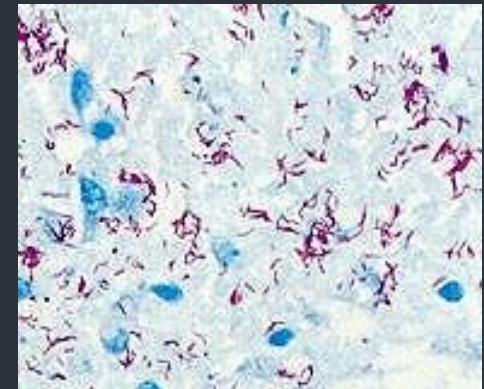
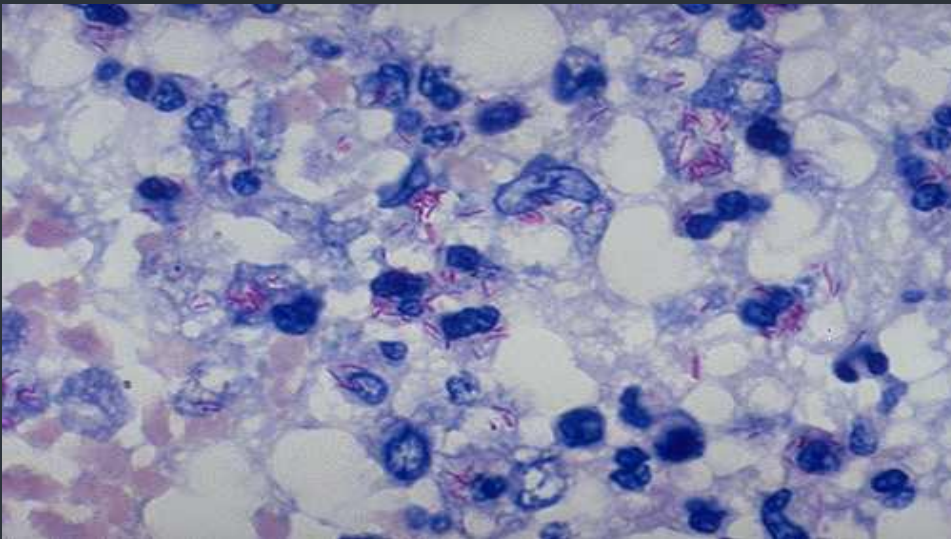
Necrosis

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-1 β , IL-6 and TNF which are all pro-inflammatory cytokines important for granuloma formation

Tuberculosis



Signs, Symptoms and Diagnosis of TB

Any long-standing cough with or without fever could be Tuberculosis (TB)!

Do you have...



...a cough longer than 14 days?



...fever of long duration?



...shortness of breath?



...blood in your cough?



...tiredness?



...chest pain?



...loss of appetite?



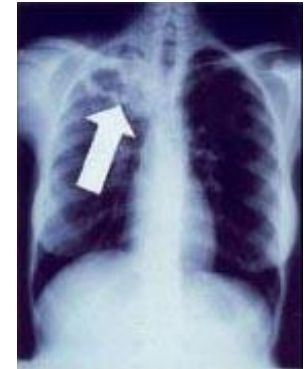
...weight loss?



...night sweats?

It could be TB.

- X-ray



Tuberculin skin testing (TST)

- Sputum smear microscopy

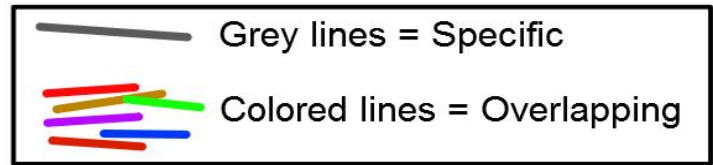


- Culture

- PCR: identification & drug resistance



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

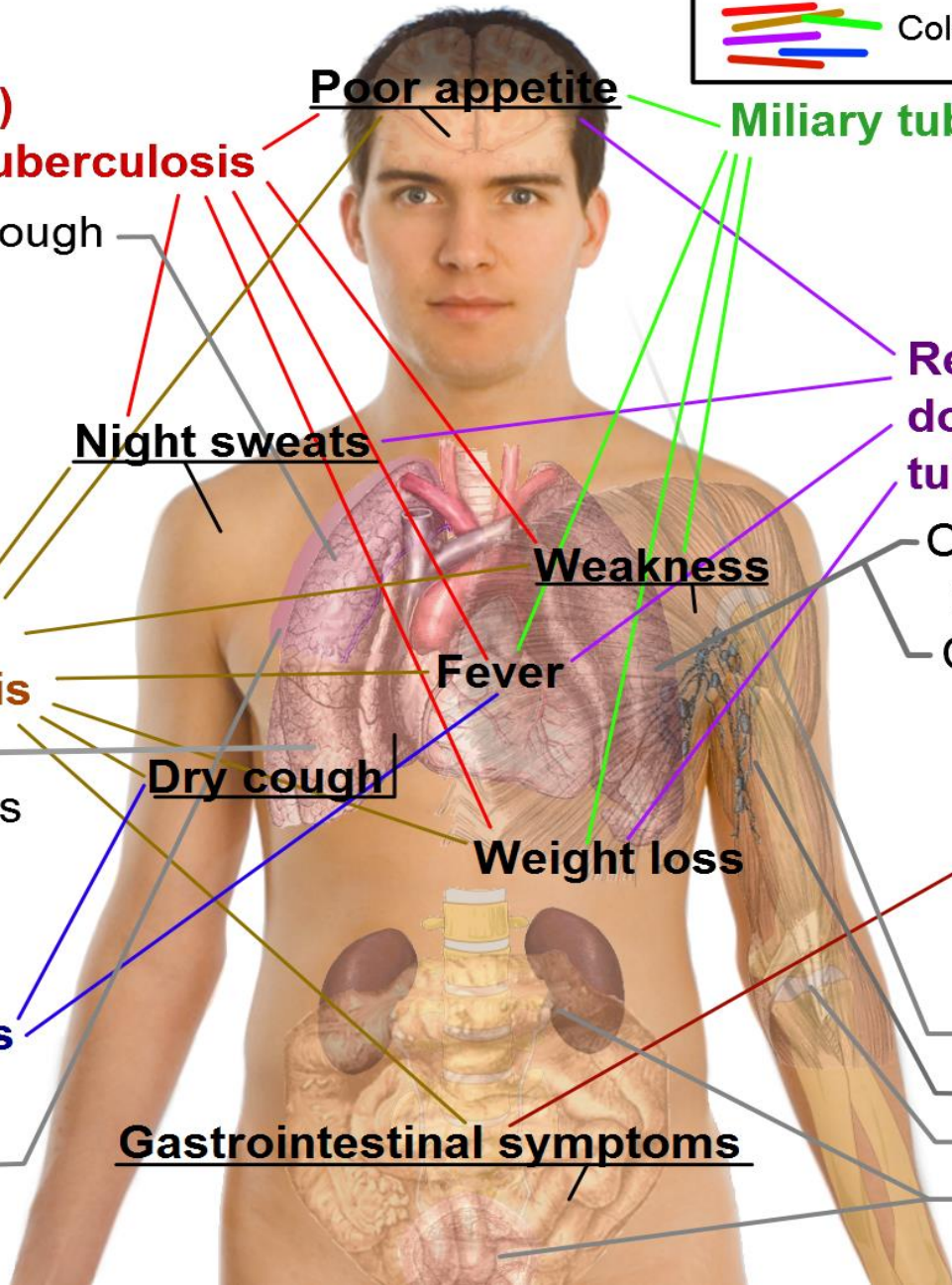
Lymph nodes

Bone and joint sites

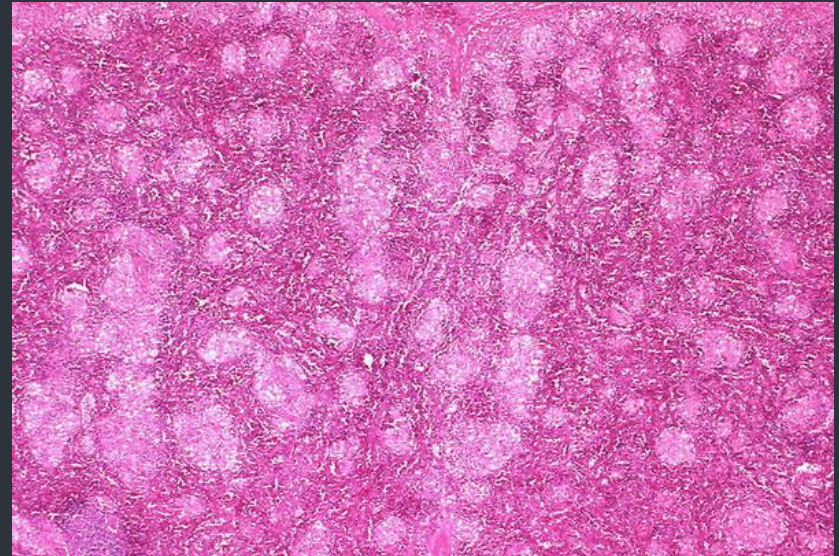
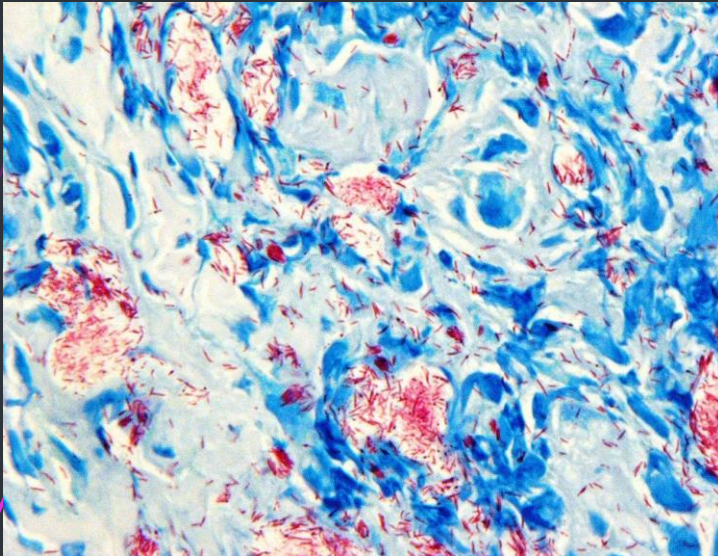
Genitourinary tract

Chest pain

Gastrointestinal symptoms



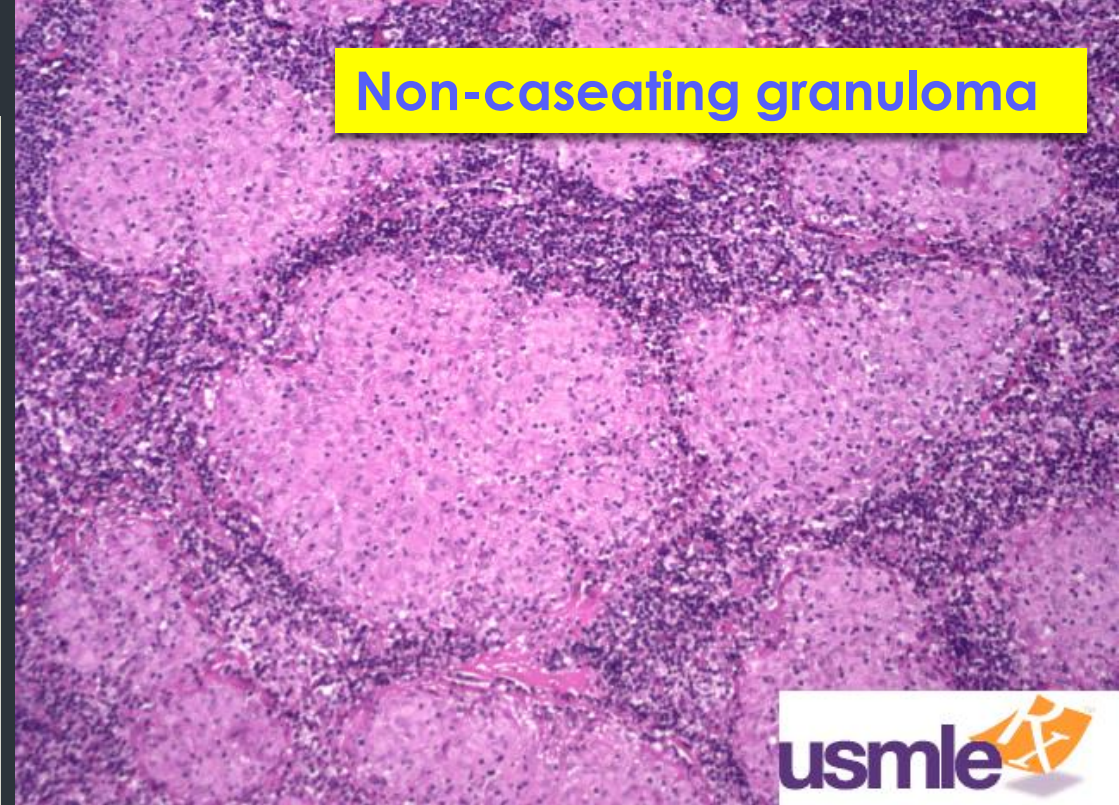
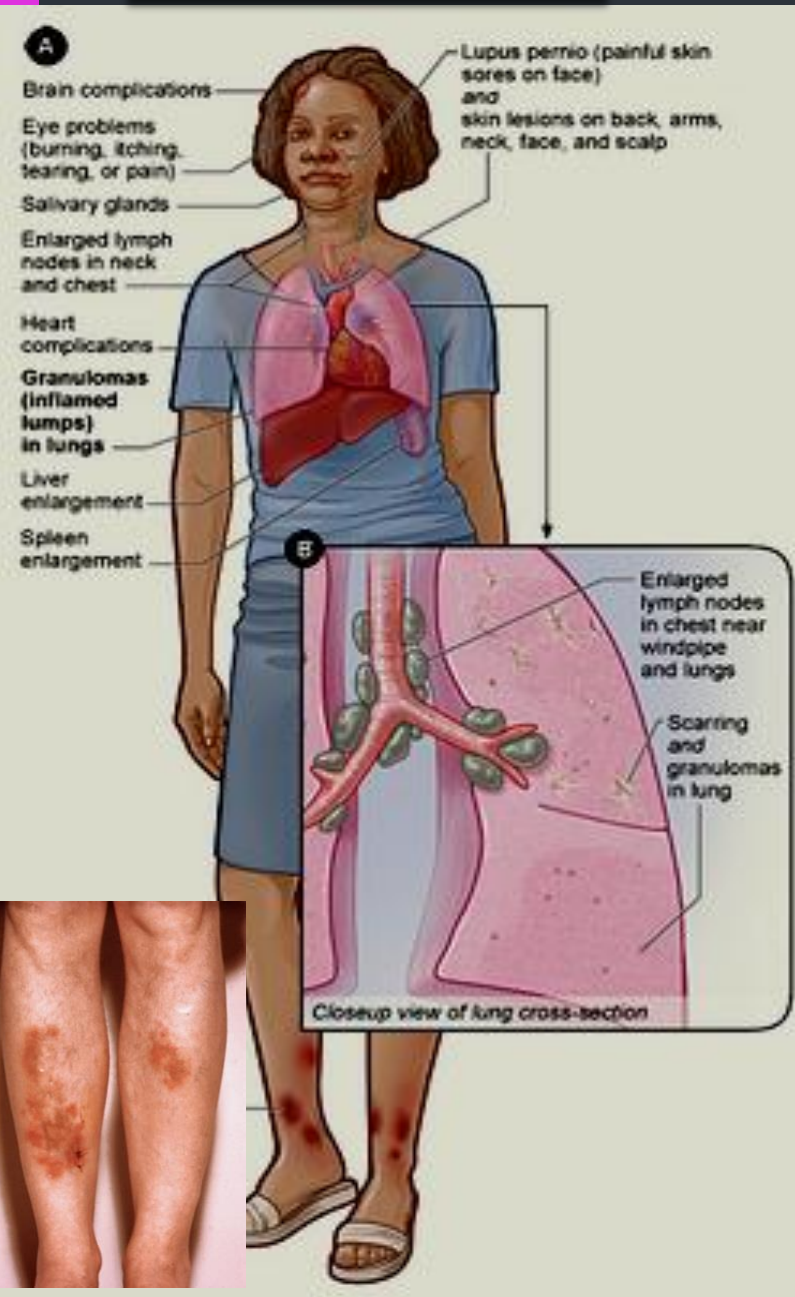
Leprosy



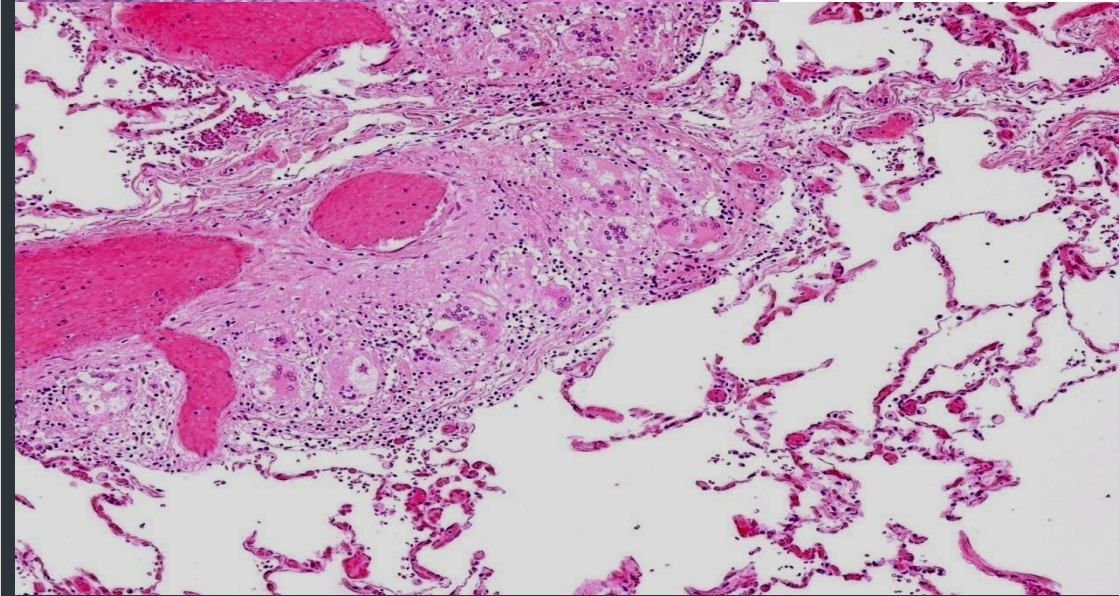
Non-caseating necrosis

Sarcoidosis

Non-caseating granuloma



usmle



Match A and B

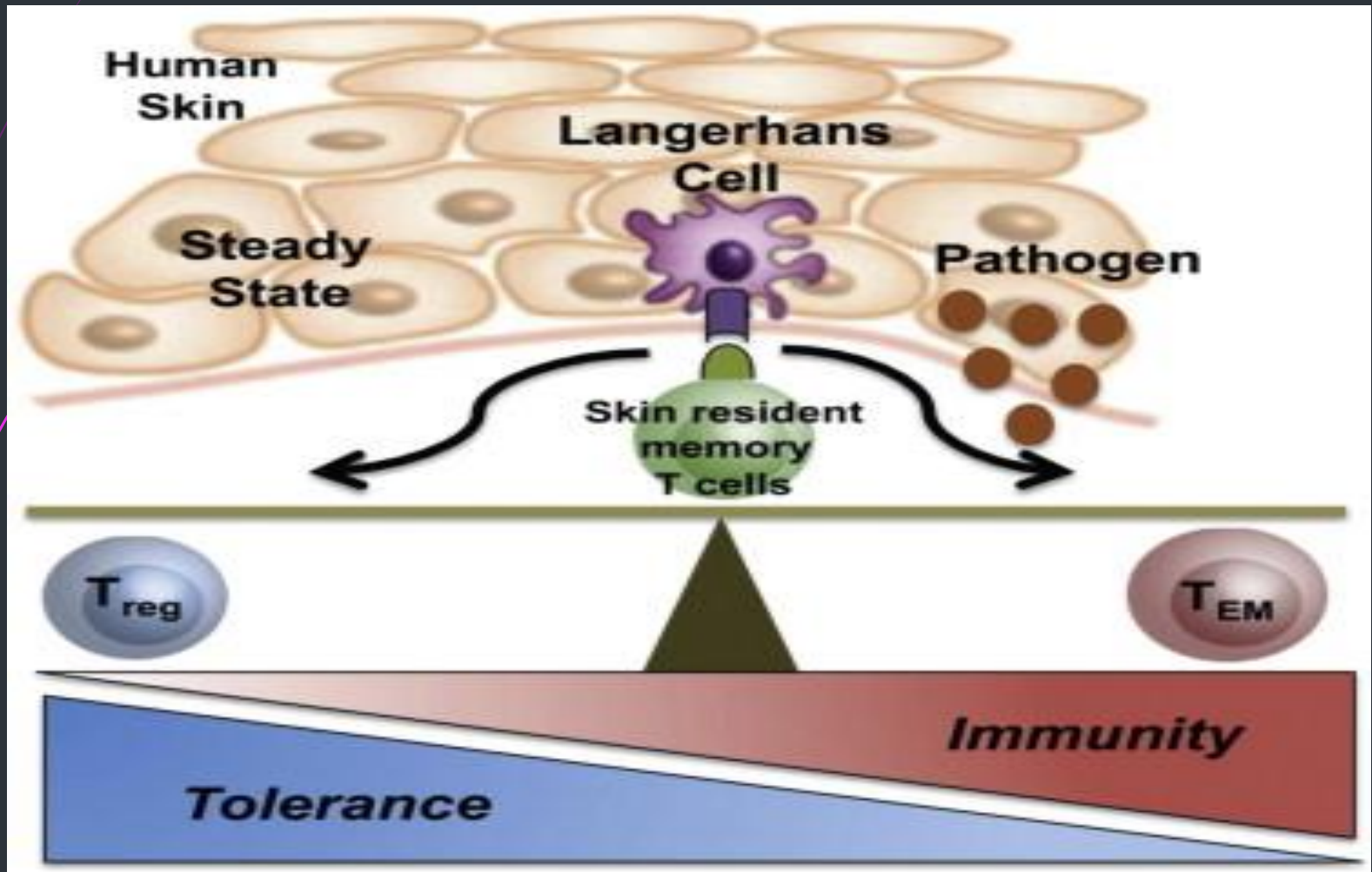
A

- 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



A decorative graphic on the left side of the slide, featuring a blue arrow pointing right at the top, and several thin, curved lines in shades of blue and purple extending downwards.

⦿ 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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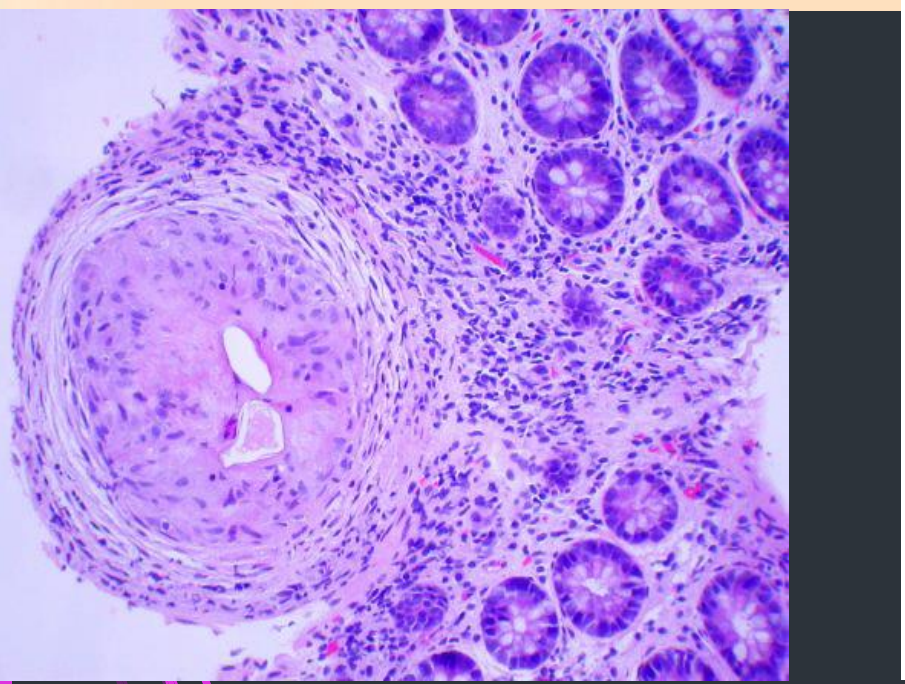
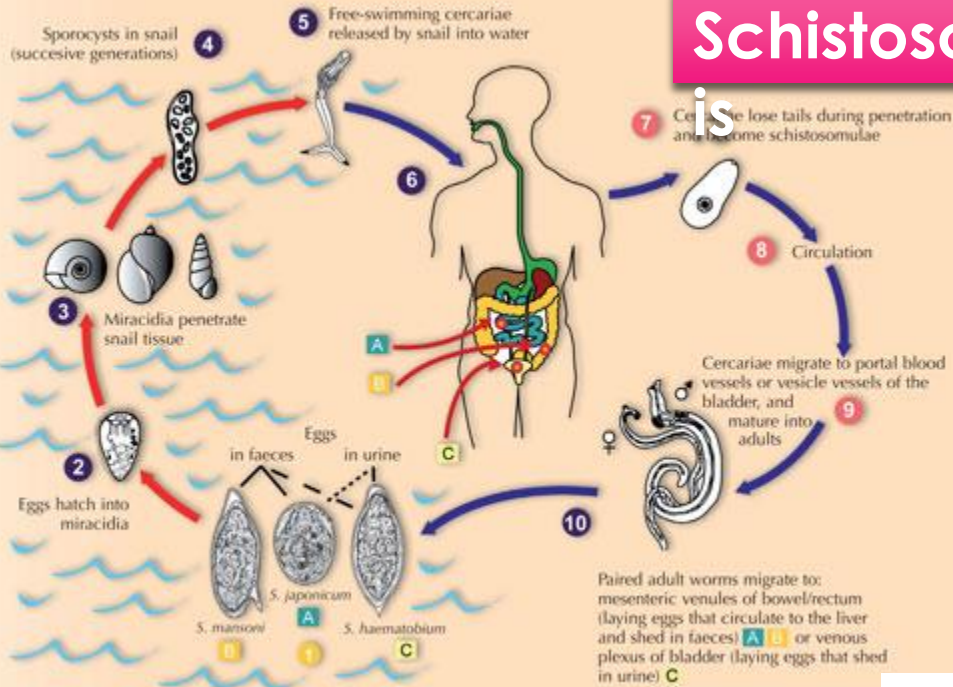
TAKE HOME MESSAGES:

- 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.

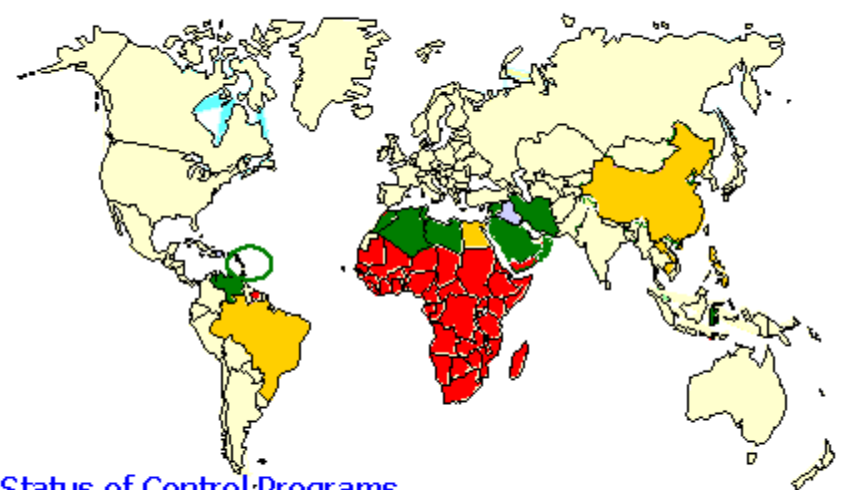
**THANK
YOU**



Schistosomiasis



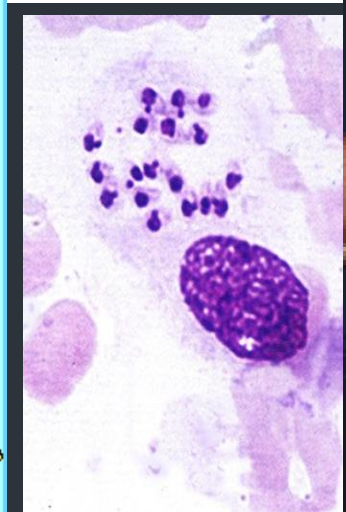
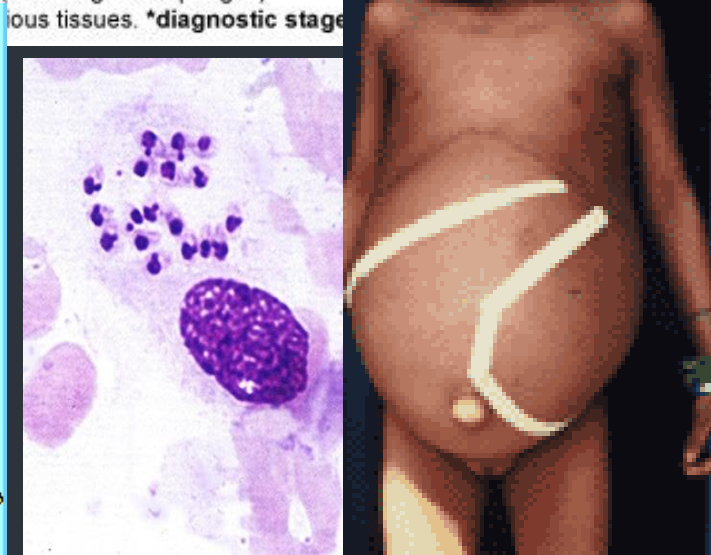
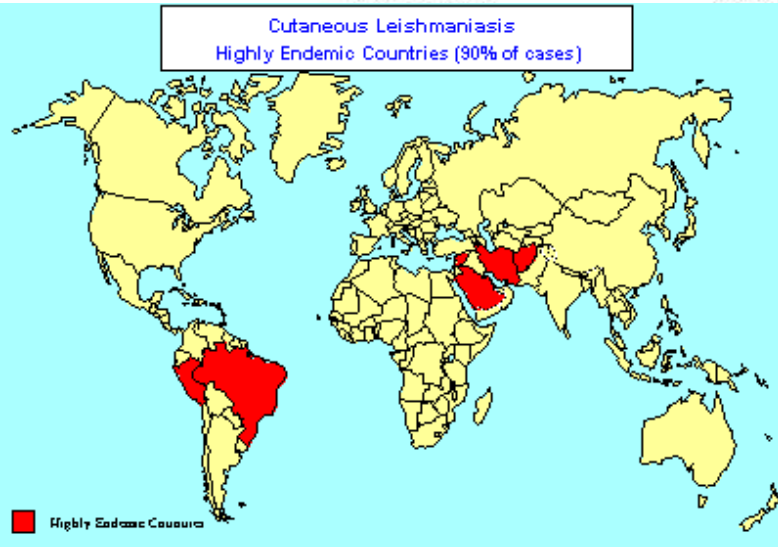
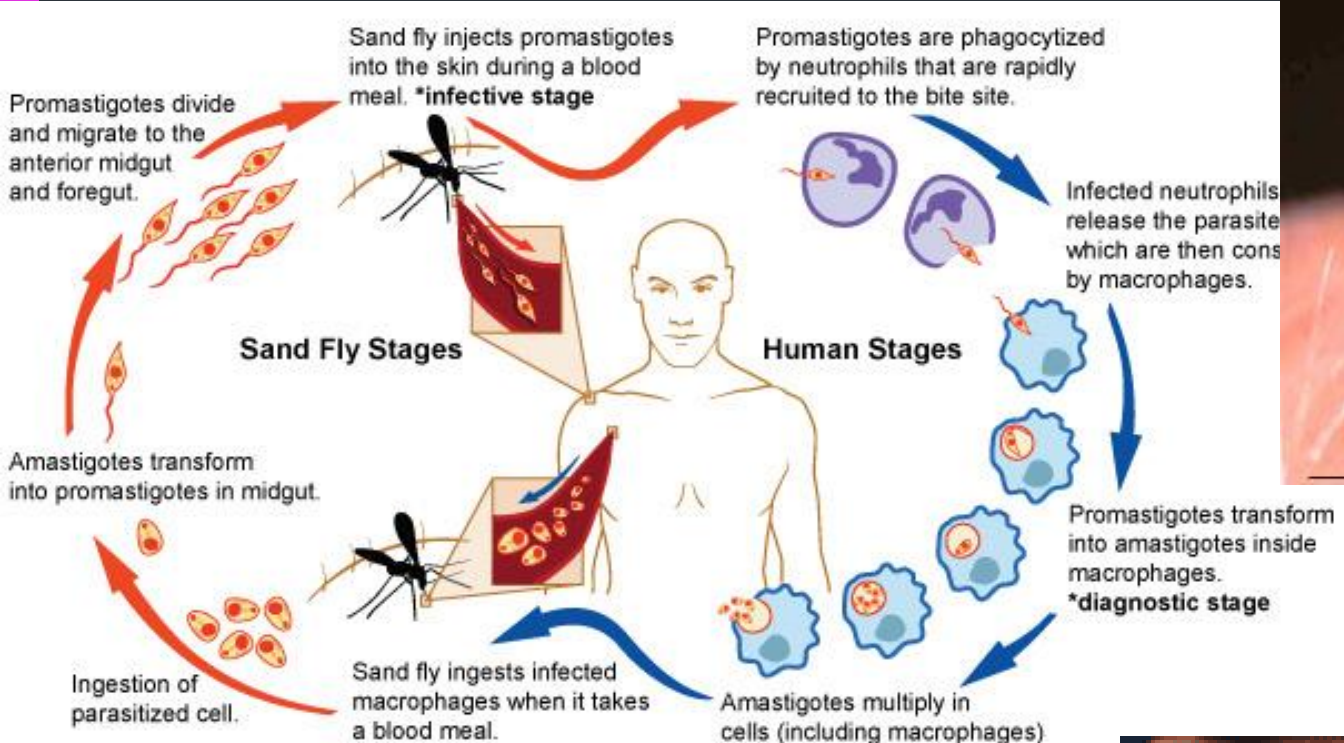
Global Distribution of Schistosomiasis



Status of Control Programs

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

Leishmaniasis



Leprosy



LEPROSY: NEW CASE DETECTION RATES 2005



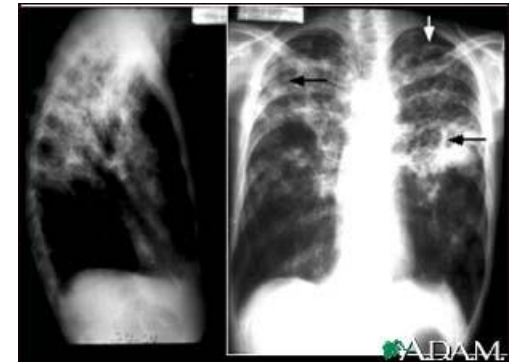
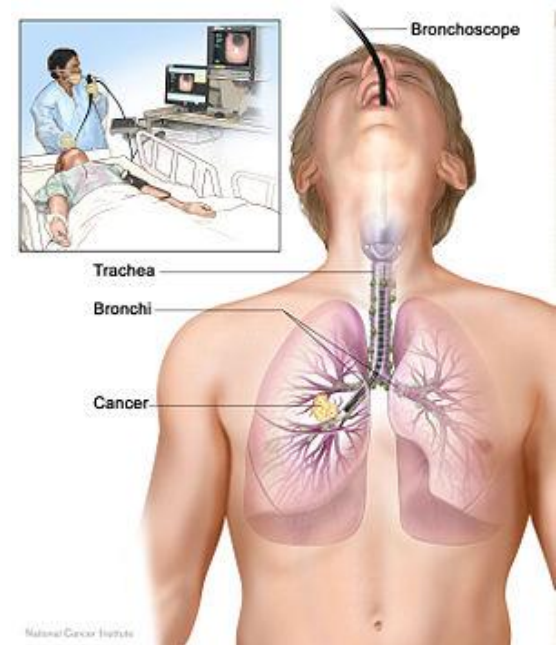
SOURCE: WHO

New case detection rates 2005 (per 100,000 population)

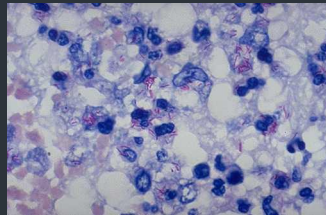
■ 22 to 26.9 people ■ 14 to 22 ■ 12 to 14 ■ 10 to 12 ■ Less than 10

Diagnosis of pulmonary TB

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

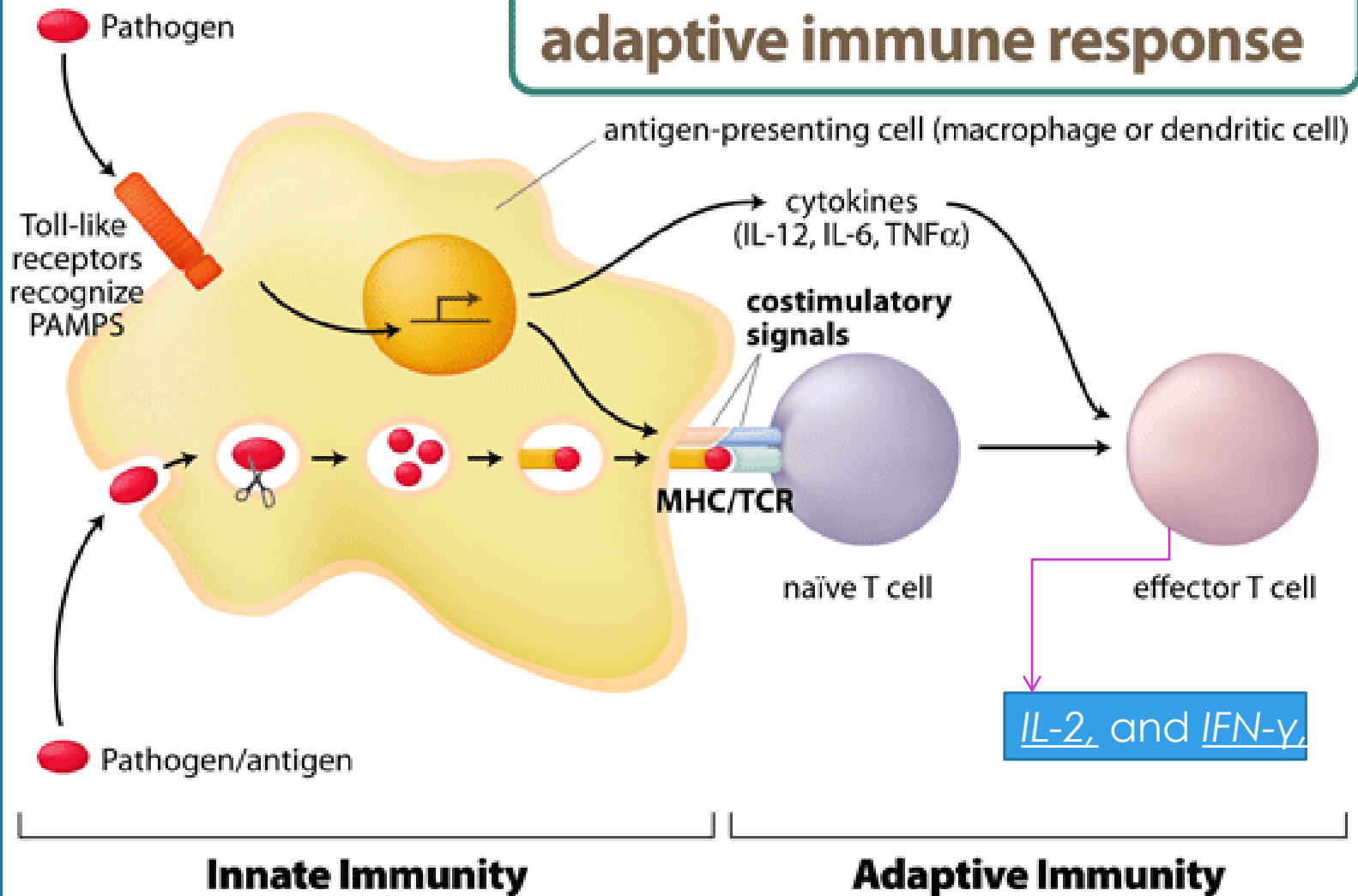


Sputum , TB bacilli



- ▶ 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



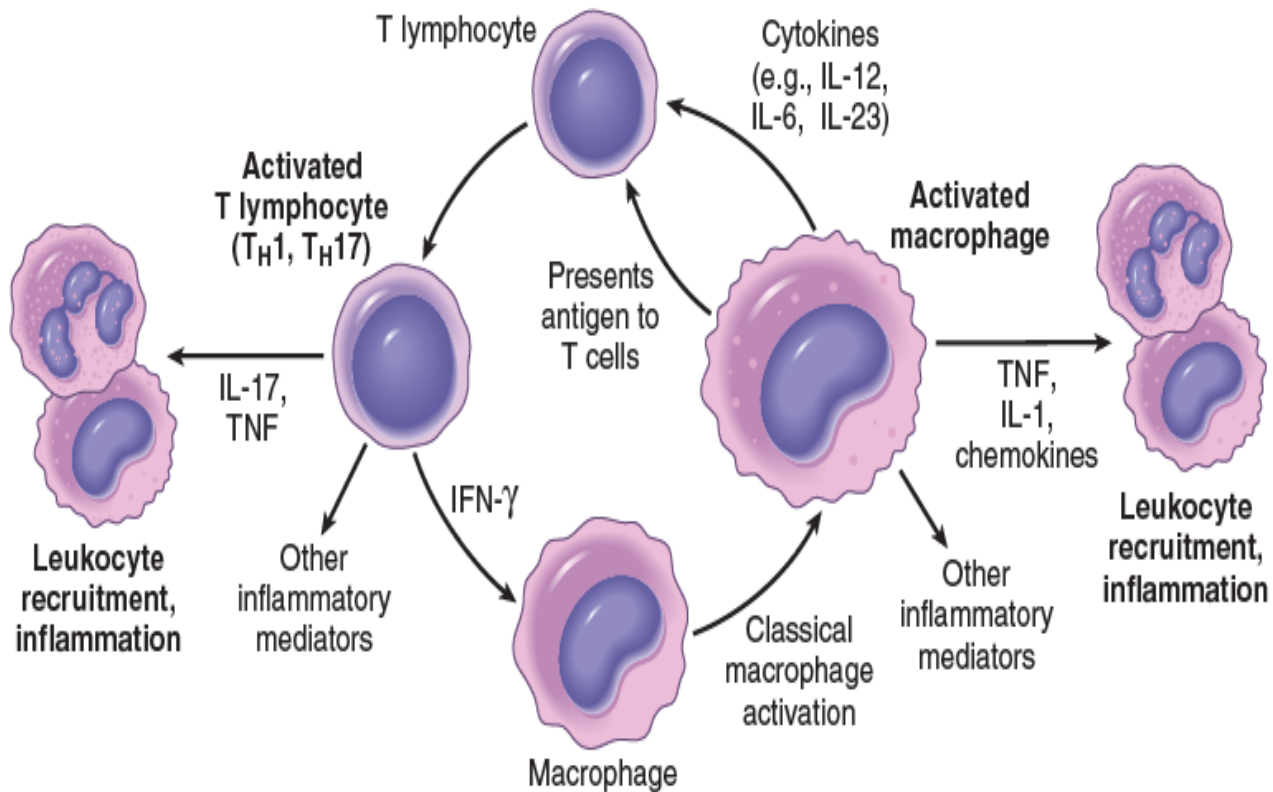


Figure 3-21 Macrophage-lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit macrophages (TNF, IL-17, chemokines) and others that activate macrophages (IFN- γ). Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines such as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