Granulomatous Inflammation

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Objectives

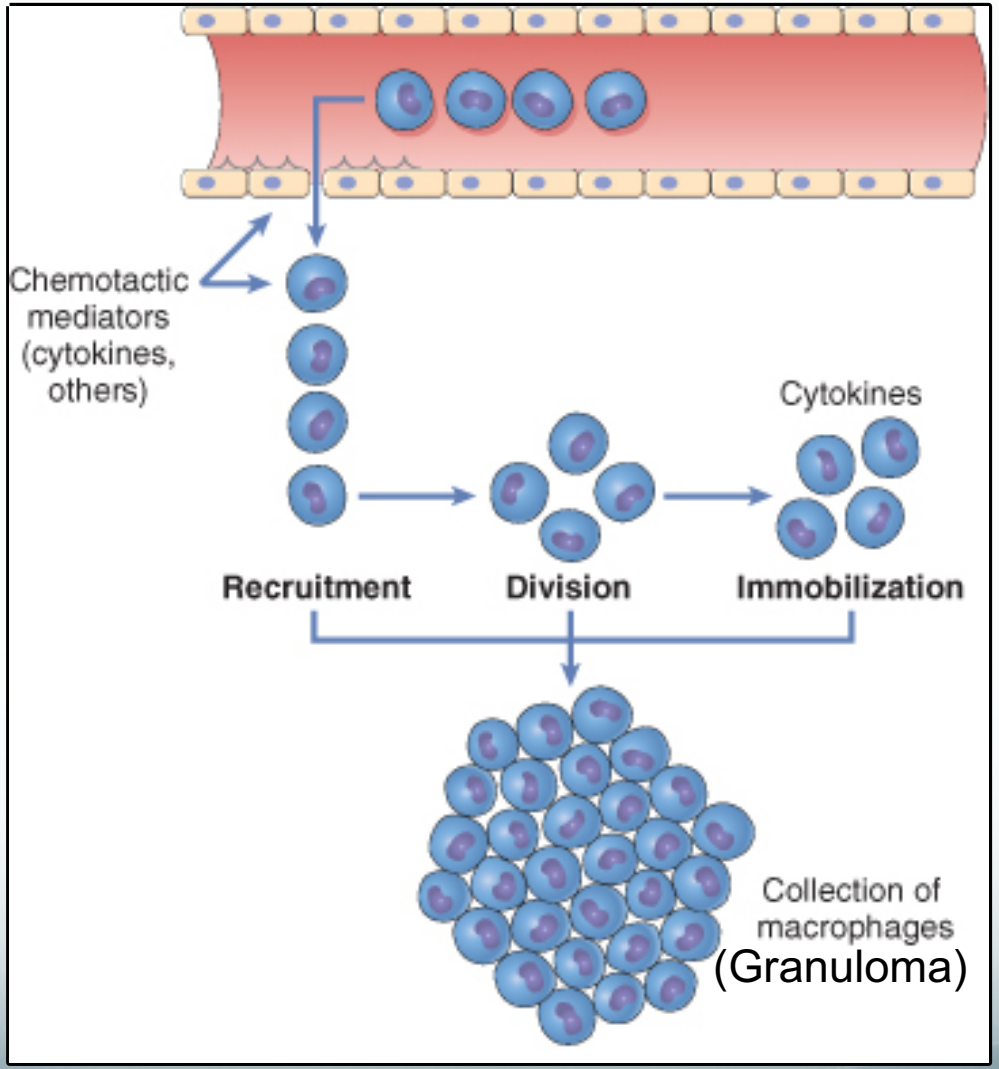
- Define granulomatous inflammation.
- Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance.
- Understand the pathogenesis of granuloma formation.
- Identify the two types of granulomas, which differ in their pathogenesis.
  - Foreign body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

Definition

- Granulomatous inflammation is a form of chronic inflammation characterized by collections of *activated macrophages*, often with T lymphocytes, and sometimes associated with central necrosis.

Why is it important?

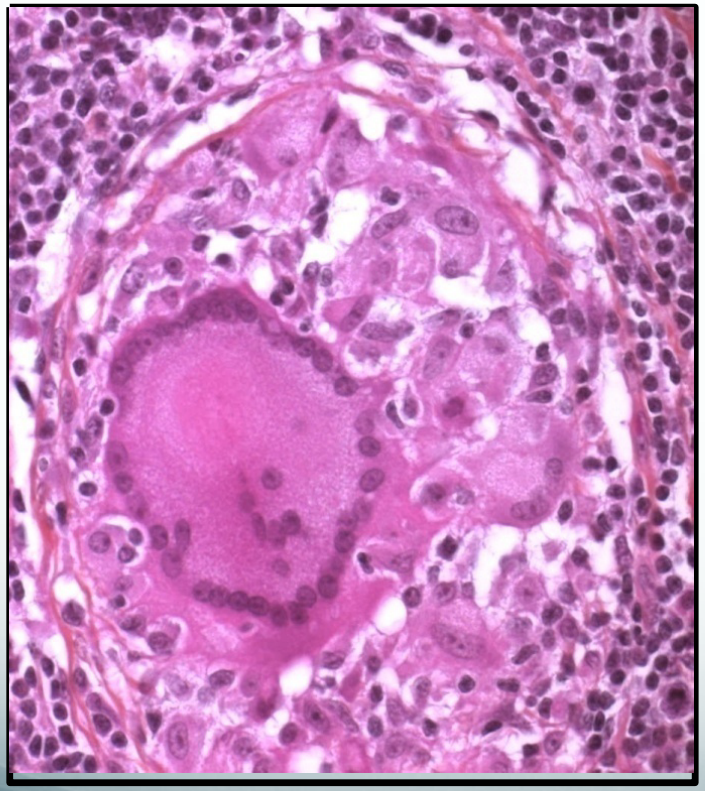
- Granulomas are encountered in certain specific pathologic states.
- Recognition of the granulomatous pattern is important because it is limited to number of conditions (some of which are life-threatening).

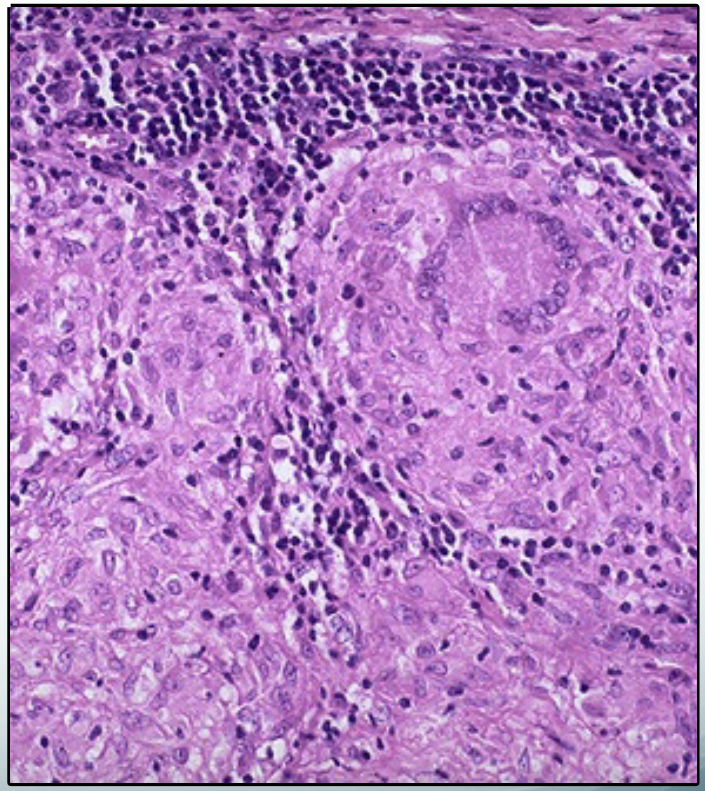

Chemotactic mediators (cytokines, others)
Cytokines
Recruitment
Division
Immobilization
Collection of macrophages
(Granuloma)

Morphology and Types of Cells

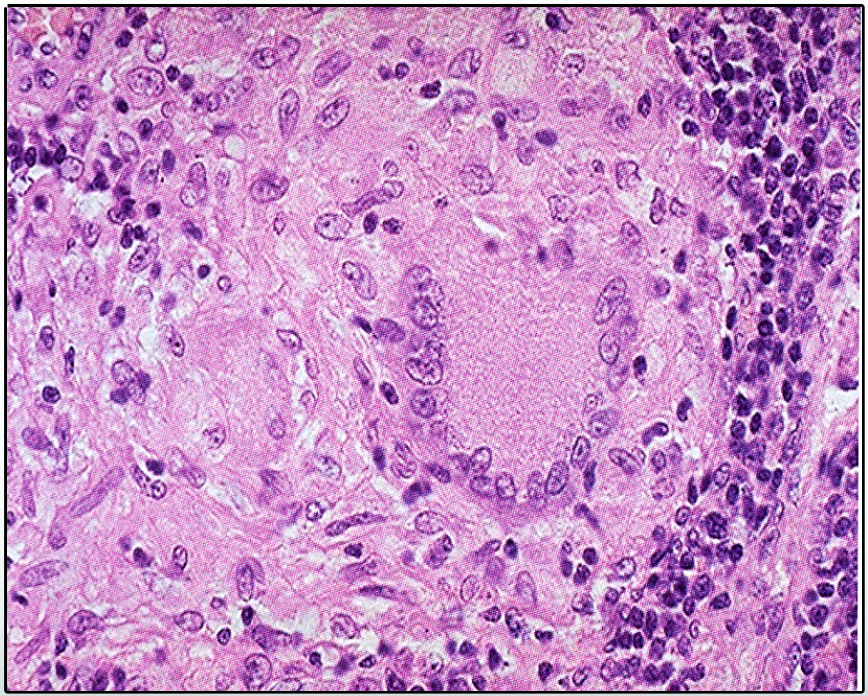
- A granuloma is a nodular collection of *epithelioid macrophages* surrounded by a rim of T-lymphocytes
- Activated macrophages develop abundant pink cytoplasm and begin to resemble epithelial cells (squamous-like appearance) ? epithelioid cells.
- Some activated macrophages may fuse, forming multinucleate giant cells.

Morphology and Types of Cells





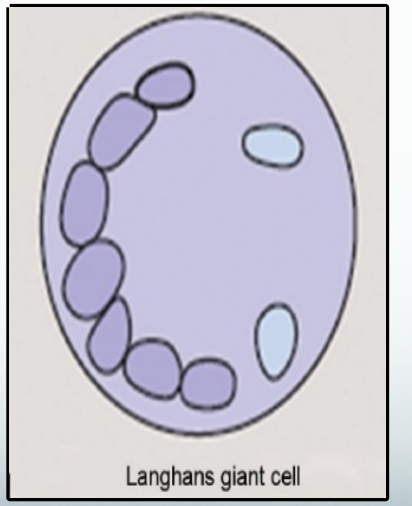
Morphology and Types of Cells

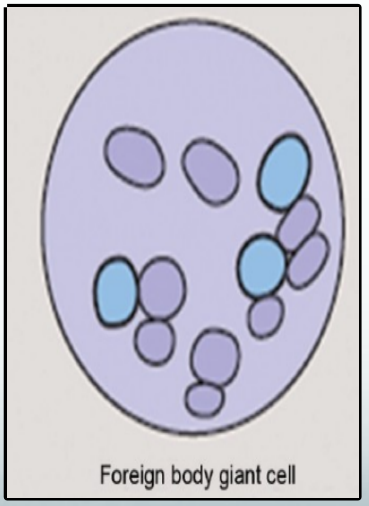


Langhans giant cell

Morphology and Types of Cells

- The nuclei arranged either peripherally (Langhans-type giant cell) or haphazardly (foreign body-type giant cell).





Morphology and Types of Cells

- Granulomas associated with certain infectious organisms (classically Mycobacterium tuberculosis) often contain a central zone of necrosis.
- Grossly, this has a granular, cheesy appearance and is therefore called caseous necrosis.
- Microscopically, this necrotic material appears as amorphous, structureless, eosinophilic, granular debris, with loss of cellular details.

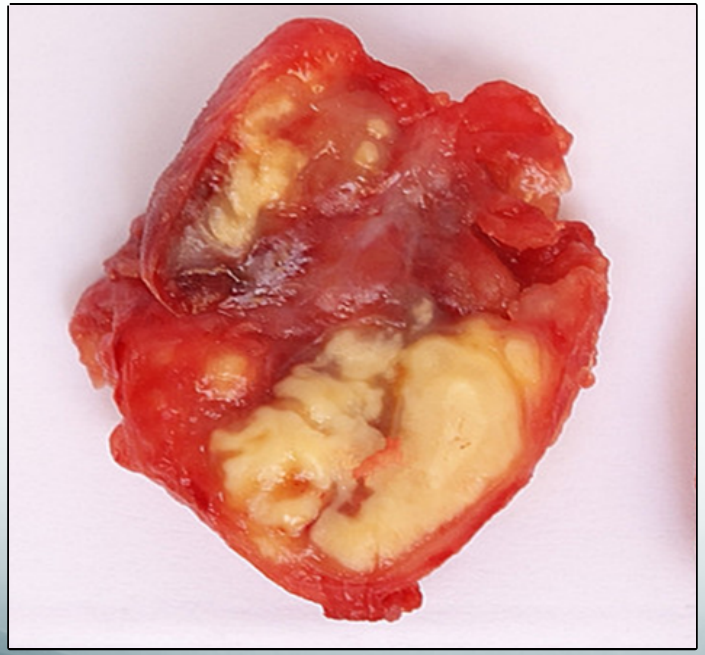
Morphology and Types of Cells

- The granulomas in Crohn disease, sarcoidosis, and foreign body reactions tend to not have necrotic centers and are said to be noncaseating.

- Healing of granulomas is accompanied by fibrosis that may be extensive.

Morphology and Types of Cells

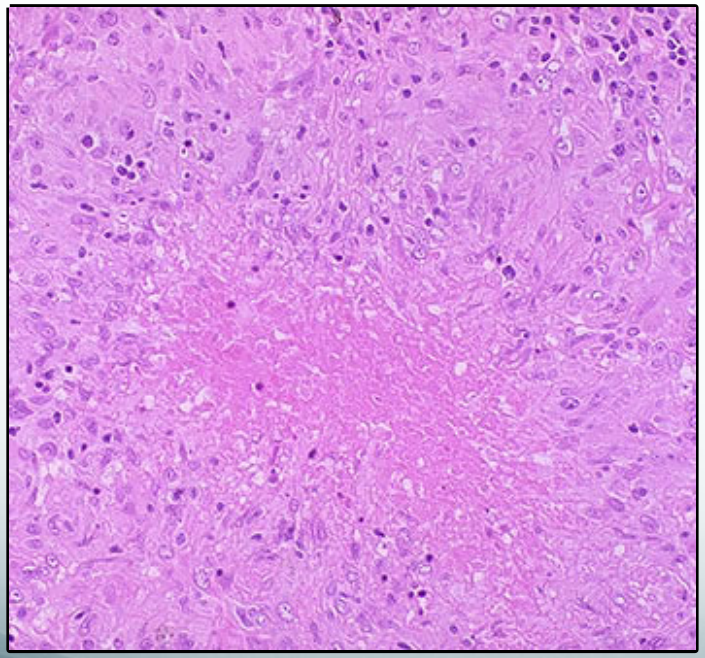
Lymph node



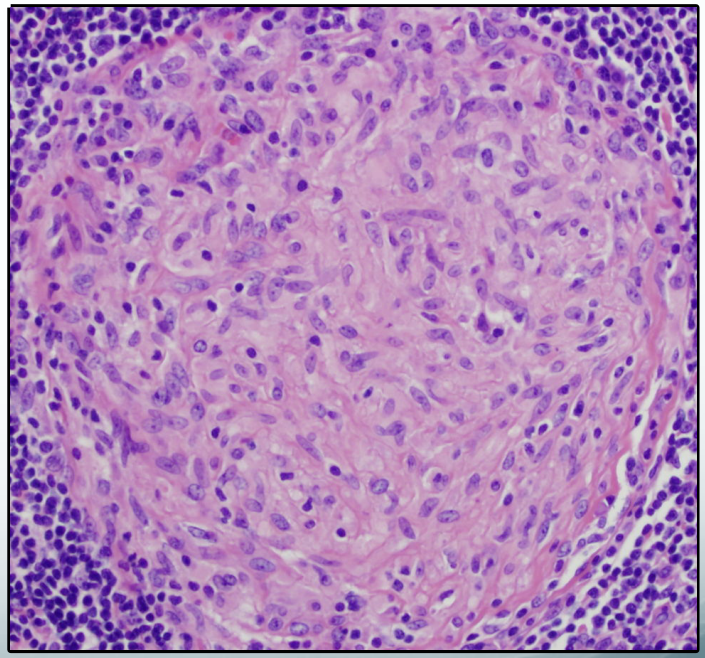
Adrenal gland

Morphology and Types of Cells

Caseating granuloma



Noncaseating granuloma



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.

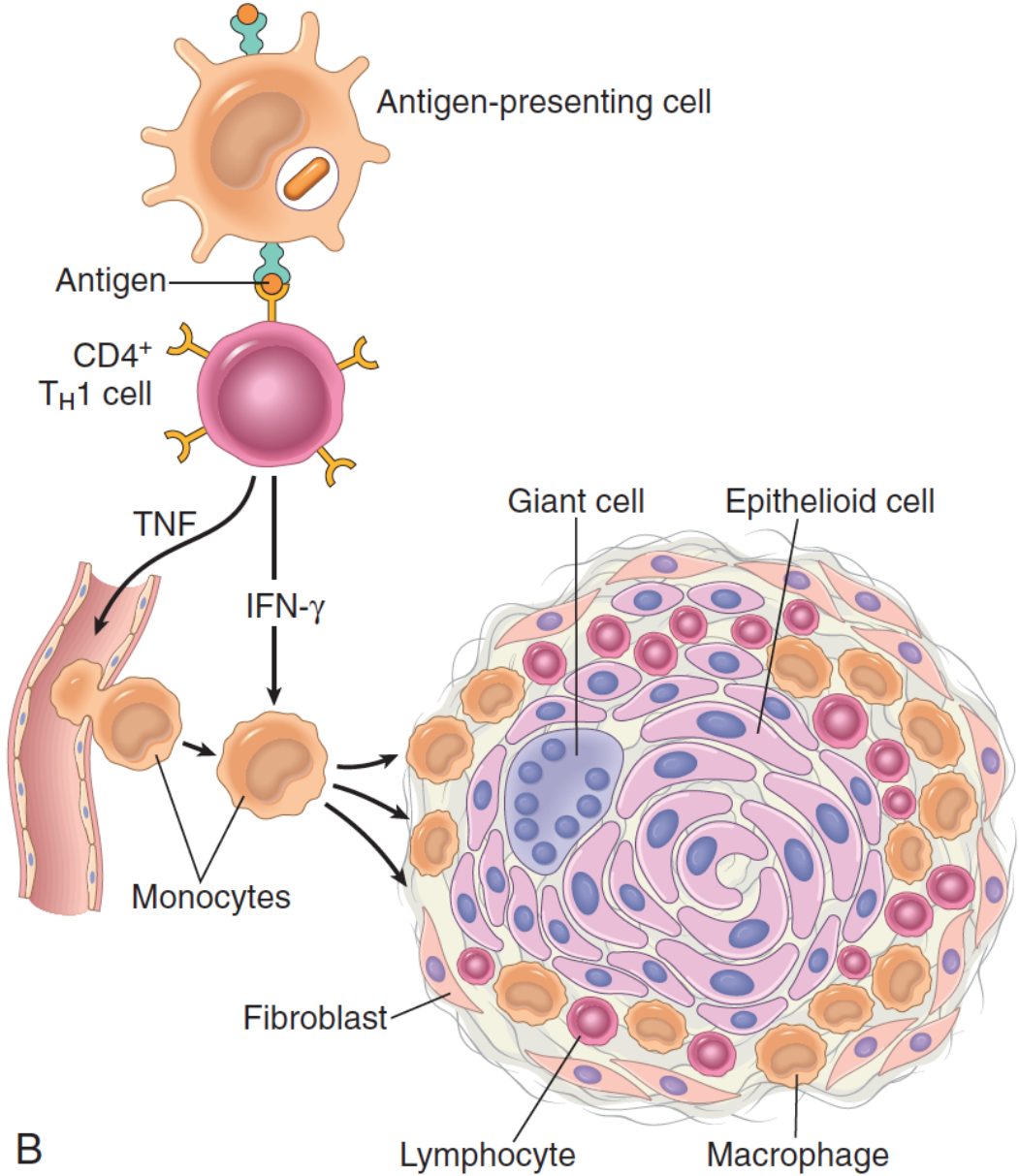
Pathogenesis

- Granuloma formation is a cellular attempt to contain an offending agent that is difficult to eradicate.

- It occurs when:

  - macrophages phagocytose the injurious agents but they survive inside them.

  - an active T-lymphocyte mediated cellular immune response occurs leading to the production of lymphokines that inhibit the migration of macrophages and cause them to aggregate in the area of injury and form granulomas.



1. Naïve T cells are activated by the recognition of indigestible antigens displayed by antigen representing cells.

2. The T cells differentiate into effector cells under the influence of various cytokines.

3. TH1 cells secrete cytokines, mainly IL-2, IFN-γ, which activate macrophages.

4. Activated macrophages produce substances that destroy microbes and damage tissues, and mediators that promote inflammation.

Types of Granulomas

- There are two types of granulomas:
  - Immune granulomas
  - Foreign body granulomas

Types of Granulomas

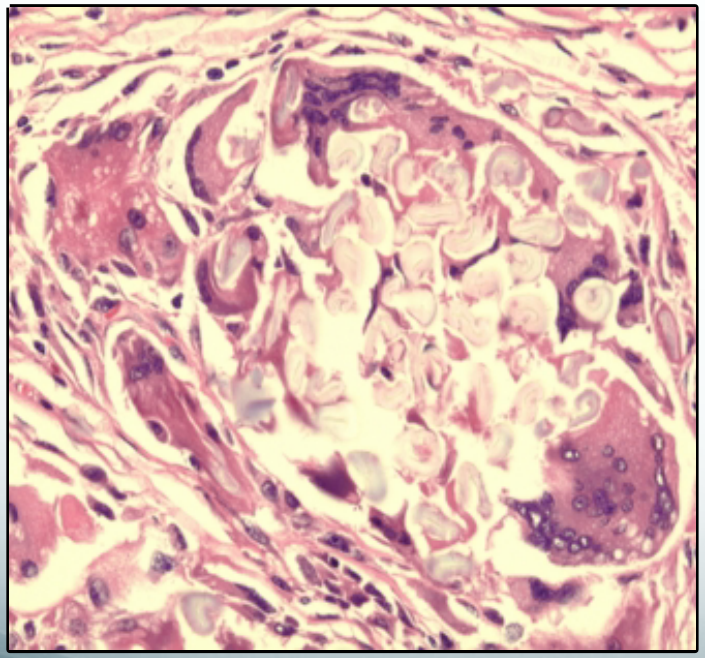
- Immune granuloma:
  - They are caused by a variety of agents that are capable of inducing a persistent T cell–mediated immune response.
  - It occurs when the inciting agent cannot be readily eliminated, such as a persistent microbe or a self antigen.
  - Macrophages activate T cells to produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN-γ, which activates the macrophages.

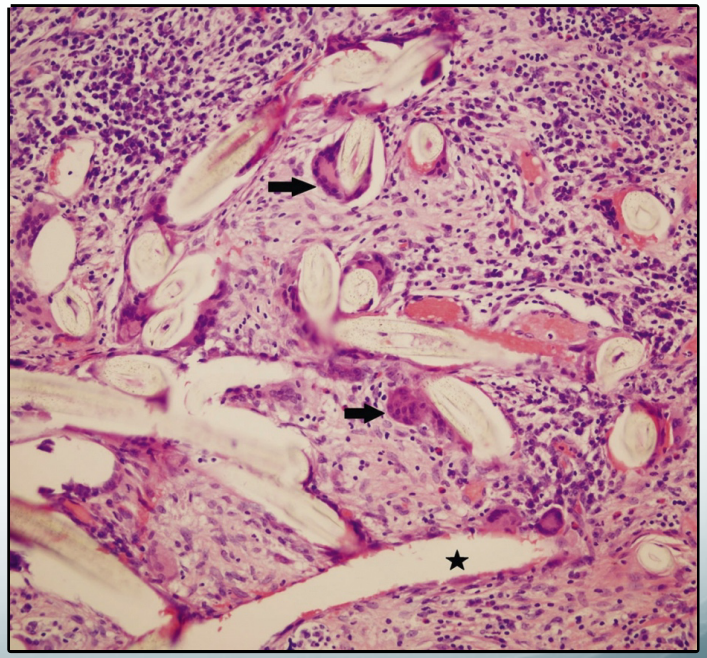
Types of Granulomas

- Foreign body granuloma:
  - They are seen in response to relatively inert foreign bodies, in the absence of T cell– mediated immune responses they do not incite a specific immune response.
  - They form around materials such as talc (associated with intravenous drug abuse), sutures, or other fibers that are large enough to preclude phagocytosis by a macrophage.
  - The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it may appear refractile.

Types of Granulomas

Foreign body granulomas





Causes of Granulomas

Foreign body granulomas

- Talc
- Sutures
- Graft material
- Hair shafts

Immune granulomas

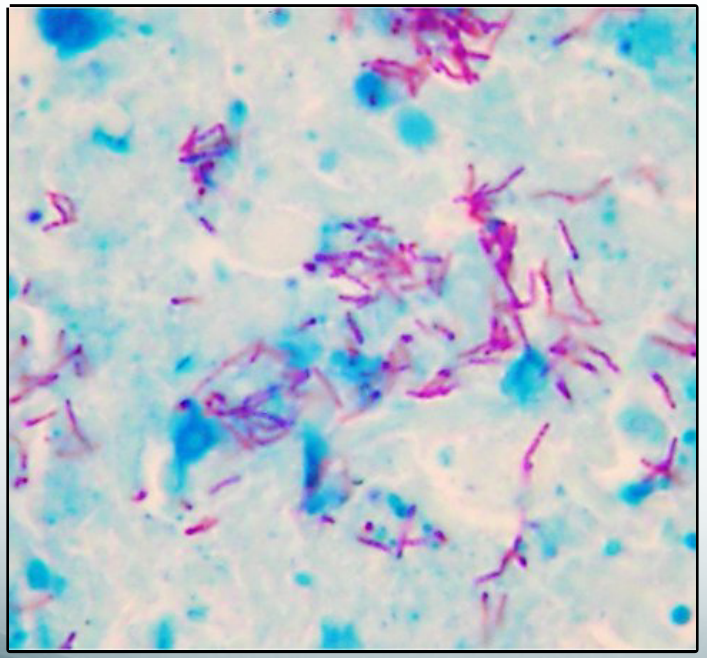
- **Bacteria**
  - Tuberculosis
  - Leprosy
  - Actinomycosis
  - Cat scratch disease
- **Fungi**
  - Blastomycosis
  - Histoplasmosis
- **Parasites**
  - Schistosomiasis
  - Leishmaniasis
- **Metals/Dust**
  - Berylliosis
- **Others**
  - Crohn's disease
  - Sarcoidosis

Tuberculosis

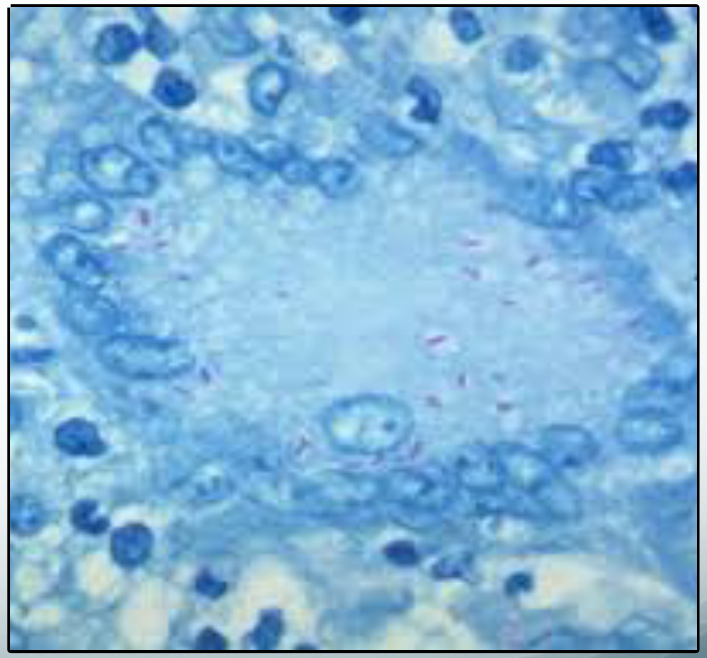
- It is caused by mycobacteria tuberculosis bacteria.
- Mycobacteria are slender rods.
- They are called acid fast bacilli [AFB] (i.e. they have a high content of complex lipids that readily bind the Ziehl -Neelsen [carbol fuchsin] stain and subsequently resist decolorization).

Tuberculosis

M. Tuberculosis in sputum

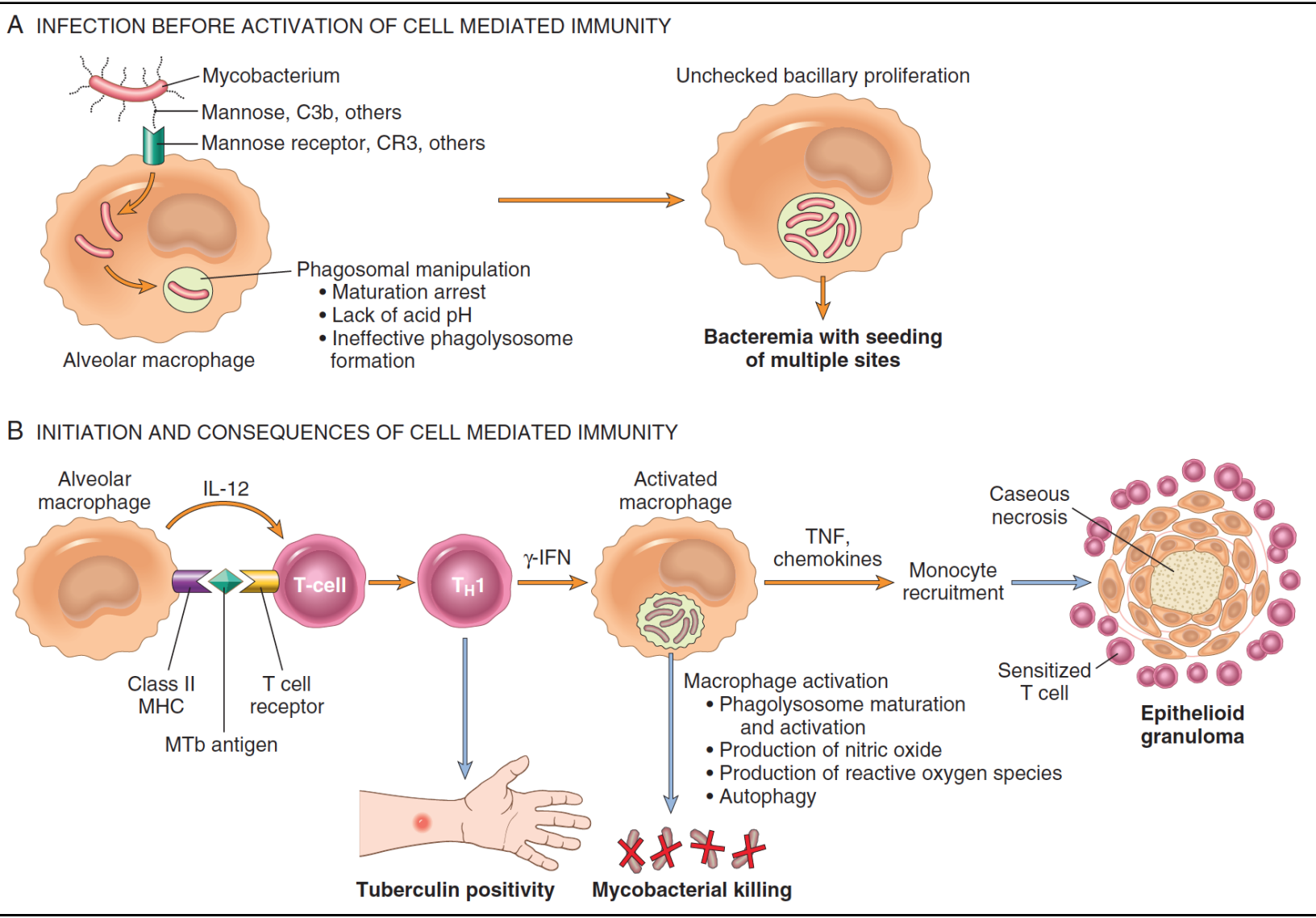


M. Tuberculosis in tissue section



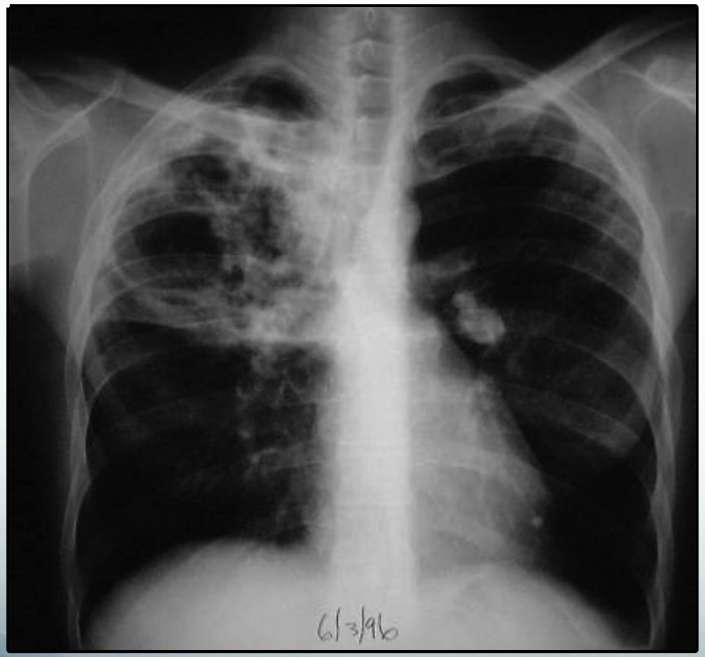
Pathogenesis of Tuberculosis

- The 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.
- The presence of cord factor increases the production of IL-12, IL-1β, IL-6 and TNF, which are pro-inflammatory cytokines important for the formation of a granuloma.

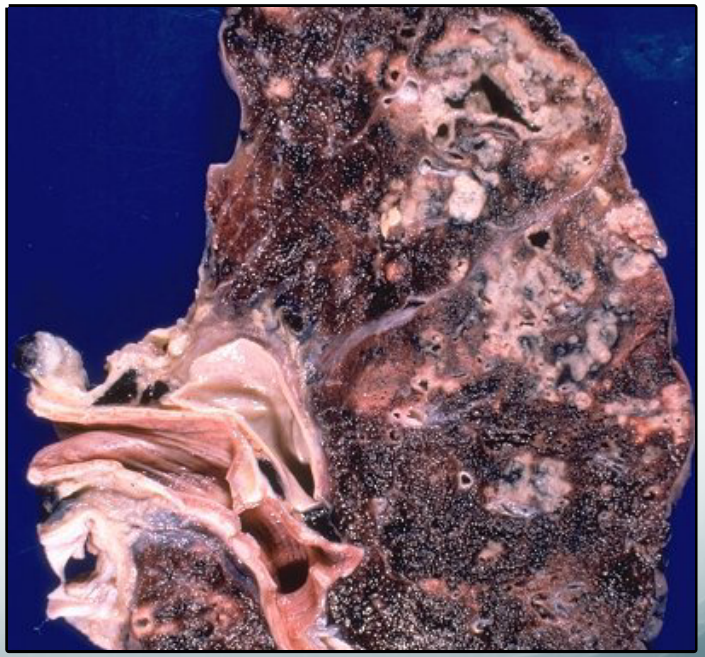

A INFECTION BEFORE ACTIVATION OF CELL MEDIATED IMMUNITY
Mycobacterium
Mannose, C3b, others
Mannose receptor, CR3, others
Alveolar macrophage
Phagosomal manipulation
• Maturation arrest
• Lack of acid pH
• Ineffective phagolysosome formation
Unchecked bacillary proliferation
Bacteremia with seeding of multiple sites
B INITIATION AND CONSEQUENCES OF CELL MEDIATED IMMUNITY
Alveolar macrophage
IL-12
T-cell
Class II MHC
T cell receptor
MTb antigen
TH1
γ-IFN
Activated macrophage
TNF, chemokines
Monocyte recruitment
Caseous necrosis
Sensitized T cell
Epithelioid granuloma
Macrophage activation
• Phagolysosome maturation and activation
• Production of nitric oxide
• Production of reactive oxygen species
• Autophagy
Tuberculin positivity
Mycobacterial killing

Tuberculosis

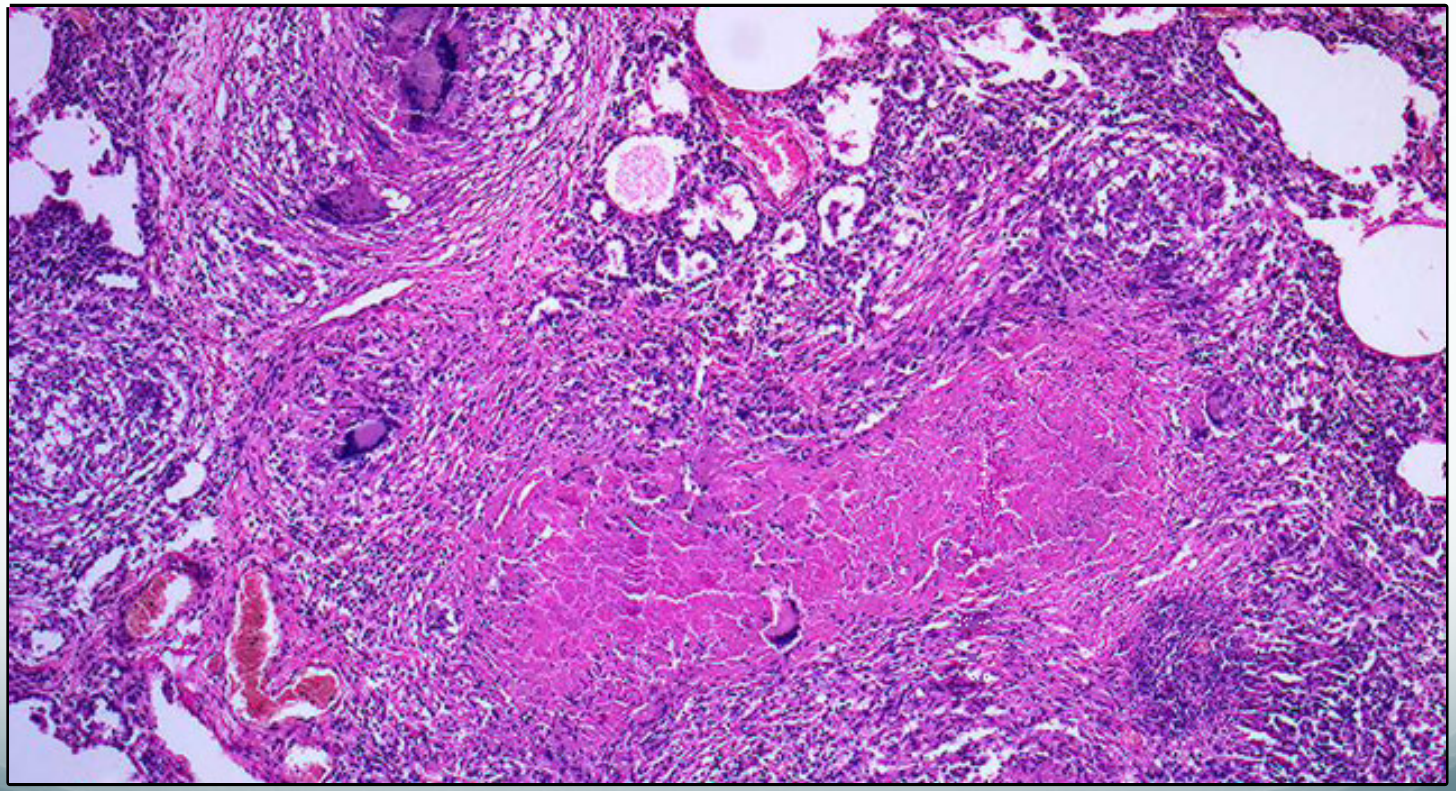
Chest X-ray

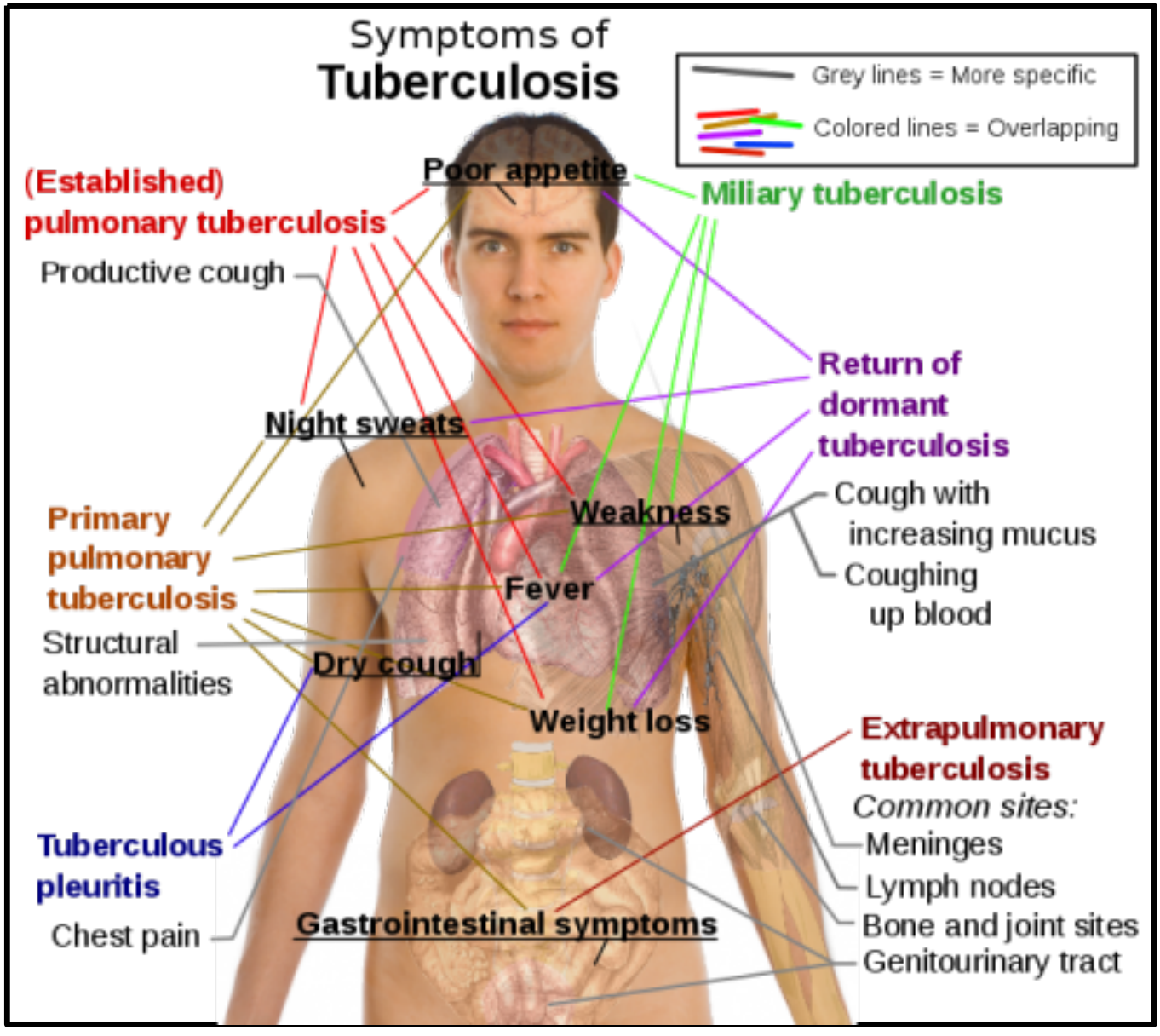


Gross pathology



Tuberculosis

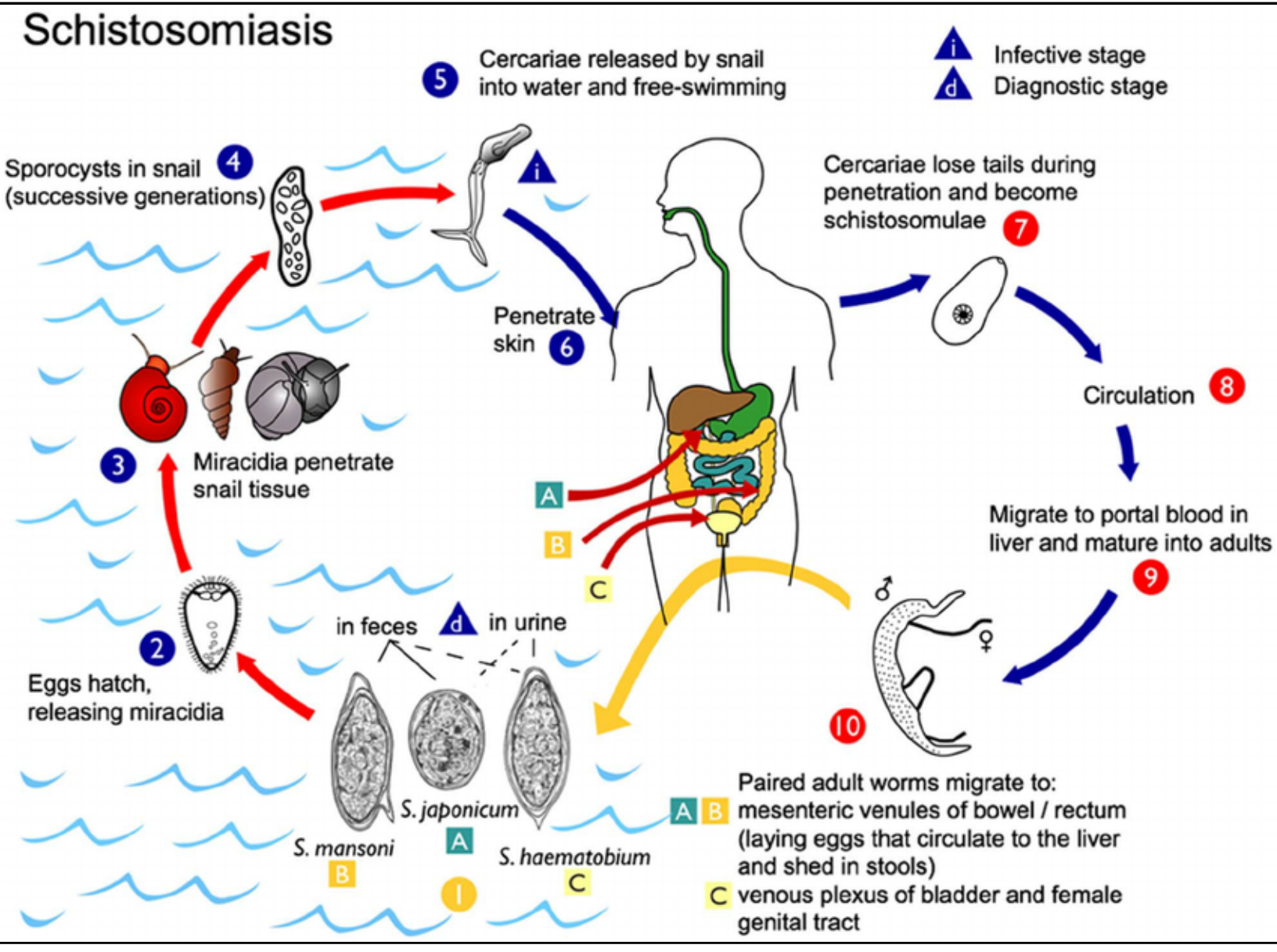



Symptoms of
Tuberculosis
Grey lines = More specific
Colored lines = Overlapping
(Established) pulmonary tuberculosis
Productive cough
Poor appetite
Miliary tuberculosis
Return of dormant tuberculosis
Night sweats
Cough with increasing mucus
Coughing up blood
Primary pulmonary tuberculosis
Weakness
Fever
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

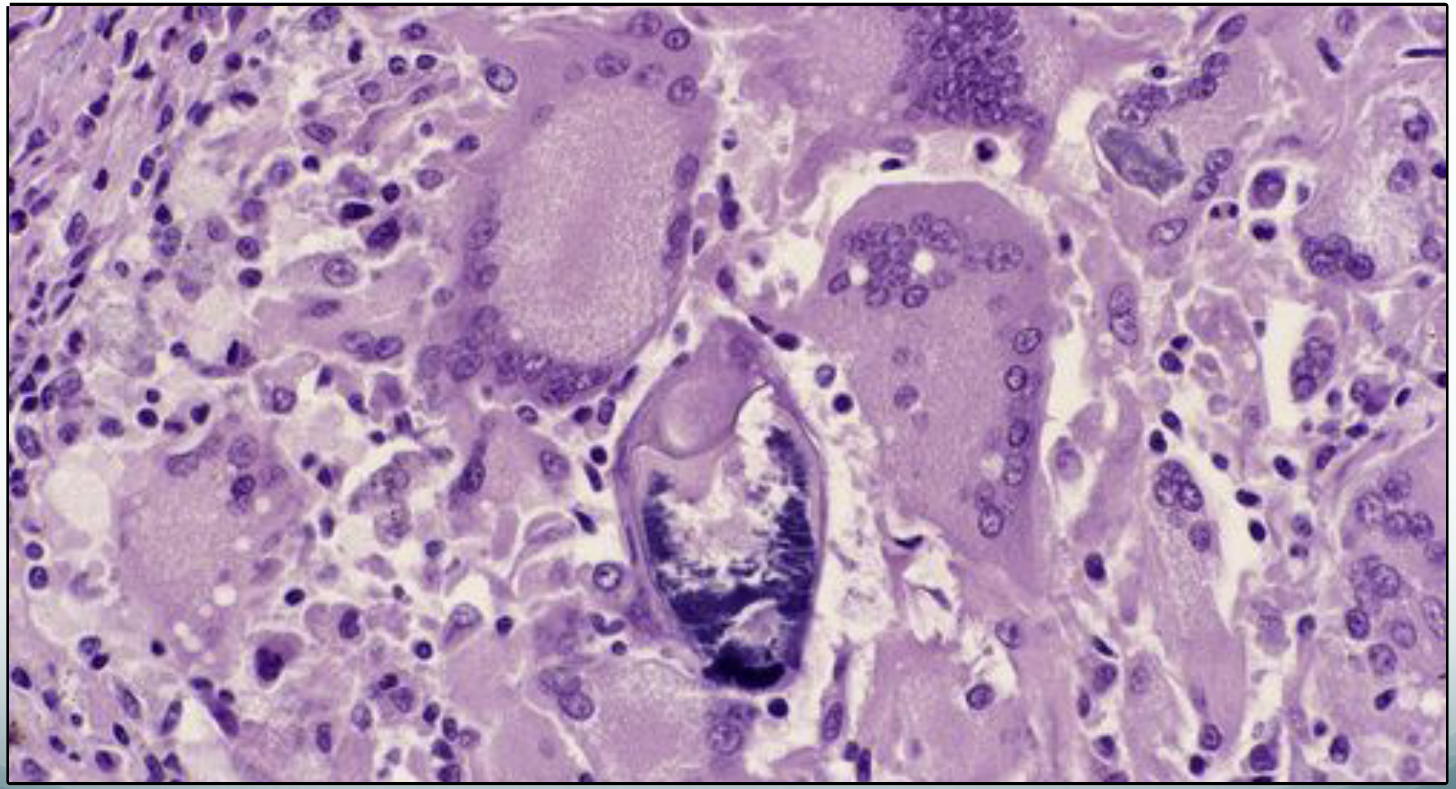
Schistosomiasis

- Schistosomiasis is most commonly found in Asia, Africa and South America.
- Schistosoma mansoni parasites penetrate the skin but eventually localize in blood vessels of the portal system and mesentery, damaging the liver and intestine.
- Schistosoma hematobium also penetrates the skin, but localizes to the urinary bladder and causes cystitis.

Schistosomiasis



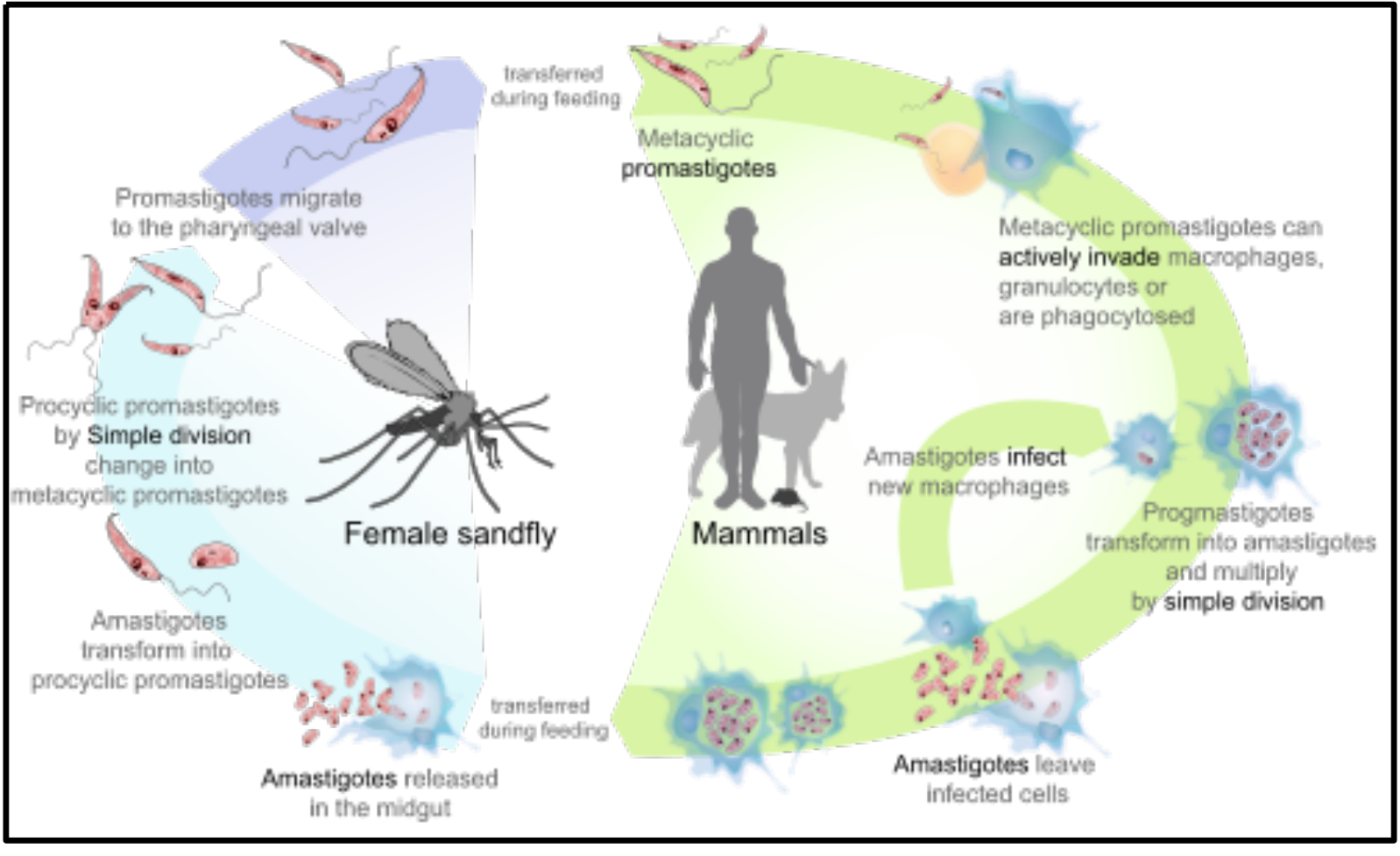
Schistosomiasis



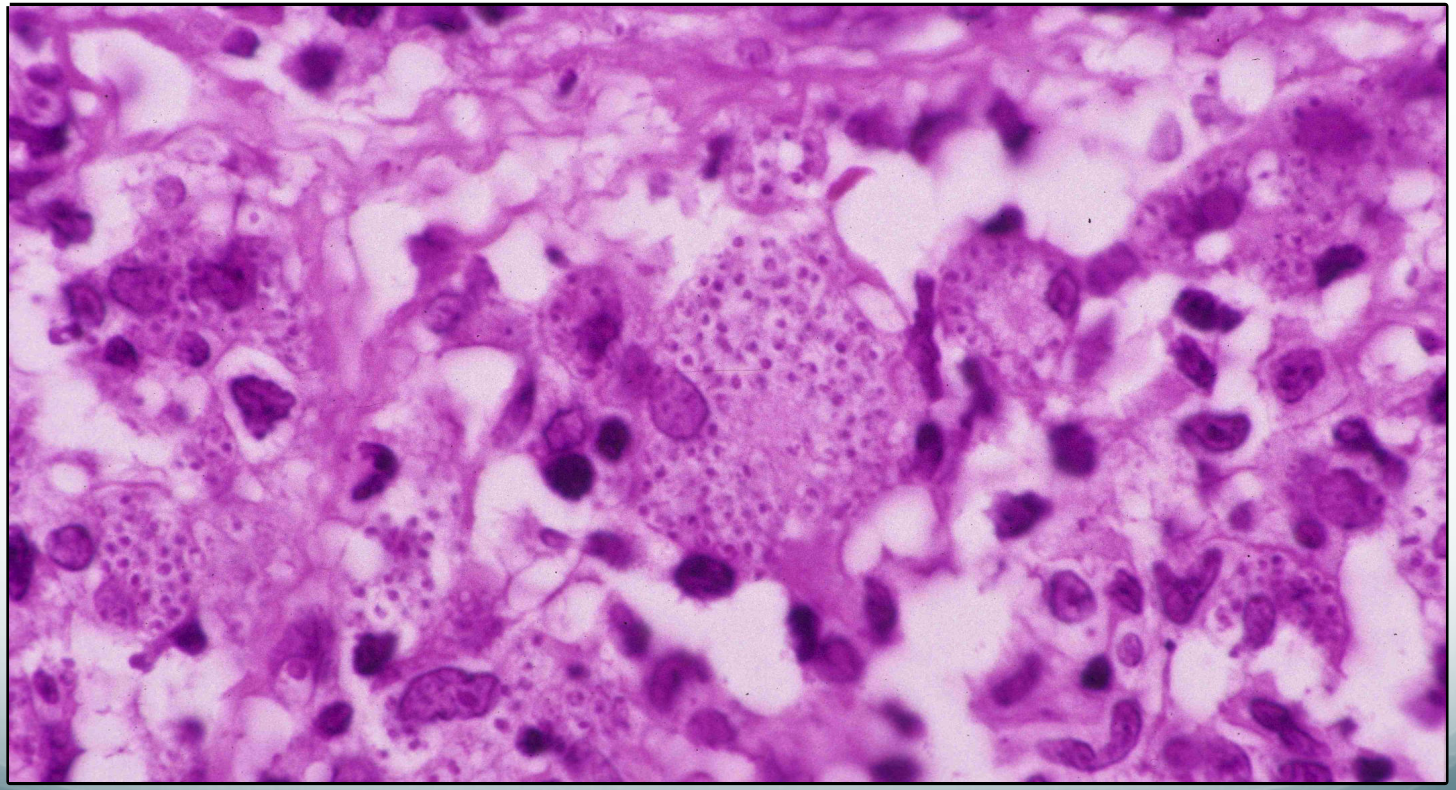
Leishmaniasis

- Leishmaniasis is common in all tropical countries.

- It causes a cutaneous, mucocutaneous or visceral disease.


transferred during feeding
Metacyclic promastigotes
Promastigotes migrate to the pharyngeal valve
Metacyclic promastigotes can actively invade macrophages, granulocytes or are phagocytosed
Procyclic promastigotes by Simple division change into metacyclic promastigotes
Female sandfly
Mammals
Amastigotes infect new macrophages
Progmastigotes transform into amastigotes and multiply by simple division
Amastigotes transform into procyclic promastigotes
transferred during feeding
Amastigotes released in the midgut
Amastigotes leave infected cells

Leishmaniasis

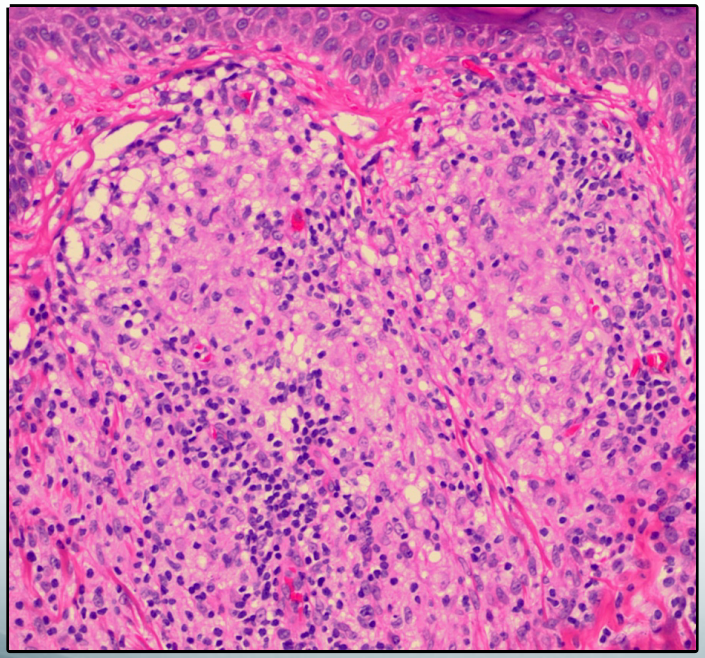


Leprosy

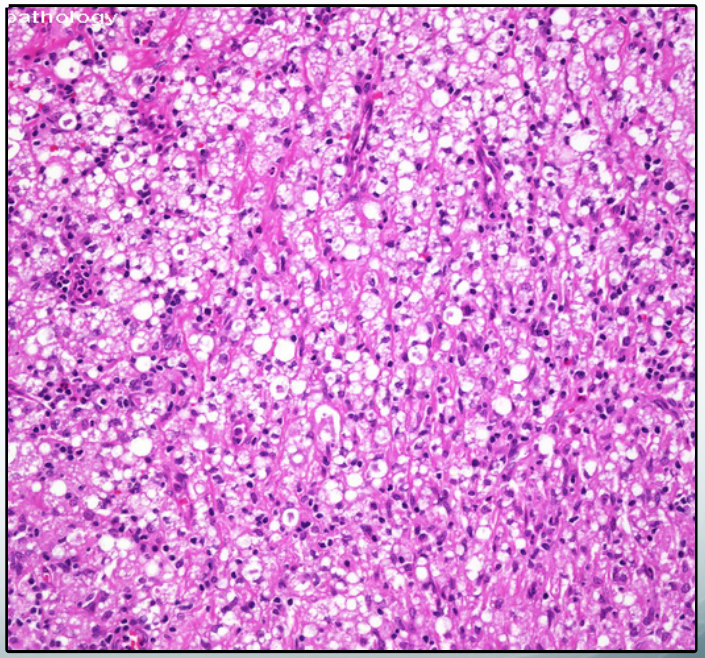
- Leprosy is endemic in tropical countries.
- It causes a chronic cutaneous infection.
- It is transmitted by nasal discharges and dermal contact.

Leprosy

Tuberculoid leprosy



Lepromatous leprosy

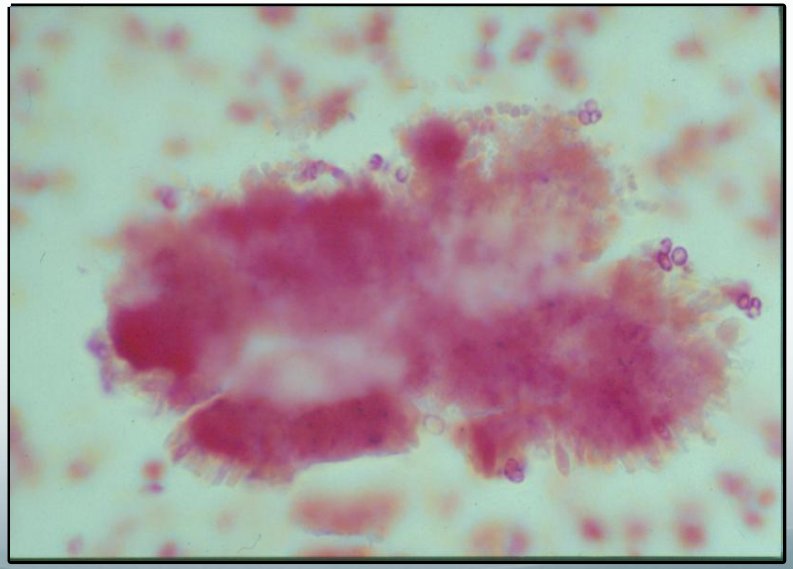


Actinomycosis

- Actinomycosis is a long-term (chronic) granulomatous bacterial infection.
- It is caused by filamentous, gram-positive, non–acid-fast, anaerobic-to-microaerophilic bacteria.
- It commonly affects the face and neck.

Actinomycosis

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

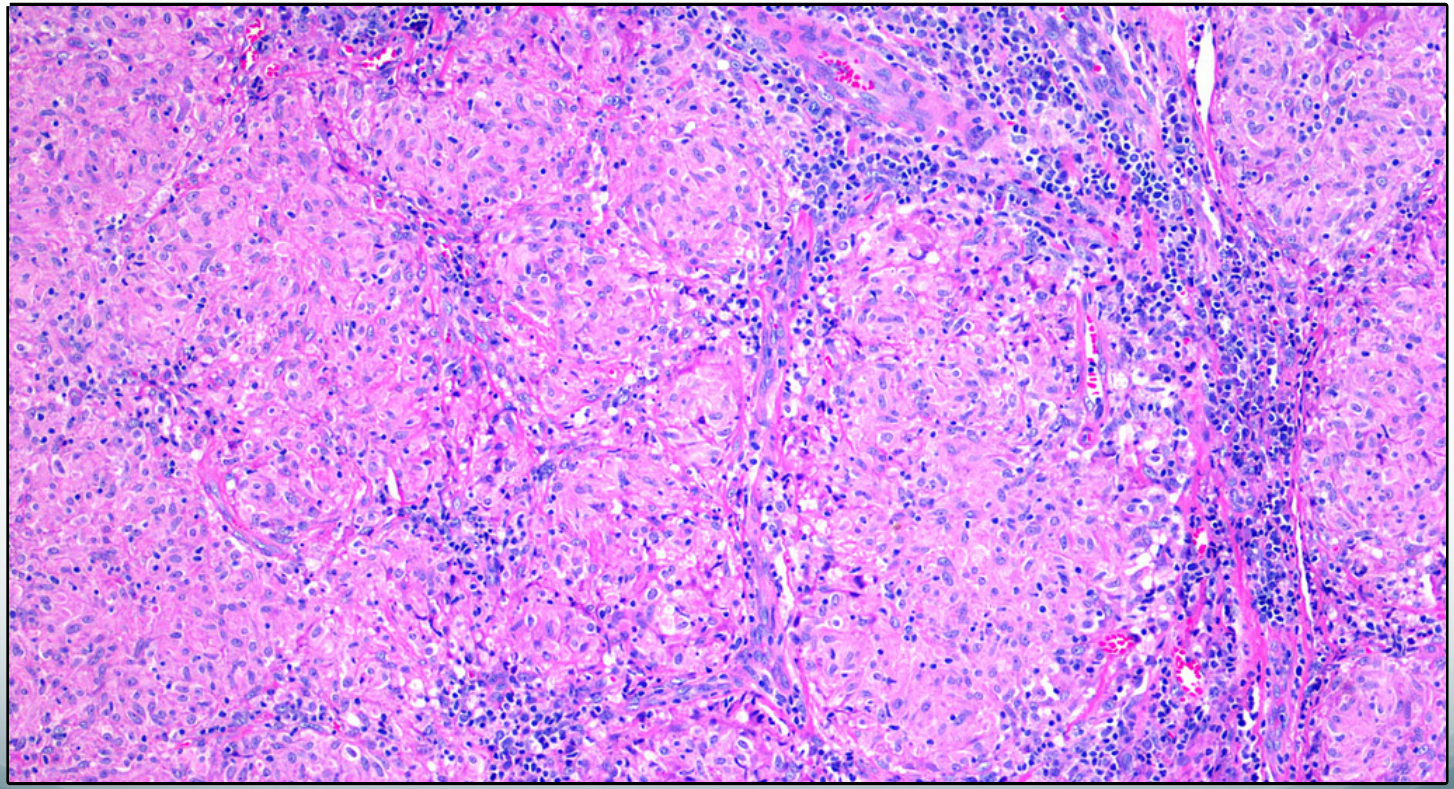


Sarcoidosis

- Sarcoidosis is a multisystemic disease of unknown origin that involves lung or bilateral hilar lymph nodes in 90% of cases.

- It causes noncaseating epithelioid granulomas.

Sarcoidosis



Summary

- Granulomatous inflammation is a distinctive pattern of chronic inflammation characterized by aggregates of epithelioid macrophages
- Damaging stimuli which provoke a granulomatous inflammatory response include microorganisms which are of low inherent pathogenicity but which excite an immune response.
- Granulomas are produced in response to:
  - Bacterial infections
  - Parasitic infections
  - Certain fungi
  - Non-living foreign materials deposited in tissues e.g. keratin from a ruptured epidermal cyst.
  - Unknown factors

Reference

Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 9th ed. Elsevier; 2013. Philadelphia, PA.

Revision

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 cells 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 mycobacteria

a. IFN-γ
b. Langhans cells
c. Epitheliod histiocyes
d. Cord factor
e. Langerhan's cells
f. Type IV hypersensitivity reaction
g. Caseating granuloma

Revision

- Which of the following diseases does not cause a granulomatous inflammation?

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

Revision

- What are the common causes of a caseous necrosis?
  - Tuberculosis, leprosy, and fungal infections.

- What is the origin of epithelioid cells?
  - They are transformed (activated) macrophages.

Revision

- How does a caseous necrosis differ from a coagulative necrosis under the microscope?

  - In caseous necrosis, there is total loss of tissue structure, whereas in coagulative necrosis, the cell outlines are retained.

Revision

- What is 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 and it is a form of chronic inflammation.

Revision

- What are the common causes of granulomatous inflammation?
  - Bacterial (e.g. *Mycobacterium tuberculosis, M. leprae, Treponema pallidum*)
  - Parasitic (e.g. Schistosomiasis)
  - Fungal (e.g., Histoplasmosis, Blastomycosis)
  - Inorganic dusts (e.g. Silicosis, Berylliosis)
  - Foreign body
  - Unknown (e.g. Sarcoidosis)

Revision

- 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 tuberculosis infection do granulomas in different organs look different?
  - No, all granulomas look similar.

End of lecture

Thank You