

Pathology of Inflammation and Repair

LEC.3

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Objectives

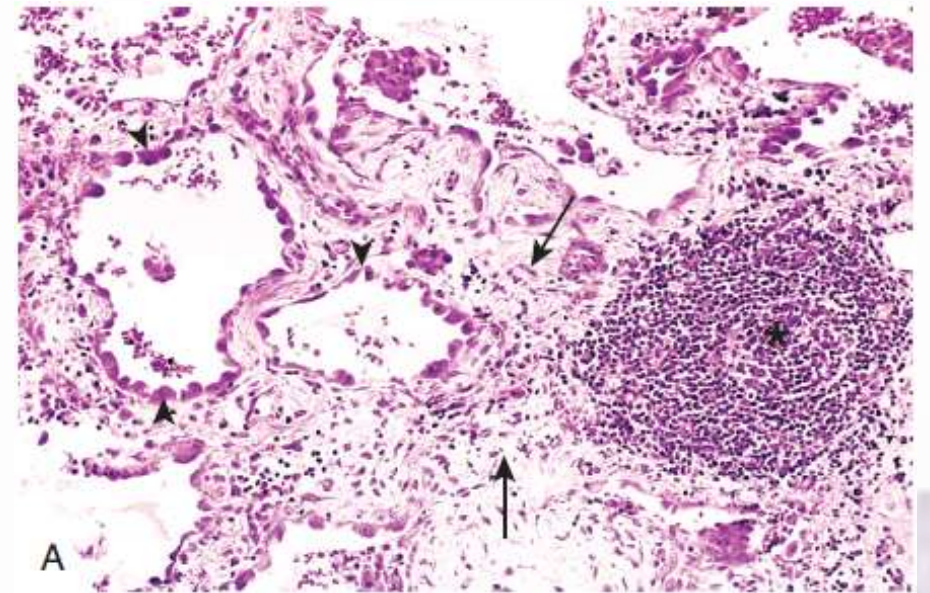
- Define chronic inflammation.
- Describe the main morphological features of chronic inflammation.
- Explain the roles of different cells and mediators involved in chronic inflammation.
- Define granulomatous inflammation and describe its pathological features.
- Recognize the systemic effects of inflammation.

Chronic inflammation

- Chronic inflammation is an inflammatory response of **prolonged duration** (weeks to months) in which **active inflammation**, **tissue destruction** and **repair** coexist.

➤ Morphologic features:

1. Infiltration with **mononuclear inflammatory cells**, including macrophages, lymphocytes, and plasma cells.
2. **Tissue destruction**, induced by persistent offending agent or by the inflammatory cells.
3. Attempts at **healing by connective tissue replacement**, accomplished by **angiogenesis** (proliferation of small blood vessels) and **fibrosis** (collagen deposition).



Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells (*), (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, arrowheads), and (3) replacement by connective tissue (fibrosis, arrows).

Causes of chronic inflammation

- May follow acute inflammation, or begin insidiously as a low-grade response without evidence of preceding acute inflammation:
1. **Persistent infections** by microorganisms that are difficult to eradicate, such as mycobacteria and certain viruses, fungi, and parasites.
 2. **Hypersensitivity diseases:** caused by excessive and inappropriate immune response results in chronic inflammation and tissue damage, including *autoimmune diseases*, examples (rheumatoid arthritis and multiple sclerosis) and *allergic diseases* as in bronchial asthma. *Such diseases may show morphologic patterns of mixed acute and chronic inflammation because they are characterized by repeated bouts of inflammation.
 3. **Unresolved acute inflammation**, as when an acute bacterial infection of the lung progresses to a chronic abscess.
 4. **Prolonged exposure to potentially toxic agents:** either: **Exogenous** (e.g., **silica** result in lung silicosis), or **Endogenous** (e.g., excessive production and tissue deposition of **cholesterol and other lipids** result in Atherosclerosis).

Cells of chronic inflammation

1. Macrophages:

- The macrophage is the dominant cells in chronic inflammation.
- They originate from hematopoietic stem cells in the bone marrow, circulate as monocytes and **migrate into tissues**, where they differentiate into macrophages.
- Tissue macrophages have specific names depending on their location:
 - * Kupffer cells in the liver
 - * Sinus histiocytes in lymph nodes and spleen
 - * Microglial cells in the central nervous system
 - * Alveolar macrophages in the lungs
- **Macrophage functions include:**
 - **Phagocytosis:** ingest and eliminate microbes, dead tissues and foreign material.
 - **Secretion of inflammatory mediators,** Thus, contribute to the initiation and propagation of inflammatory reactions.
 - **Initiation of tissue repair:** involved in scar formation and fibrosis
 - **Interaction with T-lymphocytes:** important in cell-mediated immune responses.

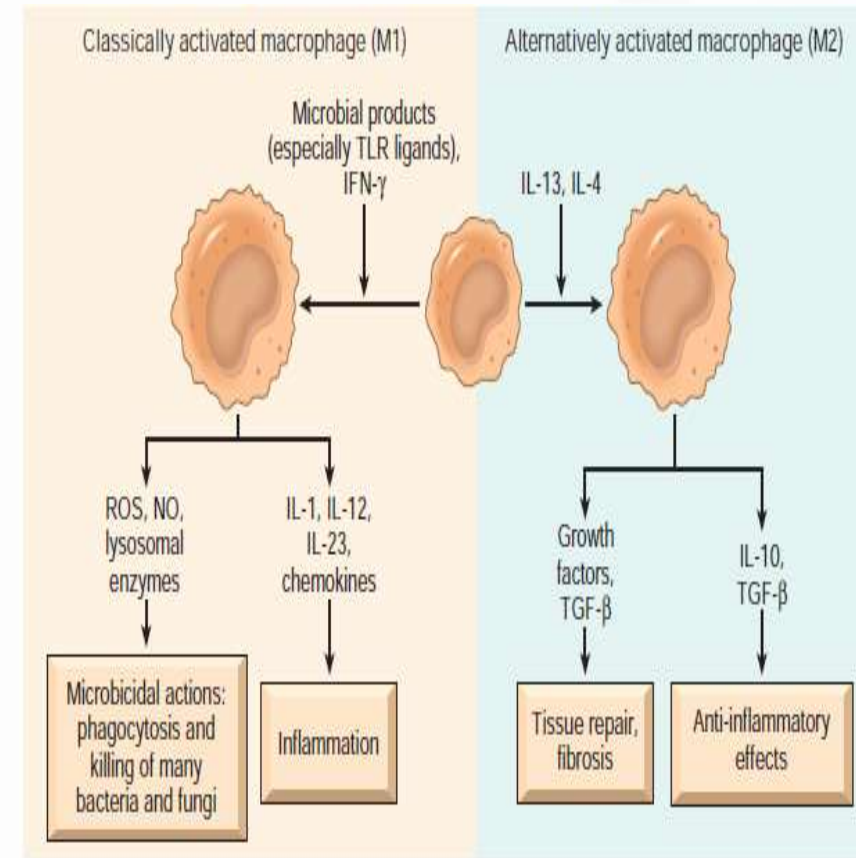
Pathways of Macrophage Activation

1- Classical (M1) Pathway

- * **Induced by:** **Microbial products**, **IFN- γ** from activated **Th1** lymphocytes
- * **Result:**
 - Production of **reactive oxygen** and **nitrogen species** (ROS, NO)
 - Upregulation of **lysosomal enzymes**
 - Secretion of **pro-inflammatory cytokines** (such as **IL-1**, **IL-12**, **IL-23**, and **TNF**)
- * **Function:** Enhanced microbicidal activity + Promotion of inflammation and tissue injury (**Killer mode**)

2- Alternative (M2) Pathway

- * **Induced by:** **Cytokines IL-4 and IL-13** from **Th2** lymphocytes and other cells.
- * **Result:**
 - Secretion of **growth factors** (TGF- β , PDGF, VEGF) promoting **tissue repair, angiogenesis**, and **fibrosis**.
 - Release of **anti-inflammatory cytokines** (IL-10, TGF- β), which suppress inflammatory responses.
- * **Functions:** Activation of macrophages toward a **tissue-repairing phenotype** (**Healer mode**).



➤ **Summary:** M1 macrophages promote **inflammation** and **microbicidal** activity, while M2 macrophages promote **healing** and **fibrosis**.

2. Lymphocytes:

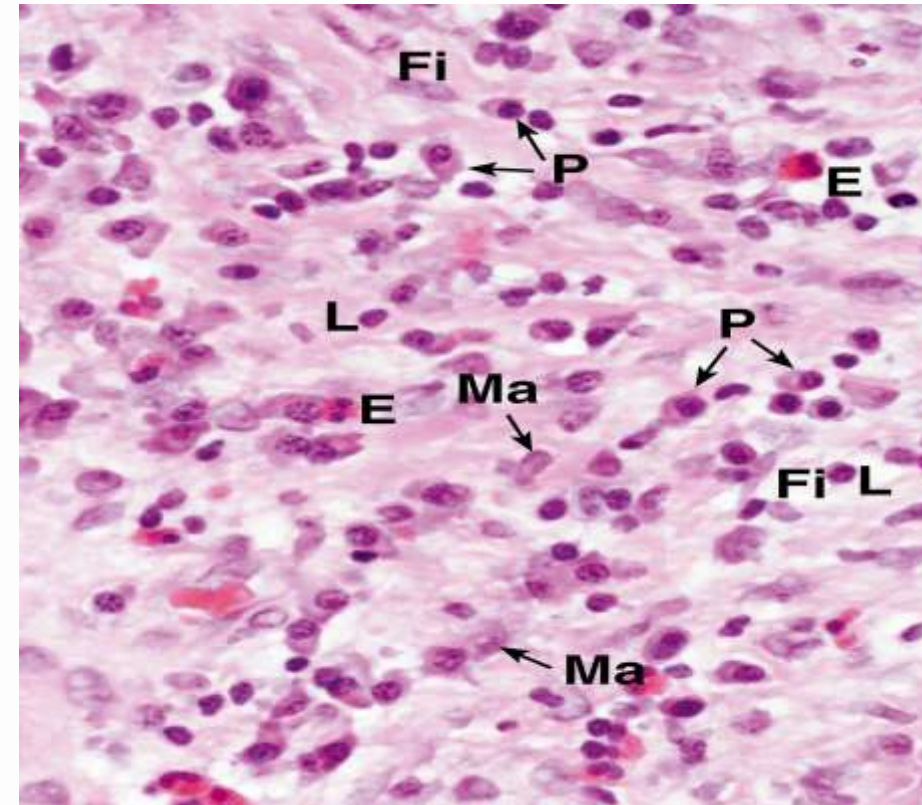
- Lymphocytes are recruited and **activated by microbial and environmental antigens**. They **amplify and sustain chronic inflammation** through cytokine secretion.

3. Plasma cells: which produce **antibodies**, which help neutralize microbes and promote phagocytosis.

4. Eosinophils: increase in **parasitic infection or IgE mediated immune reaction**. Attracted by chemokines such as **eotaxin** and contain **major basic protein**, which is toxic to parasites but can also damage host tissues.

5. Mast cells: **release histamine** (important in acute & chronic inflammation).

6. Fibroblasts: macrophages secrete fibroblast growth factor which stimulate fibroblasts.



➤ **E;** eosinophil. **Fi;** fibroblast. **L;** lymphocyte. **Ma;** macrophage. **P;** plasma cells

Chronic Granulomatous inflammation

- A distinctive form of chronic inflammation characterized by granulomas.
- **Granuloma:** Is an **aggregation of activated modified macrophages (epithelioid cells) surrounded by a collar of lymphocytes and sometimes fibroblasts.**
- Granuloma formation is a cellular attempt to contain an offending agent that is difficult to eradicate.
- In certain infections (e.g., tuberculosis), granulomas exhibit central caseous necrosis.

➤ Types of granuloma

- **1. Immune granulomas;** are caused by agents cannot be eliminated (e.g., a persistent microbe or self antigen), therefore induce a persistent T cell- mediated immune response, in which activated **Th1** cells secrete **IFN- γ** that activates macrophages.
- **2. Foreign body granulomas:** caused by inert (non-immunogenic) foreign bodies (e.g. talc, sutures or large fibers) that are too large to be phagocytosed, and not require a T-cell mediated immune response.

➤ **Examples of Diseases with Granulomatous Inflammation:**

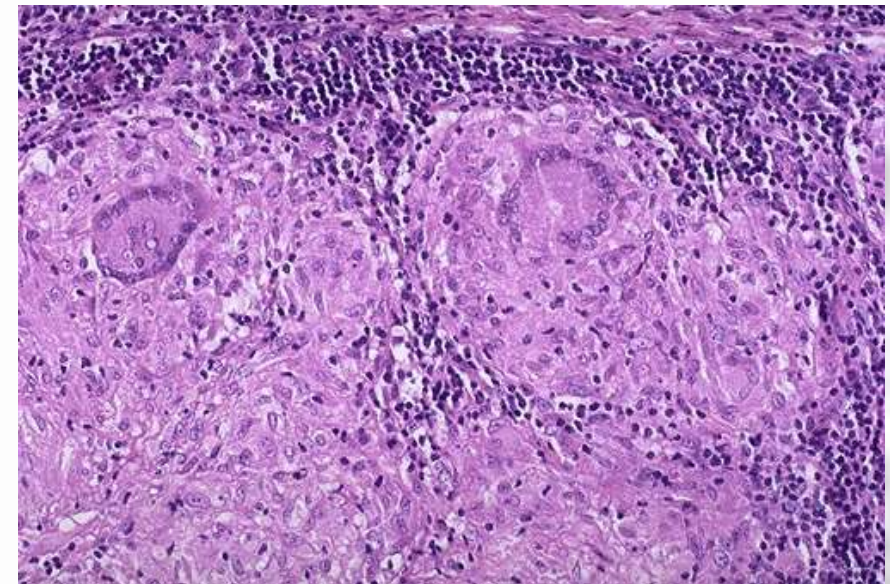
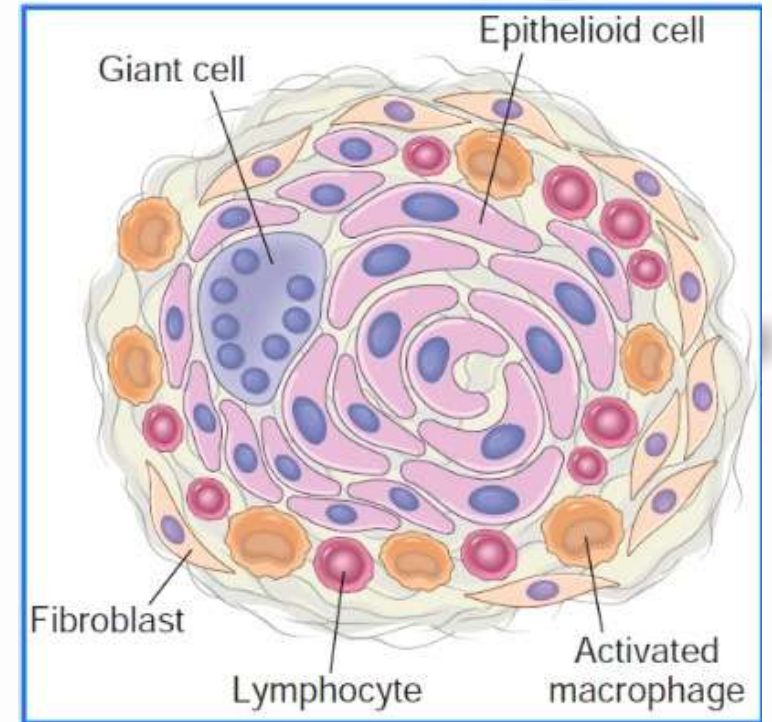
- **Bacterial** causes: (Tuberculosis, leprosy, syphilis, Cat-scratch disease).
- **Parasitic** causes: (leishmaniasis and Schistosomiasis).
- **Fungal** causes: (Histoplasmosis, cryptococcus neoformans).
- **Foreign body**: (Suture, talc, splinter, silicone).
- **Inorganic compound**: Silica, Beryllium
- **Sarcoidosis** Unknown etiology.
- **Crohn disease** (inflammatory bowel disease; Immune reaction against intestinal bacteria or possibly self-antigens).

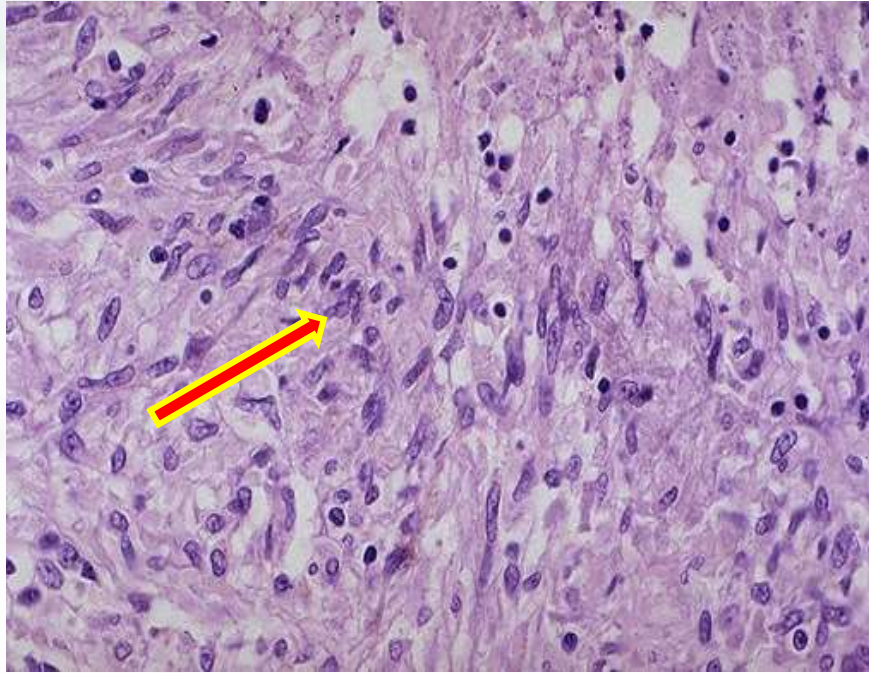
➤ Granulomatous diseases have different morphologic patterns that may suggest a specific diagnosis. However, **definitive diagnosis** requires identifying the specific etiologic agent by:

Special stains; e.g., acid-fast stain for tubercle bacilli· **Culture**; e.g., tuberculosis, fungal diseases· **Molecular techniques**; e.g., PCR for tuberculosis· **Serology**; e.g., syphilis.

Microscopic Features of Granuloma

- 1. Aggregates of epithelioid macrophages** (have pink granular cytoplasm with indistinct cell boundaries and are called epithelioid cells because of their resemblance to epithelia).
- 2. Multinucleated giant cells;** They consist of a large mass of cytoplasm and many nuclei, and they derive from the fusion of multiple activated macrophages.
- 3.** The aggregates of epithelioid macrophages are **surrounded by a collar of lymphocytes**.
 - **Older** granulomas may have a rim of **fibroblasts** and connective tissue.
 - **Caseous necrosis** may be present, (amorphous, eosinophilic debris without cellular detail).

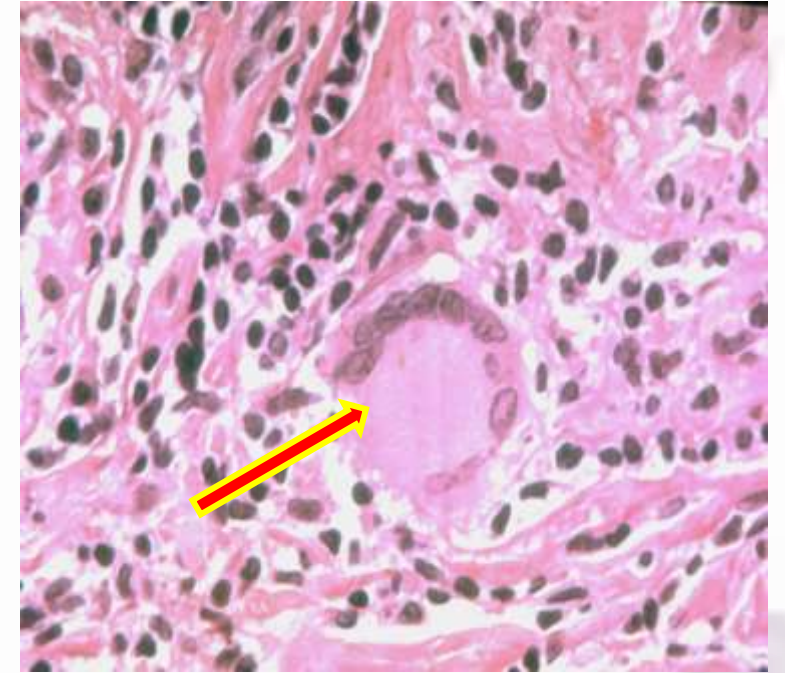




Epithelioid cell



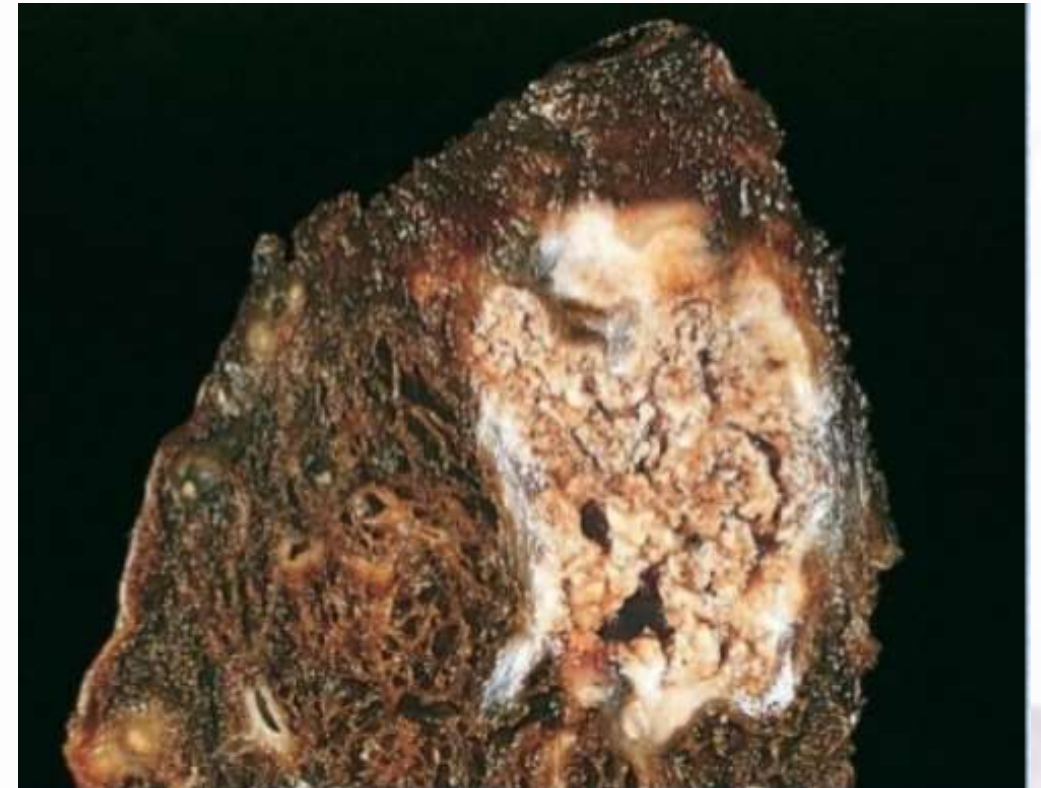
Foreign body giant cell



Langhans giant cell; nuclei arranged in a horseshoe shaped around periphery. Classic hallmark of TB.

Caseating granuloma (necrotizing granuloma)

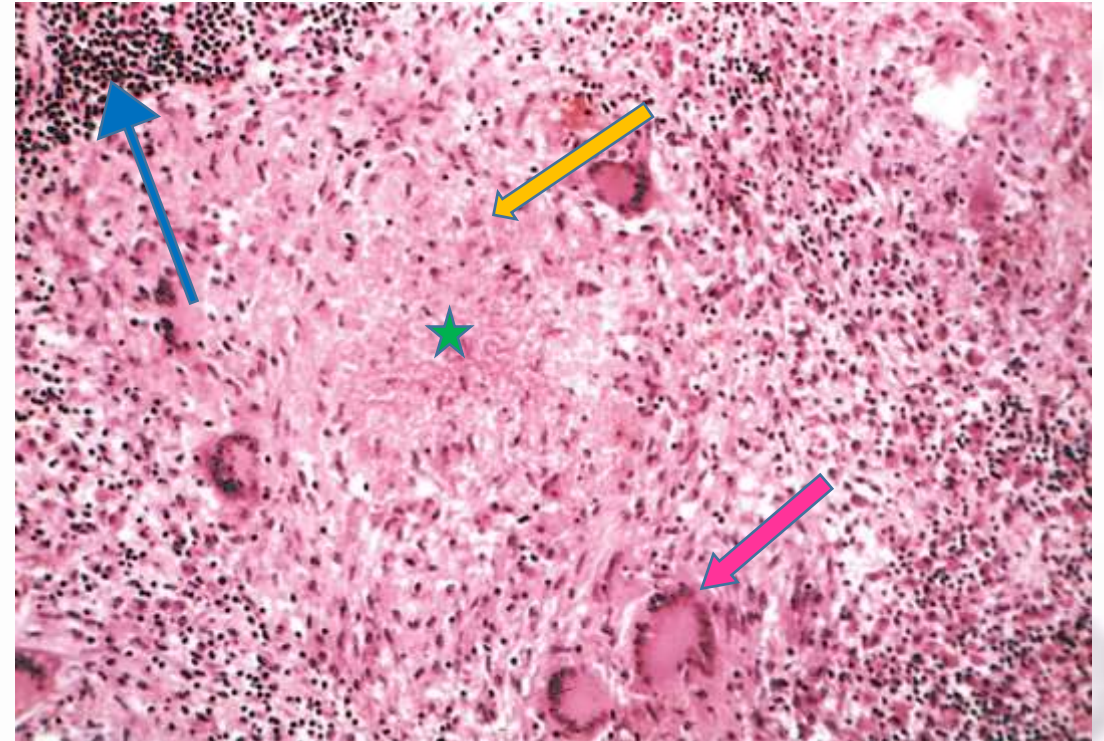
- In granulomas associated with certain infectious organisms (most classically ***Mycobacterium tuberculosis***), a combination of hypoxia and free radical mediated injury leads to a central zone of necrosis.
- **Grossly**; this has a **granular, cheesy appearance** and is therefore called caseous necrosis (caseating granuloma).



Gross appearance of lung of 35 years old patient present with productive cough and fever for 3 months.

Caseating granuloma (necrotizing granuloma)

- **Microscopically**, this necrotic material appears as **amorphous, structureless, eosinophilic, granular debris**, with **complete loss of cellular details**.
- The granulomas in Crohn disease, sarcoidosis, and foreign body reactions tend to not have necrotic centers and are said to be **non-caseating**.
- **Healing of granulomas is accompanied by fibrosis** that may be extensive in involved organs.



Typical tuberculous granuloma; showing an area of **central necrosis** surrounded by multiple **multinucleate giant cells (Langhans giant cell)**, **epithelioid cells**, and **lymphocytes**.

Systemic effects of inflammation

- Inflammation (even if localized) is associated with cytokine-induced systemic reactions called **acute-phase response**. The cytokines produced in response to bacterial products and other inflammatory stimuli, in particular **TNF, IL-1, IL-6** are important mediators of this response. The systemic reactions include:

➤ **Fever (pyrexia):**

- An elevation of body temperature, is one of the most prominent manifestations of the acute-phase response, especially when inflammation is associated with infection.

- **Mechanism of fever:**

Substances that induce fever are called **pyrogens** and include; **exogenous pyrogens**, e.g. **bacterial products** (lipopolysaccharides) and **endogenous pyrogens; cytokines, principally IL-1 and TNF.**

Pyrogens stimulate PGE₂ production in the hypothalamus, which stimulate the production of **neurotransmitters** that raises the body's temperature set point, so heat loss decreases (vasoconstriction) and heat generation increases (through effects on brown fat and skeletal muscle).

➤ Elevated levels of acute-phase proteins:

- Cytokines (IL-6, IL-1 and TNF) stimulate the liver to increased synthesis of C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA).
- **Fibrinogen** binds to red blood cells to form stacks (rouleaux); this sediment more rapidly than individual RBCs, and can be used as a measure of inflammatory response (**erythrocyte sediment rate ESR**)
- Acute phase-proteins are beneficial during acute inflammation (fight infection, clear debris, and promote healing), but prolonged production can have harmful effects (e.g. SAA can result in **secondary amyloidosis**, elevated CRP is thought to be a marker of **increased myocardial infarction risk** in patients with coronary artery disease due to predisposition to thrombosis).

➤ Leukocytosis:

- Leukocytosis, an increased white blood cell count in the peripheral blood, is a common feature of inflammatory reactions.
- Occurs initially due to **accelerated release of both mature and immature granulocytes from bone marrow** (caused by cytokines, including **TNF and IL-1**).
- **Prolonged infection** also induces **proliferation of precursors** in the bone marrow, caused by increased production of **colony-stimulating factors** from activated macrophages and marrow stromal cells.
- **Bacterial** infections typically increase neutrophil numbers (**neutrophilia**); **viral** infections increase lymphocyte numbers (**lymphocytosis**); **parasitic infestations and allergic disorders** are associated with increased eosinophils (**eosinophilia**).
- However, certain infections e.g. **typhoid fever are associated with leukopenia** instead partly due to sequestration of activated leukocytes in vascular spaces and tissues.

➤ Other manifestations

- Elevated pulse and blood pressure, decreased sweating (blood flow is redirected from cutaneous to deep vascular beds to minimize heat loss), chills, rigors, anorexia, malaise, somnolence.

➤ Septic shock:

- In severe bacterial infections, whereby the **large amounts of bacteria and their products in the blood** stimulate production of high blood levels of cytokines (esp. **TNF and IL-1**), causing disseminated intravascular coagulation (DIC), hypotensive shock and metabolic disturbances.

THANK YOU