Chronic Inflammation

- Characteristics:

1.Inflitration with **mononuclear cells.**

2.Tissue **destruction.**

3.Repair (**new angiogenesis & Fibrosis**).

- Causes:

1- **Unresolving** acute inflammation.

2- **Persistent** infections: (TB, Syphilis, Fungi, viruses).

3- Prolonged **exposure to potentially toxic agents**. (Silica, plasma lipids like in atherosclerosis).

4- **Immune-mediated** diseases (asthma).

5- **Autoimmune disease** (Rheumatoid arthritis, Inflammatory bowel disease)

Granulomatous Inflammtion

-Aggregate of **epithelioid histiocytes.**

-Mechanism:

1.**Persistent T-cell response** to certain microbes as M. tuberculosis, T. pallidum, fungi

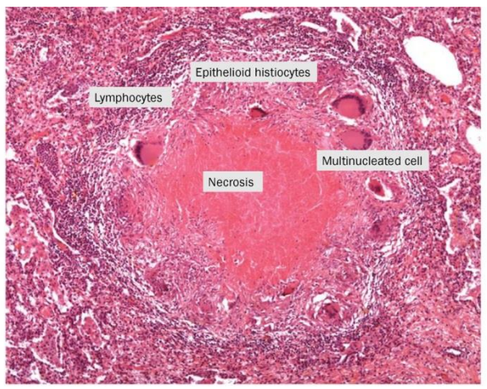
2.Foreign bodies. e.g. suture, splinter.

- Diseases associated with granulomatous inflammation:

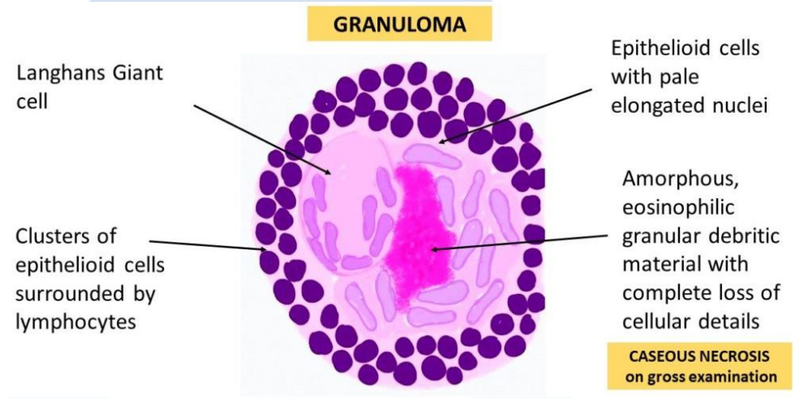
1. Tuberculosis 2. Leprosy 3. Syphilis 4. Cat-scratch disease 5. Crohn disease 6. Sarcoidosis

- Morphology

- ✓ In the usual H&E preparations epithelioid cells in granulomas have **pink, granular cytoplasm** with **indistinct cell boundaries**.
- ✓ The aggregates of epithelioid macrophages are surrounded by a collar of **lymphocytes** secreting the **cytokines** responsible for continuing macrophage activation.
- ✓ **Older** granulomas may have a **rim of fibroblasts** and **connective tissue**.



- ✓ Frequently, but not invariably, **Multinucleated Giant Cells** 40 to 50 µm in diameter are found in granulomas. They consist of **a large mass of cytoplasm** and **many nuclei**, and they derive from the **fusion of 20 or more macrophages.**
- ✓ Healing of granulomas is accompanied **by fibrosis** that may be quite extensive.
- ✓ In granulomas associated with **certain infectious organisms (TB)** a combination of hypoxia and free-radical injury leads to 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, **granular debris**, with **complete loss of cellular details**.



SYSTEMIC EFFECTS OF INFLAMMATION

1-Fever

- characterized by an **elevation of body temperature**, usually by **1° to 4°C,** is one of the **most prominent** manifestations of the **acute phase response**, especially when **inflammation is caused by infection.**
- is produced in response to substances called **pyrogens** → stimulating (PG) synthesis in the vascular and perivascular cells of **the hypothalamus**.
- Bacterial products, such as **lipopolysaccharide (LPS)** called **exogenous pyrogens** stimulate leukocytes to release cytokines such as **IL-1 and TNF (endogenous pyrogens)** → ⇧ **levels of COX** that convert AA → prostaglandins.
- In the hypothalamus the PGs, especially **PGE2**, stimulate the production of neurotransmitters → to reset the temperature **set point at a higher level.**
- **NSAIDs**, including **aspirin**, reduce fever by inhibiting cyclooxygenase and thus **blocking PG synthesis.**

Done by : Dr.Abdullah Alwikhyan

2- Rigors (shivering)

3-Chills

- (**perception** of **being cold** as the hypothalamus resets the body temperature)

4-Elevated Plasma Levels Of Acute-Phase Proteins

- are **plasma proteins**, mostly synthesized in the **liver**.

-3 types:

A- C-reactive protein (CRP)

B- fibrinogen

C- serum Amyloid A (SAA) protein.

-Synthesis of these molecules by hepatocytes is up-regulated by cytokines, **especially IL-6.**

-CRP & SAA protein act as **opsonins**.

5- Increased erythrocyte sedimentation rate (ESR)

Fibrinogen binds to erythrocytes and causes them to **form stacks (rouleaux)** that **sediment MORE rapidly** at unit gravity than do individual erythrocytes.

6-Leukocytosis

- is a **common feature** of inflammatory reactions, especially those induced by bacterial infection.
- The leukocyte count usually climbs to **15,000 or 20,000 cells/µL**, but sometimes it may reach extraordinarily high levels, as high as **40,000 to 100,000** cells/µL.
- These extreme elevations are referred to as **Leukemoid Reactions** because they are similar to the white cell counts obtained in leukemia.
- The leukocytosis occurs initially because of **accelerated release of cells from the bone marrow** postmitotic reserve pool (caused by cytokines, including TNF and IL-1) and is therefore associated with a rise in the number of **more immature neutrophils** in the blood **(shift to the left).**
- Prolonged infection → stimulates production of **colony□stimulating factors (CSFs)** → ⇧⇧ **bone marrow output of leukocytes**, which compensates for the loss of these cells in the inflammatory reaction.

✓ **bacterial infections** → increase in the blood neutrophil count, "**neutrophilia".**

✓ **Viral infections**, such as infectious mononucleosis, mumps, and German measles, are associated with **⇧⇧ numbers of lymphocytes (lymphocytosis).**

✓ **Bronchial asthma, hay fever, and parasite infestations** all involve an increase in the absolute number of **eosinophils, creating an eosinophilia**.

✓ Certain infections (**typhoid fever** and **infections caused by some viruses, rickettsiae**, and **certain protozoa**) are **paradoxically** associated with **a decreased number** of circulating white cells (**LEUKOPENIA**), likely because of cytokine-induced sequestration of lymphocytes in lymph nodes.

7-increased heart rate and blood pressure; decreased sweating,

mainly because of redirection of blood flow from cutaneous to deep vascular beds, **to minimize heat loss** through the skin.

8-anorexia, somnolence, and malaise

Probably because of the **actions of cytokines on brain cells**.

9- CACHEXIA

Chronic inflammation is associated with **A Wasting Syndrome** called **CACHEXIA**, mainly result **of TNF-mediated appetite suppression** & **mobilization of fat stores.**

10- Sepsis

- In severe bacterial infections the **large amounts of organisms** and **LPS** in the blood or extravascular tissue → stimulates the production of **TNF, IL-12 and IL□1.**
- High levels of TNF → disseminated intravascular coagulation **(DIC)**, **hypoglycemia**, **hypotensive shock.** → **CLINICAL TRIAD** is described as septic shock.

Chronic Inflammatory cells:

A- Macrophages:

- Derived from blood **monocytes** - liver (**Kupffer cells**), -spleen and lymph nodes (**sinus histiocytes**) -CNS (**microglial cells**) -lungs (**alveolar macrophages**).
- Half life of circulating monocyte is about one day .
- Emigration to ECX tissue within **24-48 hours** after onset of **Acute Inflammation.**
- Macrophages through the action of **IFN-γ fuse to form giant cell.s**

□ **Activation signals include :**

1- bacterial **endotoxin** and other microbial products

2- **cytokines** secreted by sensitized T lymphocytes (in particular the **cytokine IFN-γ**)

3- **various mediators** produced during acute inflammation

4- ECM proteins such as **fibronectin**.

Mediators secreted by macrophages

1.Acid & Neutral **proteases.**

2.Complement components & coagulation factors. **C1-5, properdin, Factor 5, 8, tissue factor.**

3.**ROS** & **NO**

4.**Eicosanoids**

5.**Cytokines**, **IL-1 & TNF**

6.**Growth factors**

B. Lymphocytes

- B & T
- Activated by interaction **with Ag presenting cells** (macrophages & dentritic cells).
- Macrophages → **IL-12** that stimulate T-cells → **IFN-γ** → activate macrophages

C. Plasma cells

-Activated B-cells

-**Antibodies production**

D. Eosinophil

-**Parasitc infection**

-IgE-mediated reactions

-Chemotactic agent is **eotaxin** derived from leukocytes or epithelial cell.

-Eosinophil granules contain **Major Basic Protein** which is **toxic to parasites** & causes **epithelial cell necrosis.**

E. Mast cells

- Connective tissue
- Acute & chronic inflammation
- **Allergic reactions** (including anaphylactic shock)
- Release :
- 1.**Histamine**
- 2.Eicosanoids
- 3.TNF
- 4.chemokines