Inflammation
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BY Prof. Dr. Maha Abu-Hashim

Objectives (ILOs)

- Definition...
- Cardinal signs of inflammation and rational for each
- Cells of the inflammatory process, their activity and where they are involved in acute or chronic inflammation or both.
- Vascular and cellular events of acute inflammation.
- Define exudate, transudate, edema and pus.
- Mediators of acute inflammation and their activities.
- Define fibrinous, serous, suppurative, cattahral, pseudomembranous and hemorrhagic inflammation.
- Define abscess, boil, carbuncle, cellulitis, ulcer, fistula and sinus.
- Chronic inflammation (how it arises, its cells, mediators and histology)
- Granulomatous inflammation...causes and morphology

Definition:
- It is a local reaction of living tissue to injurious agents.
- It is the vascular response to injury.

Causes:
1. Infection
2. Trauma
3. Physical injury (thermal, radiation)
4. Chemical injury
5. Immunoological injury
6. Tissue death...in viable tissue adjacent to necrotic tissue

Types of inflammation
1. Acute inflammation: Of sudden onset and short duration
2. Chronic inflammation: Of gradual onset and long duration.

1- Acute inflammation

- Cardinal Signs of acute inflammation
- Redness (rubor)
- Swelling (tumor)
- Heat (calor)
- Pain (dolor)
- Loss of function (fuctio laesa) (the fifth cardinal sign added by Virchow)
Major components of the acute inflammatory process

1* Vasoactive changes:

Change in diameter.
- Transient VC then permanent VD of arterioles, capillaries and post capillary venules.
- This results in marked increase of the blood flow to the area which is manifested clinically by local redness and hotness of the affected area.

Vasoactive changes

2* Increased capillary permeability:
- It is due to endothelial changes in the form of either
  i- Endothelial swelling with widening of intra-endothelial gaps of post capillary venules.
  OR
  ii- Major endothelial damage involving arterioles, capillaries and venules
- This results in leakage of protinacious fluid (exudate) which causes inflammatory edema.

- Increased permeability passes from an immediate transient phase caused by chemical mediators of inflammation into a sustained late phase induced by vascular endothelial damage caused by harmful products of inflammation or by severe injuries e.g burns and severe toxins

Transudate: (edema)
- Specific gravity <1.018 and protein content low
Exudate: (inflammation) 
specific gravity >1.018 and protein content high especially fibrin

What are the functions of this exudate?

Exudate and transudate

<table>
<thead>
<tr>
<th>Exudate</th>
<th>Transudate</th>
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<tr>
<td>- Due to increased vascular permeability.</td>
<td>- Due to increased hydrostatic pressure.</td>
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<tr>
<td>- Rich in protein esp. fibrin(turbed)</td>
<td>- Low protein content. (clear)</td>
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<tr>
<td>- Coagulates on standing.</td>
<td>- Does not coagulate on standing.</td>
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<tr>
<td>- High specific gravity (more than 1018).</td>
<td>- Low specific gravity (less than 1018).</td>
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<tr>
<td>- Contains inflammatory cells.</td>
<td>- No inflammatory cells</td>
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<tr>
<td>- Occurs late in inflammation</td>
<td>- Can occur early in inflammation</td>
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- Types of acute inflammatory exudate
  1- Serous: -
  Clear fluid with few cells and fibrin e.g in burns and common cold.
  2- Serofibrinous
  Fluid rich in fibrin mainly in serous sacs (pleura and pericardium).
  3- Pus
  Thick,turbed fluid rich in cells (living and dead neutrophils). Occurs in suppurative inflammations.

Serous inflammation  Serofibrinous inflammation  Suppurative inflammation
**Cellular response to inflammation:**

1. Types of inflammatory cells.
2. Adhesion molecules.
3. Leucocyte movement and functions.

1. **Types of inflammatory cells.**

   A. Neutrophils
   - Most prominent cell in acute inflammation.
   - Appears in the first 24 hours of inflammation. They are of short life span
   - **Neutrophilia** means increase of neutrophil count in the peripheral blood. It occurs mainly during pyogenic bacterial infection and in early phase of infarction. It comes from the bone marrow reserve pool.
   - Usually this is associated with the appearance of less mature forms (band or stab neutrophils) (left shift)

   **Neutrophil Granules**
   - H2O2 and HO are the main products produced by neutrophil activation. They produce
     1. Endothelial damage and increased vascular permeability.
     2. Inactivation of anti-peptidases as α-1 antitrypsin resulting in destruction of extracellular matrix.
     3. Injury to other cell types e.g parenchymal cells and RBCs

   **Functions of neutrophils:**
   - 1. Phagocytosis (microphage)of bacteria
B- Monocytes-Macrophages
They replace neutrophils after 2-3 days in the course of inflammation and persist in chronic inflammation

- They have longer life span than neutrophils and can divide and proliferate within the inflamed tissue.
- Monocytosis:- Increased number of peripheral monocytes
- Occurs in tuberculosis, salmonella infection, typhus and brocellosis.

*Why do monocytes and macrophages appear late during inflammation and remain for longer duration?*

Functions:-
1- Phagocytosis of larger particles.
2- Prepare the area for repair.
3- Communicate with the immune system for antigen processing and presentation.

C- Lymphocytes
The most prominent cell in chronic inflammation and viral infections.
- Lymphocytosis occurs in most viral infections (influenza, mumps, rubella and infectious mononucleosis) and some bacterial infections (whooping cough and tuberculosis)

Functions:-
1- T- lymphocytes produce lymphokines with many vital local effects.
2- B- lymphocytes produce immunoglobulins .

D- Eosinophils
- Seen both in acute and chronic inflammation.
  - The prominent inflammatory cell in allergic reactions and parasitic infestation.
  - Eosinophilia occurs in allergic inflammation (asthma, hay fever), parasitic infection (bilharziasis) and also in polyarteritis nodosa and Hodgkin’s lymphoma
Functions of eosinophils:
1- Phagocytosis, they have many of the enzymes of neutrophils.
2- They produce antihistamine in areas of histamine production.

E- Basophils and mast cells
- Blood basophils and tissue mast cells are sources of histamine (an important mediator of acute inflammation)
- Basophilia occurs in myelogenous leukemia and myeloproliferative diseases.
2- **Adhesion molecules**

They play an important role in acute inflammation
- They are divided into 3 families
  a. Selectins
  b. Immunoglobulin-family adhesion protein.
  c. Integrins

**A. Selectins**

- These molecules are induced by the cytokine interleukin-1 (IL-1) and tumor necrosis factor (TNF).
  - **L-Selectins**...are expressed on neutrophils and bind to endothelial mucin-like molecules (GlyCam-1).
  - **E-Selectins**...are expressed on endothelial cells and bind to Sialyl-Lewis X pr.on the surface of leucocytes.
  - **P-Selectins**...stored on special granules in endothelial cells and platelets, relocate to the plasma membrane after stimulation by mediators as histamine and also, they bind to Sialyl-Lewis X pr.on the surface of leucocytes.

**P-selectin** is redistributed to the cell surface from the Weibel-Palade bodies due to stimulation by thrombin, histamine, and Platelet Activating Factor (PAF).

Induction of E-selectin on endothelium by IL-1 and TNF

**b. Immunoglobulin-family adhesion proteins**

i- Intercellular adhesion molecules 1 and 2 (ICAM-1 and 2) are expressed on the endothelial cells and bind to integrin molecules on leucocytes.
ii- Vascular cell adhesion molecules (VCAMs) similarly, they are expressed on the endothelial cells and bind to integrin molecules on leucocytes.

**c. Integrins** They bind to endothelial immunoglobulin-family adhesion proteins.
- Examples are leucocyte LFA-1, MAC-1 and VLA-4.
- **Adhesion Molecules: Summary**

  **Leucocyte**
  - L-selectin
  - Sialyl-Lewis X modified protein
  - Integrons (LFA-1, MAC-1 and VLA-4.

  **Endothelium**
  - GlyCam-1
  - E-selectin
  - P-selectin
  - Immunoglobulin-family adhesion molecules (ICAM-1 and 2 & VCAMs)

3- **Leucocyte movement and functions.**

- Inside the area of inflammation, leucocytes move out of the blood vessels (emigration), they move towards the irritant (chemotaxis) to engulf and destroy it (phagocytosis).

1- **Emigration**

- It is the passage of inflammatory leucocytes between the endothelial cells into adjacent interstitial tissue. Before emigration, circulating leucocytes from the central blood flow move toward the endothelial surface.

   **A. Margination:**
   - Occurs as leucocytes localize to the outer margin of blood flow adjacent to the vascular endothelium.
   
   **What is the cause of margination?**
B- Pavementation :-
  leucocytes line the endothelial surface.

C- Rolling:-
  Is mediated by the action of E-selectins which bind endothelial cells loosely to leucocytes (Through sialyl-Lewis X modified glycoprotein) producing a characteristic rolling movement of leucocytes along the endothelial surface.

D- Adhesion:-
  Leucocytes adhere to the endothelial surface through the interaction of integines (leucocytes) and the immunoglobulin -family adhesion proteins (endothelium)

E- Transmigration:-
  It is the movement of leucocytes across the endothelium.
  - It is mediated by platelet-endothelial cell adhesion molecule-1 (PECAM-1) expressed on both the endothelium and the leucocytes.

2- Chemotaxis
  - It is the directional movement of leucocytes towards the irritant within the area of inflammation.
  - It is mediated by diffusable chemical agents, movements of leucocytes occurs along a chemical gradient.
  - Chemotactic agents act by stimulating the contractile elements within leucocytes.
Chemotactic agents include:
* Products from bacteria
* Complement components especially C5a.
* Arachidonic acid metabolites especially leucotriens B4 (LTB4).

3-Phagocytosis

- It is the ingestion and destruction of particulate material (tissue debris, living or dead bacteria and other foreign cells) by phagocytic cells mainly neutrophils and monocytes-macrophages.
- Phagocytosis is facilitated by opsonization which is the coating of particulate material by substances that immobilize the particles to the surface of the phagocytes.
- The most important opsonins are IgG and C3b

- Fragments opsonized by IgG are bound to the phagocytic cell by cell surface receptor for Fc portion of the IgG molecule.
- Fragments opsonized by C3b bind to cellular receptors for C3b

What are the factors that help phagocytosis?

Steps of Phagocytosis

- Recognition and attachment
- Engulfment
- Degradation (killing)
Steps of phagocytosis:

1. Recognition
2. Adhesion
3. Engulfment
4. Destruction
5. Intracellular killing of micro-organism

- Phagocytosis is characterized morphologically by internalization of the attached opsonized particle by pseudopodial extensions from the surface of the leucocyte which enclose the foreign particle forming a **phagosome**.
- Phagosomes fuse with cytoplasmic lysosomes and form **phagolysosomes**.
- This is associated with leucocyte **degranulation**.

**Intracellular microbial killing**

- Mediated within phagocytic cells by either **oxygen dependent** or **oxygen independent** mechanisms
- **oxygen dependent mechanism:**
  - it is the most important intracellular microbicidal process.

  A. Phagocytosis initiates activity of hexose monophosphate shunt causing an oxidative burst and supplying electrons to NADPH oxidase in the phagosomal membrane.

  B. One of the products of NAHPH oxidation reaction is superoxide anion (O2•⁻) which is further converted to hydrogen peroxide (H2O2) that may be further converted to activated hydroxyl radical (HO•).

  C. In the presence of leucocyte enzyme myeloperoxidase and halide ion as chloride, hypochloric acid is formed. It oxidizes microbial proteins and disrupts cell wall. **myeloperoxidase-halide system of bacterial killing**
**Oxygen independent mechanism:**
This mechanism is much less effective than the oxygen dependent mechanism.
- **Effectors include many proteins e.g**
  * Lysosome
  * Lactoferrin
  * Major basic protein of eosinophils.
  * Cationic proteins as defensins and bactericidal permeability increasing protein.

![Oxygen dependent pathway](image)

**Signs of leucocyte activation**
- **These include:**
  1. Expression of adhesion molecules.
  2. Activation of intracellular contractile elements.
  3. Increased intracellular calcium.
  4. O2 burst with release of O free radicals.
  5. Degranulation.
Defects in Phagocytosis

1 - Congenital

- Chediak-Higashi Syndrome (autosomal recessive)
  Defective intracellular transport protein, inability to lyse bacteria and neutropenia
- Chronic granulomatous disease (x-linked recessive)
  No oxidative burst.....defective O dependent mechanism......increased liability for bacterial infection especially catalase +ve bacteria (staphylococci) \textit{WHY??}
  - Myeloperoxidase deficiency
    Increased incidence of fungal infection.
  - Defects in leucocyte motility.
  - Leucocyte adhesion deficiency (types 1 and 2)

2 - Acquired

- Iatrogenic immunosuppression (most common)
- Overwhelming infections - Severe trauma or burn
- Diabetes mellitus - Chronic debilitating disease.

*Can phagocytosis be harmful to the host? How?

\textbf{Mediators of Acute inflammation}

- These mediators influence, vasomotor phenomena, vascular permeability, chemotaxis, pain and other aspects of the inflammatory process.
- They may be exogenous or endogenous

- **Exogenous mediators**
  Are most often of microbial origin (e.g peptides of E.coli are chemotactic to neutrophils.

- **Endogenous mediators**
  May be derived from cells or plasma.

\textbf{Cell-derived:} These include...
- Vasoactive amines histamine and serotonin (mast cells and platelets)
- Arachidonic acid derivatives (prostaglandins and Leucotreins )
- Lysosomal components

\textbf{Inactive precursors in plasma}
- These mediators influence, vasomotor phenomena, vascular permeability, chemotaxis, pain and other aspects of the inflammatory process.
I- Cell derived mediators
  * Vasoactive Amines

**Histamine:**
- Source = mast cell granules
- Main action is increased vascular permeability.
  and vasodilation of venules
- Released by trauma, heat or cold, complement, cytokines.

- **Serotonin** (5-hydroxytryptamine):
  - Source = platelet granules
  - Actions similar to histamine
  - Released by platelet aggregation (collagen, thrombin, ADP, PAF and from mast cells)

*Arachidonic acid metabolites*
- Synthesized from cell membrane phospholipids though the action of phospholipase A2 (inhibited by corticosteroids).
- Form **leukotrienes** via 5-lipoxygenase
- Form **prostaglandins and thromboxane A₂** via cyclo-oxygenase (COX-1 inhibited by aspirin and indomethacin)
- Functions
  - Prostaglandins.....V.D and pain
  - Leucotriens B4..... Chemotaxis
**Cytokines**
- Soluble proteins secreted by some cells (lymphocytes and macrophage) and influence the behavior of other cells.
- Cytokines IL-1 and TNF secreted by monocyte-macrophages have many functions in acute inflammation e.g.
  a. Fever and leucocytosis.
  b. Hepatic synthesis of acute phase proteins as C-reactive protein.
  c. Synthesis of adhesion molecules.
  d. Neutrophil degranulation

**II- Plasma derived mediators**
  - **Complement system**
    - A group of plasma proteins that participates in immune lysis of cells and plays a significant role in inflammation.
    - It has a classic and an alternative pathways
      - C3 is the critical control point, and interacts with both pathways.
      - C3a and C5a are known as “anaphylatoxins”, and are capable of releasing histamine from mast cells, along with potent chemotactic abilities (C5a)
      - Membrane attack complex (MAC) is the active agent of complement lysis and consists of C5-9

  ![Complement components diagram](image)

**Kinin system**
- Vasoactive peptides called kinins are generated by proteases called kallikrein
- Hageman factor is a potent activator of kallikrein
- Most important product is bradykinin
  - Pain + vascular dilation
Biologic effects of mediators

Vascular phenomena:
  Increase vascular permeability, histamine & kinins
  Vasodilatation...histamine & prostaglandins

Leukocyte adhesion, chemotaxis:
  C5a, leucotreins and lysosomal components
  Pain... bradykinin and prostaglandins
  Phagocytosis: C3b and C3bi Opsonins.

Role of NO in acute inflammation

Systemic effects of acute inflammation:-
Systemic effects can be seen in setting of acute or chronic inflammation
Largely mediated by cytokines

Fever
- Clinical hallmark of inflammation
  Endogenous pyrogens: IL-1 and TNF-a
  Exogenous :- as bacterial toxins
  pyrogens act by affecting the heat regulating center of the hypothalamus

* Does fever cause harm to the body?

Leucocytosis: increased total leucocytic count above 12,000/c ml
- IL-1 and TNF reach the bone marrow and cause accelerated release of leucocytes into the circulation.
  neutrophils     bacterial (pneumonia)
  lymphocytes    viral (infectious mono)
  eosinophils     parasites, allergy

NB. Infection with salmonella (typhoid) is associated with leucopenia
Role of IL-1 and TNF in acute inflammation

*Therapy for fever and inflammation targets arachidonic acid metabolism (aspirin)
Therapy for shock focuses on fluid resuscitation, and proper selection of antibiotics.

Types of acute inflammation
- According to the presence or absence of pus acute inflammation is either suppurative or non-suppurative
  - **Suppurative (purulent)**
  - Severe acute inflammation with pus formation
  - It is caused by pyogenic bacteria e.g. staph.aureus, strept. Pyogenes, E.coli.....etc.
Pus is semi fluid, viscous material formed of dead and dying neutrophils, micro-organism, plasma proteins and necrotic liquefied tissue

**Does pus coagulate on standing? Why?**

Suppurative inflammation
Types of suppurative inflammation

Localized 1.abscess 2. boil and 3.carbuncle

1 -Abscess:-
*Irregular cavity containing pus
- It is formed of 3 zones
  a. Central zone of necrotic tissue and dead neutrophils.
  b. Midzone of pus
  c. Peripheral zone of inflamed tissue (pyogenic membrane).
N.B An abscess must be well evacuated to ensure healing

Fate of an abscess
- **If not evacuated:**
  a. Change to chronic abscess.
  b. Blood or lymphatic spread.
- **If evacuated:**
  a. Healing by granulation tissue.
  b. **Sinus** formation.
  Sinus = blind ended tract opening to the surface.
  c. **Fistula** formation.
  Fistula = tract joining two surfaces
  d. **Ulcer** formation
  Ulcer = defect in the surface lining of skin or mucous membrane.g peptic ulcer

2- **Boil**
Small abscess related to hair follicles, sweat or sebaceous glands.

3- **Carbuncle**
Multiple communicating suppurative foci in the subcutaneous tissue opening to the surface by multiple sinuses. It is common in diabetic patient

- **Diffuse suppurative inflammation**
- **Cellulitis**
  due to streptococcal infection which produce enzymes that facilitate spread of infection e.g - Fibrinolysin - Hyalourinidase. - Leucocidin.
- **Sites:**
  - Loose connective e.g orbit,,wall of the appendix

Acute diffuse suppurative appendicitis.

### Non suppurative inflammation

**Types**

1. Serous inflammation.
2. Serofibrinous inflammation.
3. Catarrhal inflammation.
4. Pseudomembranous inflammation.
5. Hemorrhagic inflammation.

1. **Serous inflammation**
   - Excess watery fluid exudate.
   - Occurs in burns and some viral infections where (blisters) are formed.

2. **Serofibrinous inflammation**
   - Exudation of serous fluid rich in fibrin.
   - Occurs in serous sacs and lung alveoli in lobar pneumonia.
   - Wet type = excess serous than fibrin.  
   - Dry type = excess fibrin than serous fluid.

3. **Catarrhal inflammation**
   - Mild inflammation of mucous membrane with excess watery mucous secretion.
   - Sites.. m.m. of respiratory and GIT.
   - May be complicated by secondary bacterial infection giving mucopurulent discharge.
4 - Pseudomembranous inflammation

- A severe form of non suppurative inflammation caused by toxin producing strains as
  a. Diphtheria
  b. Shigella (bacillary dysentery).

- Pathogenesis:
  - Organism sticks to the surface of m.m and produce a potent exotoxin.
  - Exotoxin causes necrosis of superficial mucosal cells.
  - Exotoxin and products of necrotic tissue diffuse to the sub epithelial tissue and
    cause severe acute inflammation with VD of vessels and increased vascular permeability
  - Exudation of fluid rich in fibrin
  - Fibrin entangles dead tissue + inflammatory cells + micro-organism forming a dirty-
    yellow pseudmembrane on the mucosal surface.
  - Scrapping of this membrane leaves a bleeding surface.

Outcomes of Acute Inflammation

- Resolution (the hoped-for result)
- Abscess (via liquefactive necrosis)
- Scar (sometimes occurs even if pathogen is eliminated)
- Persistent inflammation (chronic inflammation) - due to a failure to completely eliminate
  the pathological
  insult (injury)
Resolution of acute inflammation
- Edema fluid passes into lymphatics or pinocytosis into macrophages
- Phagocytosis of apoptotic neutrophils and necrotic debris by macrophages
- Disposal of macrophages.

**Chronic Inflammation**
- Inflammation of prolonged duration (weeks, months).
- Active inflammation + tissue destruction + attempts at repair proceed simultaneously.
  - It can occur either de novo or on top of acute inflammation.
  - May be chronic non specific or specific (granulomatous) inflammation.

**Causes:**
- Persistent infection.
- Prolonged exposure to toxic agent.
- Autoimmunity

**Morphologic features of chronic inflammation**
- Chronic inflammation is characterized by:
  1. Mononuclear cell infiltration (lymphocytes, plasma cells and macrophages).
  2. Tissue destruction induced by the persistent offending agent or by inflammatory cells.
  3. Attempts at healing by connective tissue replacement of damaged tissue accompanied by proliferation of small blood vessels (angiogenesis) and fibrosis.

**Chronic Inflammation: Lung**
- Collection of chronic inflammatory cells
- Destruction of parenchyma
- Replacement by connective tissue (fibrosis)
Acute and Chronic Inflammation

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<tr>
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<th>Acute</th>
<th>Chronic</th>
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<tr>
<td>Onset, duration</td>
<td>-Sudden onset, Short duration</td>
<td>- Gradual onset, long duration</td>
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<tr>
<td>Irritant</td>
<td>Severe irritant</td>
<td>Mild irritant</td>
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<tr>
<td>Vascular changes</td>
<td>Vascular phenomena</td>
<td>End arteritis obliterans</td>
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<tr>
<td>Type of reaction</td>
<td>Exudative</td>
<td>Proliferative</td>
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<tr>
<td>Inflammatory cells</td>
<td>Polymorphs &amp; macrophages</td>
<td>Lymphocytes, plasma cells &amp; macrophages</td>
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<td>Repair</td>
<td>Followed by repair</td>
<td>- Associated with repair</td>
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Types of chronic Inflammation

- **Chronic non-specific:**
  - Characterized by diffuse infiltration of mononuclear cells (macrophages, lymphocytes and plasma cells), with proliferation of fibrous tissue.
  - Blood vessels show sub intimal fibrosis resulting in thickening of the wall and narrowing of the lumen (end arteritis obliterans)

Chronic specific:

- **Granuloma** =
  - Distinct pattern of chronic inflammation in which the chief reactive cell is activated macrophage which aggregates together forming nodular collections.

- **Pathogenesis:**
  a. Phagocytosis of the antigen by macrophages
  - antigen is processed and presented to T lymphocytes (CD4 +ve) through antigen specific T cell receptor.
b. Activated CD4+ve T-lymphocytes release cytokines especially interferon γ (INF-γ).

c. (INF-γ) mediates the transformation of monocytes and macrophages to epithelioid cells and giant cells.

d. Activated macrophages also secrete IL-12, IL-1 and TNF which in turn cause activation of new CD4+ve T-lymphocytes.

**Macrophage activation**
- Via cytokines from immune-activated T-cells
- By non-immunologic stimuli: endotoxin, fibronectin, mediators.

**Lymphocyte-macrophage interactions**
- Activated lymphocytes and macrophages influence each other
- Release mediators that affect other cells
Macrophage accumulation

M/E of a granuloma
- Macrophages, Epithelioid Cells, and Giant Cells. Lymphocytes & Fibroblasts.
- Giant Cells
- Multinucleated giant cells originate by fusion of macrophages. They have stronger phagocytic power than macrophages.
  - There are two types of giant cells
    - *Langhans giant cells* have nuclei arranged in a horse-shoe shaped pattern around the periphery of the cell. This type is characteristic (but not specific) for tuberculosis.
    - *Foreign body giant cells* have the nuclei dispersed in the cytoplasm.

Caseating granuloma with central caseation necrosis and Langhans giant cells

Types of granulomas
- (1) Infec*ective granuloma*: Bacteria, Virus, Parasite, Fungi…. *Give examples*
- (2) Non infective granuloma: Allergic granuloma: as Rheumatic fever.
- Foreign body granuloma: around foreign bodies as beryllium
- Foreign body giant cells are a prominent feature.
- Granulomas of unknown cause: as sarcoidosis.