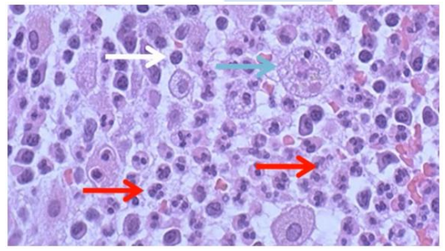
Inflammation

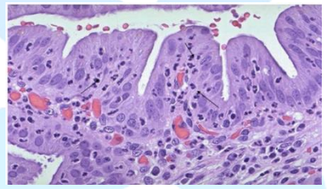
- Is essentially a **protective response** to eliminate both **the initial cause of cell injury (e.g. microbes)** and **to remove necrotic cells and tissue arising as consequence of cell injury.**
- **Inflammatory response** : **dilutes**, **destroys**, or **isolates** the causative agent and arrange for a series of events → healing of the damaged tissues.
- 2 types of inflammation : **Acute** and **Chronic**

➢ Acute Inflammation

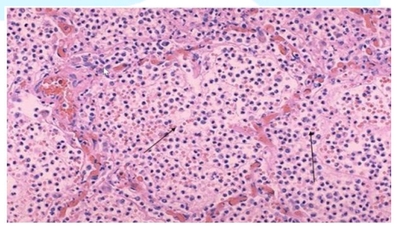
- **immediate** and **rapid** response to injury which is of **short duration (minutes/days).**
- The main characteristics are the **exudation** of fluid and plasma proteins (edema) and the **emigration of leukocytes**, predominantly **Neutrophils** (also called **PMN** leukocytes).



- Various examples of acute inflammation are **Sore Throat**, **Reaction In The Skin To A Scratch** Or **A Burn** or **Insect Bite.**



- The neutrophils are seen infiltrating the **mucosa** and **submucosa** of the gallbladder in this patient with **Acute Cholecystitis.**



- **Neutrophils** fill the alveoli in this case of **Acute** pneumonia.

- Acute inflammatory response has **2 main functions**:
  1.**Eliminating causative agent.**
  2. **Removal of necrotic cells.**

Causes of Acute Inflammation

1. Microbial Infections

- One of the commonest cause of inflammation is microbial infection by producing specific 1- **Exotoxins (Chemicals),** 2- **Endotoxins**, (associated with their cell walls).
- Some organisms cause 3- **Immunologically-Mediated Inflammation** through hypersensitivity reactions.

2. Hypersensitivity Reactions

- occurs when an **altered state** of immunological responsiveness → an **inappropriate** or **excessive immune reaction** → damages the tissues that produce **damage and cell necrotic at site of reaction.**

3. Physical Agents

- Physical trauma (like direct trauma that causes damage of skin or bone)
- Radiation (causing damage of the cells)
- Burns
- Excessive cooling
- Acids, alkalies and oxidizing agents

4.Tissue necrosis

- **Death** of tissues from **lack of oxygen** or **nutrients** resulting from **inadequate blood flow (e.g. infraction).**
- is a **potent** inflammatory stimulus (cell necrosis in living body always associated with inflammatory response)

5. Foreign bodies : sutures ,splinters and dirt

Effects of Inflammation

- The local effects are usually **clearly beneficial** however the destruction of normal tissue on the other hand **may appear to be harmful.**

A. Beneficial effects:

- Both the fluid and cellular exudates may have useful effects, beneficial effects of the fluid and exudate are as the following:

1 - Dilution of toxins:

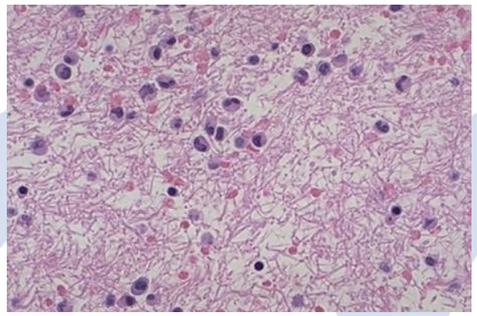
- such as those produced by bacteria, are carried away by the lymphatics.

2- Entry of antibodies & drugs

- ↑↑ vascular permeability allows antibodies to enter extra vascular space.

3- Fibrin formation

- Fibrin formation from **exuded fibrinogen** may **impede** the movement of microorganisms trapping them and so **facilitating phagocytosis** .



fibrin mesh in fluid with PMN's (polymorphonuclear) ,that has formed in the area acute inflammation.

4- Delivery of nutrients and oxygen.

- It is essential for the cell. such as neutrophils which have high metabolic activity, is aided by increase fluid flow through the area.

5- Stimulation of immune response.

- The drainage of this fluid exudate into the lymphatics allows particulate and soluble **antigens** to **reach the local lymph nodes** where they may **stimulate the immune response .**

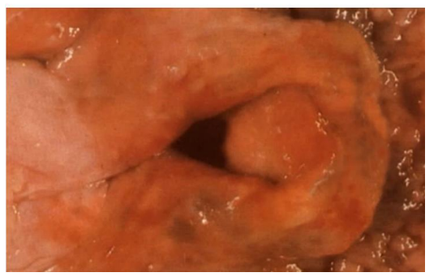
B. Harmful effects

- release of **lysosomal enzymes** by inflammatory cells may also have harmful effects:

I - Digestion Of Normal Tissues.

- Enzymes such as **collagenases** and **proteases** may digest normal tissues, resulting in their destruction.

2- Swelling



- The swelling of acutely inflamed tissues may be harmful: for example the swelling of the **Epiglottis** in **acute epiglottitis** in children due to Haemophilus Influenzae infection may **obstruct the airway,** resulting in death.
- Inflammatory swelling is especially serious when it occurs in an **Enclosed Space** such as the cranial cavity, when intracranial pressure is raised to the point where blood flow into the brain is impaired, resulting in ischemia damage **(e.g. acute meningitis).**

Clinical Aspects of Acute Inflammation

The 5 signs of acute inflammation are:

I - Redness (rubor).

- An acutely inflamed tissue appears red e.g. skin affected by sunburn
- It is due to **dilatation of small blood vessels** within the inflamed area.

2- Heat (calor)

-Increase in temperature is seen **Only** in peripheral parts of the body, such as the skin

- It is due to **increased blood flow (hyperaemia)** → **vascular dilatation** and the **delivery of warm blood** to the area.
- **Systemic fever**, which results from some of the chemical mediators of inflammation, also contributes to the local temperature.

3- Swelling (tumor)

-Swelling results from **edema** (the accumulation of fluid in the extra vascular space as part of the fluid leakage)

- And to a much lesser extent, from the **physical mass of the inflammatory cells migrating into the area.**

4- Pain (dolor)

- For the patient, **Pain is the best known features** of acute inflammation.
- It can be due to :

1. **distortion of tissues** due to inflammatory edema (it making pressure on the nerves) .
2. some of the **chemical mediators** of acute inflammation, including the **prostaglandins** and **serotonin.**

5- Loss of function:

- is a well-known consequence of inflammation, **movement of an inflamed area is consciously inhibited** by pain.

Acute inflammation has two major components

1.Vascular Change

a.vasodilation (Changes in vessel caliber → increase blood flow)

b.increased vascular permeability (**transudate** & **exudate** formation) by leakage of the fluid from inside blood vessel to the outside and accumulation producing swelling and edema .

2. Cellular Events "cellular recruitment & activation".

1.Vascular Changes

1- Changes in Vascular Flow & Vessel Caliber

- These changes occur **quickly** after injury.
- develop at **variable rate** depending on the nature & severity of the injury.
- the following sequential changes take place:

A. Arteriolar vasoconstriction :

- smooth muscle of arterioles contracting as a direct responses to injury. (transient, seconds) occurs early after injury in very short time.

B. Vasodilatation: stasis of blood vessels → increase blood flow, which is the cause of **heat and redness (erythema)** and **local elevation of temperature (warmth)** at the site of inflammation.

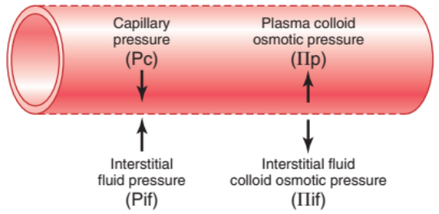
2- Vascular Leakage (Increased vascular permeability)

A. Transudate

- accumulation of ultrafiltrate of blood plasma which contains **little protein in extravascular space** due to **increase of blood hydrostatic pressure.**

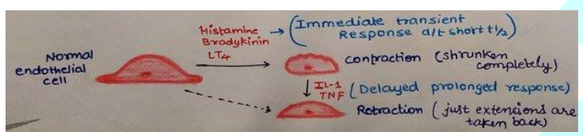
B. Exudate (protein-rich fluid with leukocytes)

- **Accumulation of exudate** in the interstitium → **reduces the intravascular osmotic pressure**, ↑↑ the osmotic pressure of the interstitium.
- The net result is **out-flow of water and ions** → extra-vascular tissues, fluid accumulation is called **edema**.



Mechanism of increased vascular permeability

1 - Endothelial Cell Contraction



- **MCC** of increased vascular permeability, **reversible process.**
- results in **intercellular gaps** in **postcapillary venules .**
- Stimulated by **Histamine**, **Bradykinins** and **leukotrienes**, others mediators.
- occurs rapidly after binding of the **mediators** to **a specific receptors** on the endothelial cells which **line venules 20-60uM**, but **not endothelium in capillaries and arterioles.**
- It is short lived **(15-30 min)** and called **Immediate Transient Response.**

2- Junctional Retraction

- Occur **4-6 hours after initial stimulus** and may persist for **24 hours** or more.
- Induced by a **variety of cytokines mediators** (including **Tumor Necrosis Factor (TNF)** & **Interleukin 1 (IL-1).** → a structural **reorganization of the cytoskeleton**, so that the endothelial cells junctions are disrupted.

3- Direct Endothelial Injury.

A. Immediate sustained response

- Usually **after severe injuries** like **burns**.
- → vascular leakage by causing cell necrosis and detachment, which is usually associated with platelet adhesion and thrombosis.
- Leakage begins **immediately** after injury and persists for **several hours or days** until damaged vessels are repaired.
- **Venules**, **capillaries**, and **arterioles** can **All Be Affected**.

B. Delayed Prolonged Leakage

- Begins after **a delay of 2 - 12 hours**, and last for **several hours to days**.
- Involves **venules** and **capillaries**.

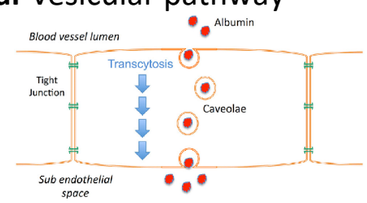
- Caused by:

1. mild to moderate **thermal injury**
2. **X-ray or Ultraviolet irradiation** like late sun-burns.
3. certain **bacterial infection**

4- **Leukocyte - mediated endothelial injury**.

-Occurs as a consequence of the leukocyte accumulation along the vessel wall **releasing many toxic mediators** that may cause endothelial cell injury.

5- **Increased transcytosis of proteins via an intracellular** vesicular pathway (channels formed by fusion of intracellular vesicle.)



- Augments venular permeability
- Modified by **VEGF mediator**

6- Leakage from new blood vessels.

a. **Immaturity** of proliferating endothelial cells

b. **sensitivity** of newly formed endothelial cells to vaso-active mediators as VEGF.

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2. Cellular Events “cellular recruitment & activation”

The sequence of events in the extravasation of **leukocytes** from **the vascular lumen** to the **extra vascular space** is divided into:

1. Margination, Rolling and adhesion

2. Firm adhesion to the endothelium

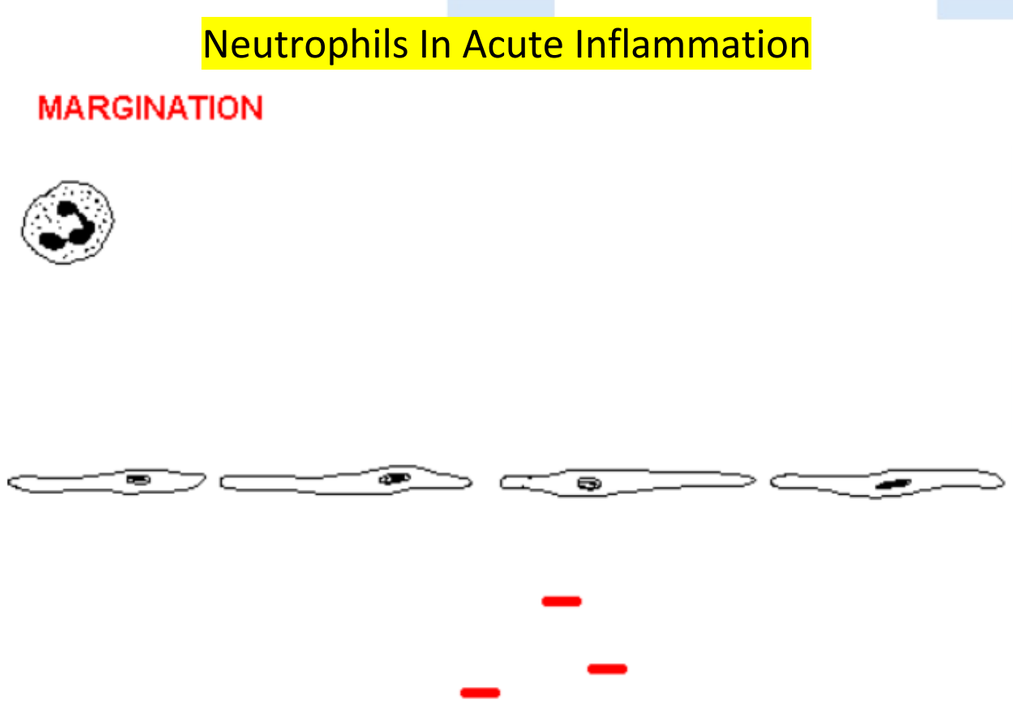
3. Transmigration between endothelial cells

4. Migration in interstitial tissue

5. Chemotaxis

6. Phagocytosis and Degranulation

Neutrophils In Acute Inflammation



1. Margination Of Neutrophils & Rolling.

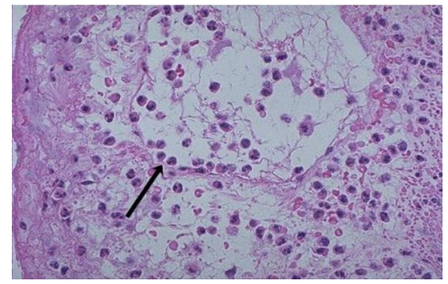
- accumulation of leukocytes **within extra-cellular space** is the **diagnostic histological** feature of **acute inflammation**.
- **Margination: Accumulation** of leukocytes at **the periphery of vessels**.

A. Normally, cells are **confined to the central (axial)** stream in blood vessels, and **do not flow** in the **peripheral zone** near to the endothelium.

B. ↑↑ vascular permeability in early inflammation → fluid exits the vascular lumen & blood flow slows → leukocytes settle out of central column, **mariginating to vessels periphery.**

C. **Leukocytes** transietly **stick** along the **endothelial surface** is a process called **Rolling.**

- PMN's that are **marginated along the dilated venule wall** (arrow) are **squeezing** through the basement membrane (the process of **diapedesis**) and spilling out into extravascular space.



- **Weak & transient adhesion** involved in rolling is **mediated by selectin family of adhesion molecules.**
- Selectins are expressed on **leukocytes** & **endothelial cells** that contain extracellular domain that binds sugars.

✓ **Types of selectins:**

1. **E**-selectin (CD62E): **E**ndothelial cells
2. **P**-selectin (CD62P): Endothelial cells & **P**latelets.
3. **L**-selectin (CD62L): Most **L**eukocytes

- binding of leukocytes is largely **restricted** to endothelium **at sites of infection** or **tissue injury** (where the mediators are produced).

e.g :

- in nonactivated endothelial cells, **P-selectin** is found primarily in intracellular **Weibel-Palade bodies**; however, within minutes of exposure to mediators such as **histamine** **or** **thrombin**, P-selectin is distributed to the cell surface, where it can facilitate leukocyte binding.
- Similarly, **E-selectin**, which is not expressed on normal endothelium, is induced after stimulation by inflammatory mediators such **as IL-1 and TNF**.

2.Adhesion & Transmigration

- Firm **adhesion** of leukocytes to endothelial surface is mediated by **integrins**.
- **Integrins :**
  - ✓ **are transmembrane glycoproteins** function as cell receptors for extracellular matrix
  - ✓ **normally expressed on leukocytes surface** in a **low affinity form** & **don't adhere** to their ligands **unless leukocytes are stimulated by chemokines** (chemo-attractant cytokines).
  - ✓ expressed on **leukocytes cell surface** interacting with their **ligands on endothelial cells.**
- When the adherent leukocytes encounter the displayed chemokines**, the cells are activated**, and their **integrins** undergo **conformational changes** and **cluster together** → a high-affinity form.
- **TNF & IL-1** → Stimulate endothelial cells to **increase ligands for intergrins** as :

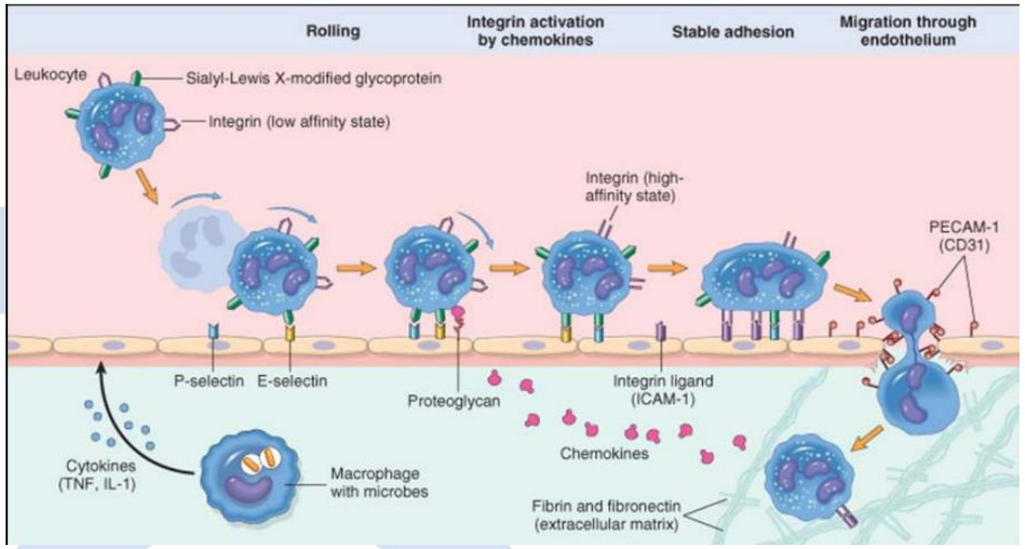
1. ICAM-1 (InterCellular Adhesion Molecule- 1), which binds to the integrins LFA-1 (CD11a/CD18) Mac-1 (CD11b/CD18)

2. VCAM-1 (Vascular Cell Adhesion Molecule 1), which bind to the integrin VLA-4

- The net result is to **increase intergrin affinity** & **to increase expression of intergrin ligands** → stable attachment of leukocytes to endothelial cells at inflammation site .

3.Migration

- After adhesion to endothelial surface leukocytes migrate through the vessel wall by **squeezing between cells at the intercellular junctions** and this is called **DIAPEDESIS**.
- Diapedesis occurs mainly in the **venules of systemic vessels** & **capillaries of pulmonary circulation.**
- Migration is produced by **chemokines** produced by extravascular tissue → migration of leukocytes **toward chemical gradient**.
- **PECAM-1 (CD31)** is a cellular adhesion molecule that **present** on **leukocytes & endothelial cells** & mediates the binding needed for leukocytes to traverse the endothelium.
- After passing the endothelium leukocytes **cross vascular basement membrane** by focally degrading them by **secreted collagenases**.



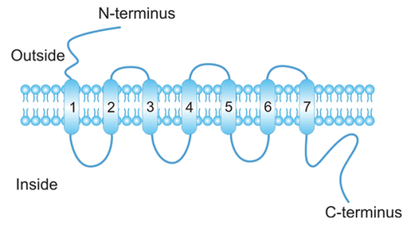
4.Chemotaxis

- After transmigration leukocytes migrate toward **sites of infection** or **injury along the chemical gradient** called **Chemotaxis**.
- **Chemetactic Agents:**

1.**Bacterial products**
2.**Cytokines** esp. Chemokines
3.Complement system components esp. **C5a**
4.Products of lipoxygenase pathway of arachidonic acid (AA) metabolism as **leukotriene B4 (LTB4).**

- **Leukocytes infiltration occurs due to the action of various combinations of mediators that are secreted in response to** :

1. infections
2. tissue damage
3. immunologic reactions



- **Chemotactic molecules** bind to specific cell surface receptors which are members of the **7-transmembrane G-protein coupled receptor family**.
- → signal transduction → ↑↑ cytoslic Ca++ → Assembly of cytoskeletal contractile elements (actin) → leukocyte movement (pseudopods).
- The direction of movement is specified by **a higher density of receptor-chemotactic ligand interaction** at the leading edge of the cell.

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- **The type of emigrating leukocytes varies with:**

1- The **AGE** of the inflammatory response 2- The **TYPE OF STIMULUS.**

- In acute inflammation the predominant cells are **neutrophils during the first 6-24 hours** replaced by **monocytes in 24-48 hours.**
- **This is due to the fact that Neutrophils are:**

a. **more numerous** in the blood

b. **respond more rapidly** to chemokines

c. **attach more** firmly to the adhesion molecule as P- & E- selectins.

d. **short-lived in tissues**,they die by apoptosis & **disappear within 24-48 hours** while monocyte survive longer.

- Exceptions:

1. **Pseudomonas** infection → **Neutrophils** dominate for **SEVERAL DAYS**
2. **Viral infection → LYMPHOCYTES** predominate
3. **Hypersensitivity** reaction → **EOSINOPHILS** predominate

5.Leukocyte Activation

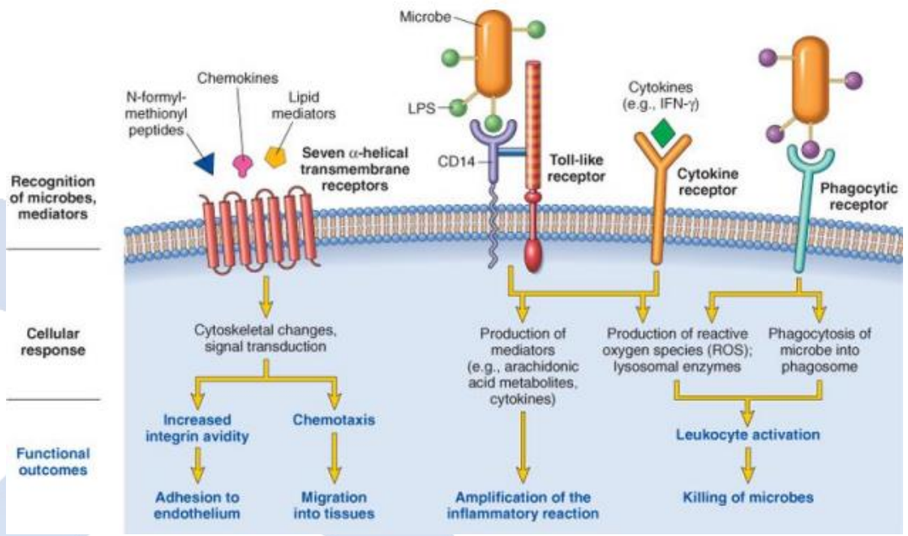
- Leukocytes at the site of infection or tissue necrosis **must be activated to perform their function.**
- **Stimuli for activation include:**

  1. **Microbes** 2. **Products of necrotic cells** 3. **Mediators**
- **Leukocyte receptors that sense microbes:**

  1-**Toll-like receptors** --- **endotoxins** (LPS)

  2- **7-transmembrane G-protein-coupled receptors** --- certain **bacterial peptides & mediators.**
- Engagement of these receptors by **microbial products** or by **various mediators** of inflammation → **induces** responses in **leukocytes** that are part of their normal defensive functions.
- **Leukocyte activation results in many enhanced functions:**

1. **Phagocytosis** of particles & **elimination** of harmful substance.
2. Production of **substances** that **destroy phagocytosed** substances (M.O & dead tissue) **as Lysosomal enzymes** and **free radicals.**
3. Production of mediators that **amplify the inflammatory reaction** as **cytokines**.



6.Phagocytosis

- **Include 3 steps**:

1. **Recognition** & **attachment** of the particles to ingesting leukocyte.
2. **Engulfment** with subsequent **formation of phagocytic vacuole.**
3. **Killing** & **degradation** of the ingested material

- **Leukocytes** bind & ingest most **M.O & dead cells** via specific receptors (**components of the microbes & dead cells** or **host proteins** called **(opsonins).**
  - ✓ **Opsonization:** a Process that include **covering** or **coating** microbes or dead cells by **host proteins to facilitate phagocytosis**.
- **The most important opsonins are:**

1.**Antibodies** esp. IgG

2.**Complement protein C3b**

3.**Collectins**: Plasma carbohydrate-binding lectins which bind to M.O cell wall sugar groups.

Leukocyte receptors for opsonins:

1.**Fc receptors** for IgG

2.**Complement receptors 1 & 3**

3.**C1q** for the collectins.

- Opsonins either are **present in the blood** ready to coat microbes or are **produced in response** to the microbes.
- **Importance of opsinization:**

1.**Enhancement** of **engulfment**

2.**Cellular activation** that enhance **degradation of ingested microbes**.

- Engulfment →extension of pseudopods →phagocytic vacuole → fusion with lysosome → phagolysosome → discharge of lysosomal granules.

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