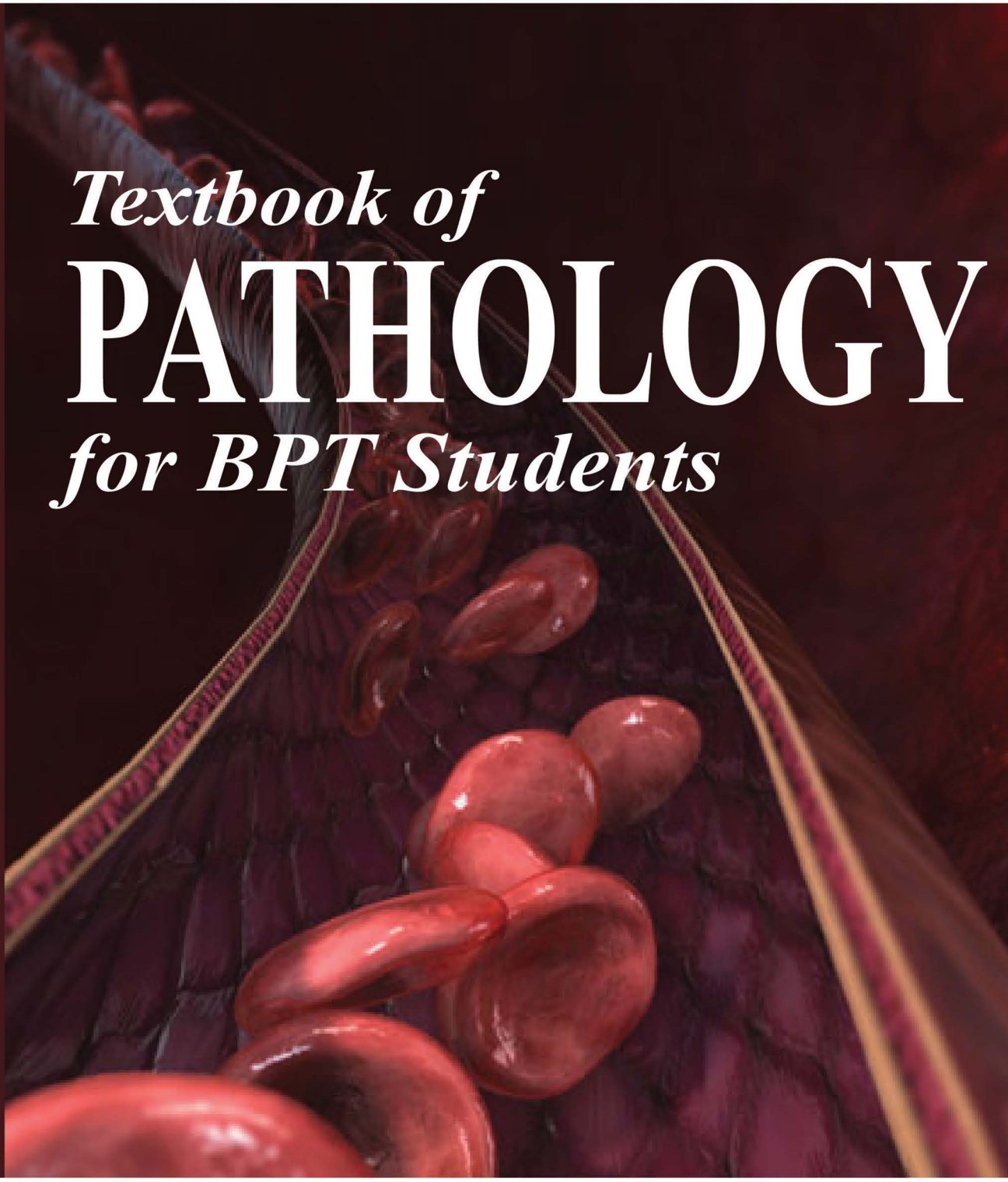
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Textbook of PATHOLOGY *for BPT Students*

Ramadas Nayak

Foreword
CV Raghuveer

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Chapter 3

Inflammation and Repair

Chapter Outline

- Acute inflammation
- Sequence of events in acute inflammation
- Chemical mediators of inflammation
- Outcomes of acute inflammation
- Morphological types/patterns of acute inflammation
- Systemic effects of inflammation
- Chronic inflammation
- Granulomatous inflammation
- Repair
- Healing
- Healing by repair, scar formation and fibrosis
- Cutaneous wound healing
- Factors that influence wound healing
- Complications of wound healing
- Healing of a fracture
- Self-assessment exercises

ACUTE INFLAMMATION

Definition: Inflammation is a complex **local response of the living vascularized tissues to injury (infections and damaged tissues)** and mainly consists of responses of blood vessels and leukocytes. **It brings cells and molecules of host defense from the circulation to the sites of injury, in order to eliminate the offending agents/cause.**

Type of inflammation: Inflammation may be divided into **acute or chronic**.
Differences between acute and chronic inflammation are listed in Table 3.1.

Table 3.1: Differences between acute and chronic inflammation

	Acute inflammation	Chronic inflammation
Onset	Rapid in onset (usually in minutes or hours).	May follow acute inflammation or be slow in onset (days).
Duration	Short duration. Lasts for hours or a few days.	Longer duration; may be months.
Predominant cells	Neutrophils (also called polymorphonuclear leukocytes).	Lymphocytes, monocytes/macrophages and sometimes plasma cells.
Characteristics	Exudation of fluid and plasma proteins (edema) and the emigration of leukocytes.	Inflammatory cells associated with the proliferation of blood vessels, tissue destruction and fibroblast proliferation.

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	Acute inflammation	Chronic inflammation
Injury/damage to tissue and fibrosis	Usually mild and self-limited; can progress to a chronic phase.	Usually severe and progressive with fibrosis and scar formation.
Signs: Local and systemic	Prominent	Less prominent

Cardinal Signs of Inflammation

- The four cardinal signs of inflammation as mentioned by **Celsus** are listed in Table 3.2.
- A fifth clinical sign, **loss of function** (functio laesa), was later added by Rudolf Virchow.

Table 3.2: Cardinal signs of inflammation

Cardinal sign	Mechanism
Rubor (redness)	Increased blood flow and stasis.
Calor (heat)	Increased blood flow.
Tumor (edema/ swelling)	Increased vascular permeability causing escape of a protein-rich fluid from blood vessels.
Dolor (pain)	Chemical mediators: Prostaglandins and kinins.

Causes of (Stimuli for) Acute Inflammation

- **Infections** (bacterial, viral, fungal, and parasitic) and **microbial toxins**.
- **Tissue necrosis:**
  - **Ischemia,** e.g. myocardial infarction.
  - **Physical agents**.
    - Mechanical trauma, e.g. blunt/penetrating/crush injuries.
    - Thermal injury, e.g. burns or frostbite.
    - Radiation.
    - Electric shock.
    - Sudden changes in atmospheric pressure.
  - **Chemical injury,** e.g. strong acids and alkalies, insecticides, and herbicides.
- **Foreign bodies,** e.g. sutures and talc.
- **Immune reactions:**
  - **Hypersensitivity reactions**.
  - **Autoimmune diseases**.

SEQUENCE OF EVENTS IN ACUTE INFLAMMATION

Acute inflammation has two major components, namely: **(1) reactions of blood vessels (vascular changes)** and **(2) reactions of leukocytes (cellular events)** characterized by leukocyte recruitment to sites of inflammation and their activation to eliminate the causative agent.

Reactions of Blood Vessels (Vascular Changes)

Purpose: To deliver the circulating cells (leukocytes), fluids and plasma proteins from the circulation to sites of infection or tissue injury.

The reactions of blood vessels in acute inflammation (Figs 3.1 and 3.2) consist of **changes in the vascular flow and caliber** and **increased vascular permeability**.

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Changes in Vascular Flow and Caliber

- **Vasodilatation:** It is the earliest feature of acute inflammation; sometimes it follows a transient constriction of arterioles. Vasodilation first affects the arterioles followed by opening of new capillary beds in the area.

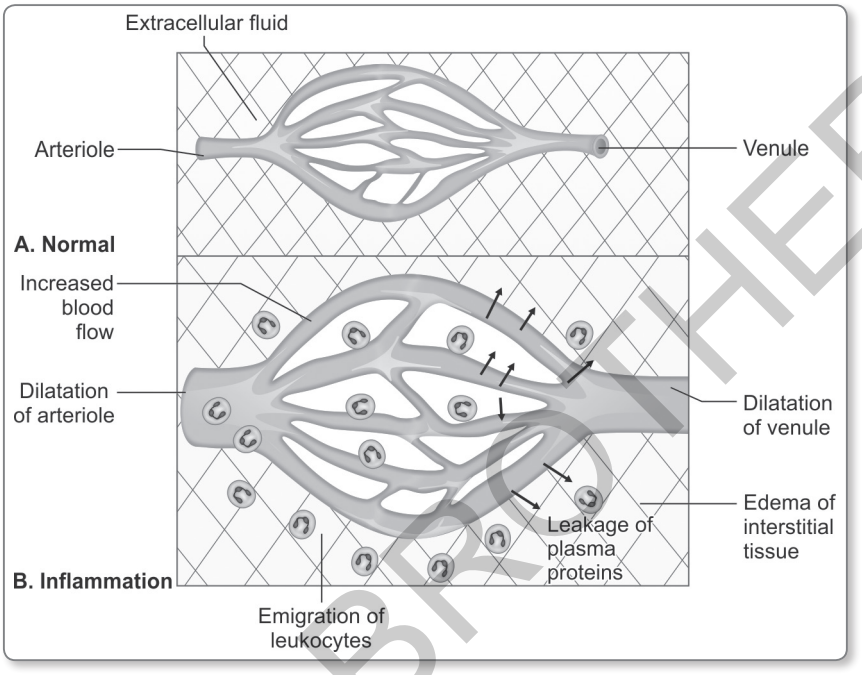
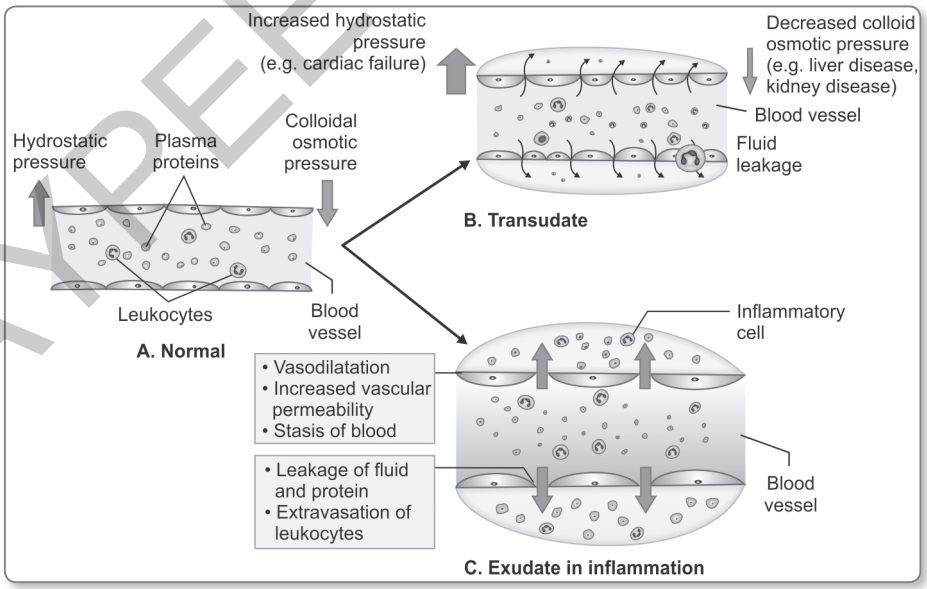


Fig. 3.1: Local features of acute inflammation, compared to normal are vasodilatation, increased blood flow, leakage of plasma fluid and proteins and emigration of leukocyte



Figs 3.2A to C: A. Normal fluid exchange between blood and extracellular fluid; B. Formation of transudate; C. Formation of exudate in inflammation

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  - **Effect:** Result is increased blood flow which causes local heat and redness.
  - **Chemical mediators involved:** Histamine, prostaglandins, platelet activating factor, kinins and nitric oxide (NO).
- **Increased permeability of the microvasculature:** It leads to escape of protein-rich fluid from the circulation into the extravascular tissues.
  - **Chemical mediators involved:** Histamine, leukotrienes, platelet activating factor, kinins.
- **Slowing of blood flow:** Vasodilatation and loss of fluid leads to concentration of RBCs in small vessels and increased viscosity of the blood. These changes result in ***engorgement of small vessels with slowly moving red cells, a condition termed stasis***.
- **Stasis:** It is responsible for vascular congestion and localized redness of the involved tissue.
- **Leukocyte events:** As stasis develops, **blood leukocytes (mainly neutrophils), accumulate along the vascular endothelium** (leukocyte events are described later).

Increased Vascular Permeability (Vascular Leakage)

Exudation: It is defined as the **process of escape of fluid, proteins and circulating blood cells** from the blood vessels into the interstitial tissue or body cavities.

Escape of a protein-rich fluid **causes edema** and is one of the cardinal signs of inflammation. Differences between transudate and exudate are listed in Table 3.3.

Mechanism of Increased Vascular Permeability

Several mechanisms can cause increased vascular permeability of postcapillary venules:

1. **Contraction of endothelial cells:** It produces increased interendothelial spaces and results in edema.
   - It is the most common mechanism of vascular leakage.

Table 3.3: Difference between transudate and exudate

Characteristics	Transudate	Exudate
Cause	Noninflammatory process	Inflammation process
Mechanism	Ultrafiltrate of plasma, due to increased hydrostatic pressure with normal vascular permeability.	Increased vascular permeability.
Appearance	Clear, serous	Cloudy/purulent/hemorrhagic/chylous
Color	Straw yellow	Yellow to red
Specific gravity	<1.018	>1.018
Protein	Low, <2 g/dL, mainly albumin	High, >2 g/dL
Clot	Absent	Clots spontaneously because of high fibrinogen.
Cell count	Low	High
Type of cells	Few lymphocytes and mesothelial cells.	Neutrophils in acute and lymphocytes in chronic inflammation.
Bacteria	Absent	Usually present
Lactate dehydrogenase (LDH)	Low	High
Example	Seen in congestive cardiac failure.	Pus
Character of edema	Pitting type	No pitting

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2. **Direct endothelial injury:** It causes necrosis and detachment of endothelial cells, e.g. burns, or infection by microbes. In most cases, leakage starts immediately after injury and is sustained for several hours until the damaged vessels are thrombosed or repaired. Hence, it is called as **immediate sustained response**.
3. **Leukocyte-mediated vascular injury:** The leukocyte (mainly neutrophils) which adheres to the endothelium during inflammation may themselves injure the endothelial cells.
4. **Increased transcytosis:** Process of transport of fluids and proteins through the endothelial cell (channels called vesiculovacuolar organelle) is known as transcytosis. However, their role in the vascular permeability of acute inflammation is uncertain.
5. **Leakage from new blood vessels:** During repair new blood vessels are formed (angiogenesis). These vessels are leaky till the endothelial cells mature.

Responses of Lymphatic Vessels and Lymph Nodes

- Apart from blood vessels, lymphatic vessels also participate in acute inflammation. Lymphatic vessels normally drain the small quantity of extravascular fluid that has escaped out of capillaries. Increased vascular permeability in inflammation produces accumulation of fluid in the extravascular space (i.e. edema). In inflammation, there is increased flow of lymph that helps to drain this edema fluid. In addition to fluid, leukocytes, cell debris, and microbes, may also flow into lymph way along with lymph.
- Secondary inflammation may occur in the draining lymphatics (**lymphangitis** characterized by the presence of red streaks along the course of the lymphatic channels draining a skin wound) and also in the draining lymph nodes (**lymphadenitis**). Inflamed draining lymph nodes are often painful and enlarged. These lymph nodes are termed as reactive, or inflammatory lymphadenitis.

Leukocytic/Cellular Events

This process **delivers leukocytes** capable of phagocytosis (neutrophils and macrophages) **to the site of injury**. The events can be divided into: **leukocyte recruitment and phagocytosis and clearance of the injurious agent**.

Leukocyte Recruitment/Extravasation

Normally, leukocytes move rapidly in the blood, and during inflammation, they slow down and escape to the site of injury/causative agent in the extravascular space. Leukocyte extravasation is the **process of migration of leukocytes from the lumen of the vessel to the site of injury** in the extravascular tissues. It is a multistep process that is mediated and controlled by adhesion molecules and cytokines called chemokines.

Steps in Leukocyte Recruitment/Extravasation (Fig. 3.3)

In the Vascular Lumen:

1. **Margination:** When the blood flow slows down (stasis), **leukocytes** (mainly neutrophils) **move towards the peripheral column** and accumulate along on the endothelial surface of vessels. This process of redistribution of leukocyte is termed margination.
2. **Rolling:** Marginated leukocytes attach weakly to the endothelium, detach and bind again with a mild jumping movement. It causes rolling of leukocyte along the endothelial surface.
   - **Molecules involved:** Selectin family of adhesive molecules and its complementary ligands.

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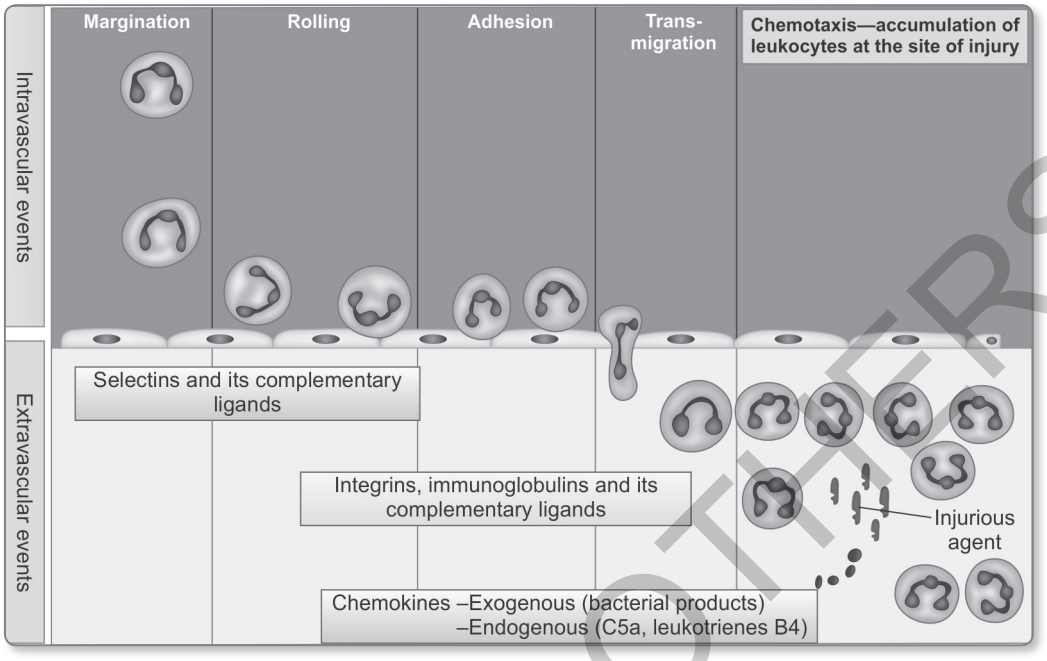


Fig. 3.3: Various steps of leukocyte migration through blood vessels. The leukocytes first roll and then firmly adhere to endothelium, followed by transmigration across the endothelium. Leukocytes pierce the basement membrane and migrate toward chemoattractants from the source of injury. Selectins are involved in rolling; integrins in adhesion; and CD31 (PECAM-1) in transmigration

3. **Adhesion of leukocyte to endothelium:** Endothelium gets activated and leukocytes bind more firmly.
   - **Molecules involved:** The adhesion/attachment of leukocytes to endothelial cells is mediated by complementary adhesion molecules on these two cell types. The expression of adhesive molecules is enhanced by cytokines.

Leukocyte Migration through Vessel Wall:

1. **Leukocyte migration through endothelium: Migration of the leukocytes through the endothelium is called transmigration or diapedesis.** Leukocytes migrate through the vessel wall by squeezing through the intercellular junctions between the endothelial cells.
   - **Molecules involved:** CD31 (platelet endothelial cell adhesion molecule [PECAM-1]) expressed on leukocytes and endothelial cells, and ICAM-1. Leukocytes migration occurs mainly in postcapillary venules.
2. **Migration across the basement membrane:** Leukocytes penetrate the basement membrane of the blood vessel by secreting collagenases.

Outside the Vessel Wall

After penetration of the basement membrane of blood vessel, leukocytes move in the tissues toward the site of injury by a process called **chemotaxis.** It can be simply **defined as locomotion of leukocyte along a chemical gradient**.

1. **Chemotaxis of leukocytes**

   Definition: Chemotaxis is defined as process of **migration of leukocytes toward the inflammatory stimulus** in the **direction of the gradient** of locally produced chemoattractants.

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Chemoattractants:

- **Exogenous: Bacterial products** (e.g. N-formylmethionine terminal amino acid).
- **Endogenous:**
  - Cytokines, mainly chemokine family (e.g. **IL-8**).
  - Complement components: **C5a**, **C3a**.
  - Arachidonic acid metabolites of lipoxygenase pathway: **Leukotriene B_4 (LTB_4)**.

2. **Accumulation of leukocytes at the sites of infection and injury:** Achieved by binding of leukocytes to the extracellular matrix proteins through **integrins and CD44**.
   - **Type of leukocytes infiltrates:**
     - **Neutrophils:** Predominantly during the first 6–24 hours.
     - **Monocytes:** Neutrophils are replaced by monocytes in 24–48 hours.

Phagocytosis and Clearance of the Offending Agent

Develops in two sequential events:

Recognition of microbes, necrotic cells and foreign substances: Leukocytes recognize microbes, necrotic cells and foreign substances by cell surface receptors known as "**pattern recognition receptors**".

Activation of leukocytes: Recognition of microbes or dead cells by the receptors initiates several responses in leukocytes together known as **leukocyte activation**. The most important functional responses of leukocyte activation is phagocytosis and intracellular killing.

Phagocytosis

Many leukocytes **recognize, internalize, and digest** foreign materials, microorganisms, or cellular debris by a process termed phagocytosis. It consists of three steps (Fig. 3.4):

- Recognition and attachment.
- Engulfment.
- Killing or degradation of the ingested material.

Recognition and Attachment

- Receptors on the surface of phagocytic cells recognize components of microbes and necrotic cells. Leukocytes express several receptors that recognize external stimuli. These include: (1) receptors for microbial products, e.g. Toll-like receptors (TLRs), (2) G protein–coupled

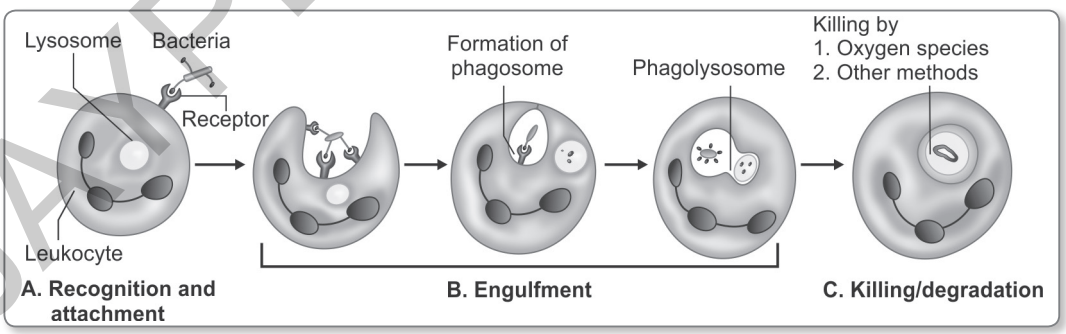


Fig. 3.4: Different steps in phagocytosis. A. Recognition and attachment, which involves binding to receptors on the leukocyte membrane to injurious agent (e.g. bacteria); B. Engulfment, formation of phagosome and fusion of lysosomes with phagocytic vacuoles to form phagolysosome; C. Killing/degradation of ingested particles within the phagolysosomes by lysosomal enzymes and by reactive oxygen and nitrogen species

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receptors (recognize N-formyl methionie residues), (3) receptors for cytokines (for INF-γ) and (4) receptors for opsonins.

- **Receptors for opsonins (phagocytic receptor):** The phagocytosis is enhanced when leukocyte receptors recognize microbes coated by specific host proteins known as **opsonins**. The major opsonins are IgG antibodies, the C3b breakdown product of complement, and certain plasma lectins called collectins.

Engulfment

Next step in phagocytosis is engulfment and formation of a phagocytic vacuole.

- **Phagosome:** Extensions of the **cytoplasm of leukocyte form pseudopods surrounding the particle to be ingested** and forms a vesicle or vacuole called a phagosome.
- **Phagolysosome:** The membrane of **phagosome fuse**s with membrane of **lysosome to form a phagolysosome**. Lysosomal **granules are discharged** into this phagolysosome.

Killing and Degradation

Killing and degradation of ingested microbial agents/particles occurs within neutrophils and macrophages. Most important microbicidal agents are: (1) reactive oxygen species and (2) lysosomal enzymes.

Reactive Oxygen Species (ROS)

Types of ROS are:

- Superoxide anion ($O_2^{\bullet-}$, one electron)—**weak**.
- Hydrogen peroxide (H_2O_2, two electrons)—**weak**.
- Hydroxyl ions ($^{\bullet}OH$), three electrons—**highly reactive**.

Mechanism of production: In the phagocytic vacuole of leukocyte, rapid activation of NADPH oxidase (also called **phagocyte oxidase**), oxidizes NADPH (reduced nicotinamide-adenine dinucleotide phosphate) to NADP. During the process oxygen is reduced to superoxide anion ($O_2^{\bullet-}$).

- $O_2^{\bullet-}$ is converted into hydrogen peroxide (H_2O_2) by spontaneous dismutation $O_2^{\bullet-} + 2H \rightarrow H_2O_2$.
- Amount of H_2O_2 is insufficient to kill most of the microbes by itself but the enzyme **myeloperoxidase** (MPO) present in the azurophilic granules of neutrophils can convert H_2O_2 into a powerful ROS. MPO in the presence of a halide such as Cl^-, converts H_2O_2 to hypochlorous radical ($HOCl^{\bullet}$), which is a potent oxidant and antimicrobial agent. Hypochlorite ($HOCl^{\bullet}$) destroys microbes either by **halogenation** or by proteins and lipid peroxidation.
- H_2O_2 is also converted to hydroxyl radical ($^{\bullet}OH$) which is also powerful destructive agent.

Reactive nitrogen species: NO, which is generated from arginine by the action of nitric oxide synthase (NOS), can kill microbes similar to ROS.

Lysosomal Enzymes

Acid hydrolases of lysosomes degrade the dead microorganisms. Elastase can kill bacteria.

- **Constituents of leukocyte granules:** The microbicidal substances within leukocyte cytoplasmic granules include:
  - Bactericidal permeability—increasing protein.
  - Lysozyme and lactoferrin.
  - **Major basic protein (MBP) present in eosinophils is cytotoxic to many parasites**.

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- Defensins are toxic to microbes.
- Cathelicidins: These are anti-microbial proteins in the neutrophils and other cells. They are very effective against *Mycobacterium tuberculosis*.

CHEMICAL MEDIATORS OF INFLAMMATION

Definition: Substances that initiate and regulate inflammatory reactions are called as **mediators of inflammation**. Numerous chemical mediators are responsible for inflammatory reactions.

General Features of Mediators

- **Source of mediators:** Mediators are derived either from cells or from plasma proteins.
  - **Cell-derived mediators:**
    - Present either as **preformed molecules** (e.g. histamine in mast cell granules) or are **synthesized de novo** (e.g. prostaglandins, cytokines) in response to a stimulus.
    - Produced usually by platelets, neutrophils, monocytes/macrophages, and mast cells.
  - **Plasma-derived mediators:** Produced mainly in the **liver** and present in the circulation as **inactive precursors, which require activation** (e.g. complement proteins, kinins).
- **Chemical mediators have hightly regulated actions**.
- **Short-lived:** Most of these mediators have a short-lifespan.

Main mediators involved in the inflammatory reaction are listed in Table 3.4.

Cell-Derived Mediators

Vasoactive Amines: Histamine and Serotonin

Histamine and serotonin are the first mediators to be released during inflammation, which are stored as preformed molecules in cells.

1. **Histamine:** It is a preformed vasoactive mediator. Responsible for immediate transient response.
   Source: Mast cells (richest source), **blood basophils and platelets**.
   Actions: (1) **Dilation of arterioles** and (2) **increase of the vascular permeability**.

Table 3.4: Main chemical mediators of acute inflammation

Cell-derived	Plasma protein-derived
• **Vasoactive amines** – Histamine – Serotonin	• **Complement components** – C3a – C5a – C3b – C5b-9 (MAC)
• **Arachidonic acid (AA) metabolites** – Prostaglandins – Leukotrienes	• **Kinins** – Bradykinin – Kallikrein
• **Platelet-activating factor (PAF)**	• **Coagulation/fibrinolytic system**
• **Reactive oxygen species (ROS)**	
• **Nitric oxide (NO)**	
• **Cytokines (TNF, IL-1) and chemokines**	

Abbreviation: IL-1, interleukin-1; TNF, tumor necrosis factor; MAC, membrane attack complex.

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2. **Serotonin (5-hydroxytryptamine):** It is a preformed vasoactive mediator.
   Source: Platelets, some **neurons** and **enterochromaffin cells** in the gastrointestinal tract.
   Actions: Similar to those of histamine.

Arachidonic Acid (AA) Metabolites (Prostaglandins, Leukotrienes, and Lipoxins)

Arachidonic Acid (AA)

- **Source:** Derived from cell membrane phospholipids mainly by the enzyme phospholipase A_2.
- **AA metabolism: Occurs along two major enzymatic pathways** (Fig. 3.5). These are **cyclooxygenase pathway** (produce prostaglandins) and **lipoxygenase pathway** (produces leukotrienes and lipoxins).

A. Products of cyclooxygenase pathway:

- **Local effects:**
  - **TxA_2: Vasoconstriction** and promotes **platelet-aggregation**.
  - **Prostacyclin (PGI_2): Vasodilator** and **inhibits platelet aggregation**.
  - **PGD_2 and PGE_2: Vasodilation and increased permeability**. PGD_2 is also a chemoattractant for neutrophils.

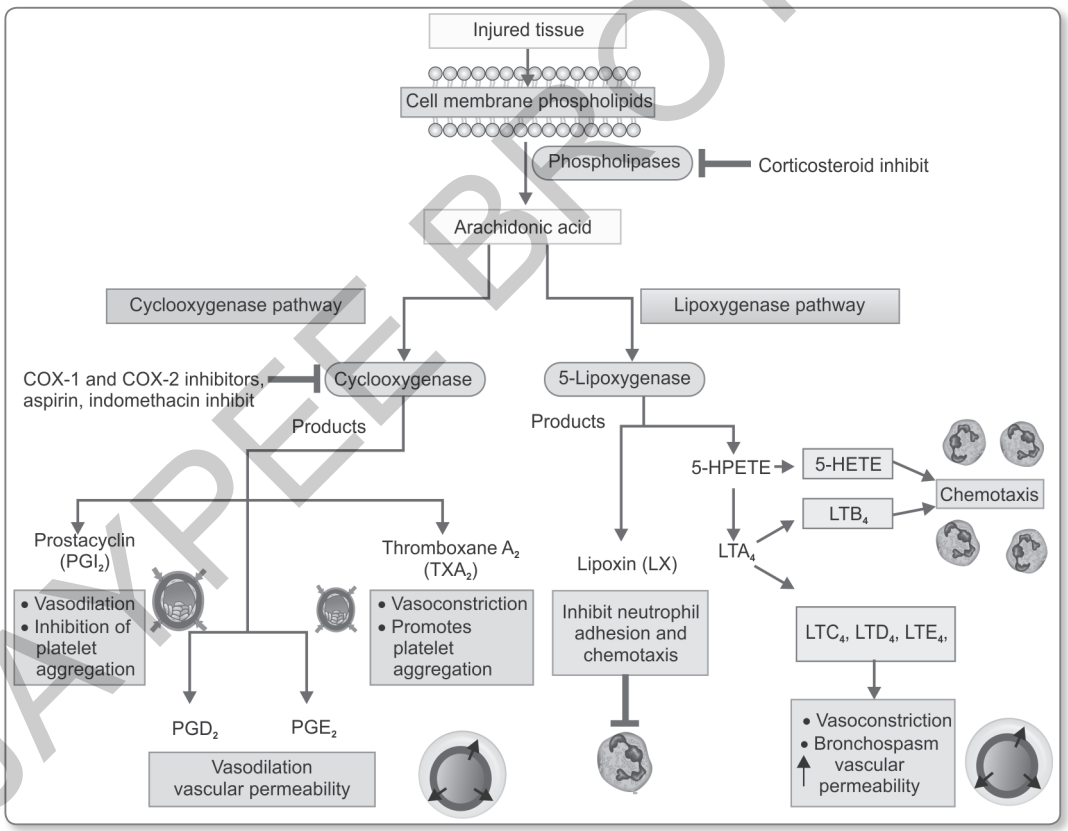


Fig. 3.5: Arachidonic acid metabolites involved in inflammation. The cyclooxygenase pathway generates prostaglandins (PGIs) and thromboxane (TXA_2). The lipoxygenase pathway forms lipoxins (LXs) and leukotrienes (LTEs)
Abbreviation: COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid

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- **Systemic effects:**
  - Prostaglandins are responsible for **pain and fever** in inflammation.
  - PGE_2 causes cytokine-induced **fever** during infections.

B. Products of lipoxygenase pathway: 1) Leukotrienes and 2) lipoxins.

1. Leukotrienes: Products and their actions:
   - **5-hydroxyeicosatetraenoic acid (5-HETE):** Chemotactic for neutrophils, and is the precursor of the leukotrienes.
   - **LTB_4: Chemotactic agent**.
   - **Leukotrienes C_4, D_4, and E_4**(LTC_4, LTD_4, LTE_4): **Increased vascular permeability**.

2. Lipoxins (LXs): Inhibit inflammation.

Main actions of arachidonic acid metabolites (eicosanoids) involved in inflammation are presented in Table 3.5.

Cytokines and Chemokines

These are polypeptides which function as mediators in **immune responses** and in **inflammation (acute and chronic)**.

Tumor Necrosis Factor and Interleukin-1

Actions in Inflammation (Fig. 3.6)**:**

- **Local effects:**
  - **Endothelial activation**.
  - **Activation of leukocytes and other cells**.
- **Systemic effects:**
  - Fever.
  - Leukocytosis.
  - Systemic acute-phase reactions.
  - Suppresses appetite: TNF contributes to cachexia seen in some chronic infections.

Chemokines

Chemotactic cytokines or chemokines are small proteins, which selectively attracts various leukocytes to the site of inflammation.

Action: Chemotaxis of **monocytes, eosinophils, basophils, and lymphocytes** except neutrophils. They activate **leukocyte and promote their recruitment to the sites of inflammation**.

Lysosomal Constituents of Leukocytes

Neutrophils

Types of Granules:

1. **Smaller specific (or secondary) granules:** They contain lysozyme, collagenase, gelatinase, lactoferrin, plasminogen activator, histaminase, and alkaline phosphatase.
2. **Larger azurophil (or primary) granules:** They **contain myeloperoxidase**, bactericidal factors (lysozyme, defensins), acid hydrolases, and a variety of neutral proteases (elastase, cathepsin G, nonspecific collagenases, proteinase).

Monocytes and Macrophages

They also contain acid hydrolases, collagenase, elastase, phospholipase, and plasminogen activator. These are active mainly in chronic inflammation.

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Plasma-Derived Mediators

Chemical mediators derived from plasma proteins belong to three interrelated systems:

1. Complement system.
2. Kinin system.
3. Clotting systems.

Complement System

The complement system is a group of plasma proteins synthesized in the liver, and are numbered C1 to C9.

Pathways of complement system activation (Fig. 3.6)**:** The decisive step in complement activation is the proteolysis of the third component, C3.

Cleavage of C3 can occur by any one of three pathways:

1. **Classical pathway:** It is activated by **antigen-antibody** (Ag-Ab) complexes.
2. **Alternative pathway:** It is triggered by microbial surface molecules (e.g. endotoxin, or LPS), complex polysaccharides, cobra venom, and other substances, **in the absence of antibody**.
3. **Lectin pathway:** It directly activates C1 when plasma mannose-binding lectin binds to mannose on microbes.

Functions of Complement

1. **Leukocyte activation, adhesion and chemotaxis:** C3a and C5a are **powerful chemotactic** agents for neutrophils, monocytes, eosinophils, and basophils.

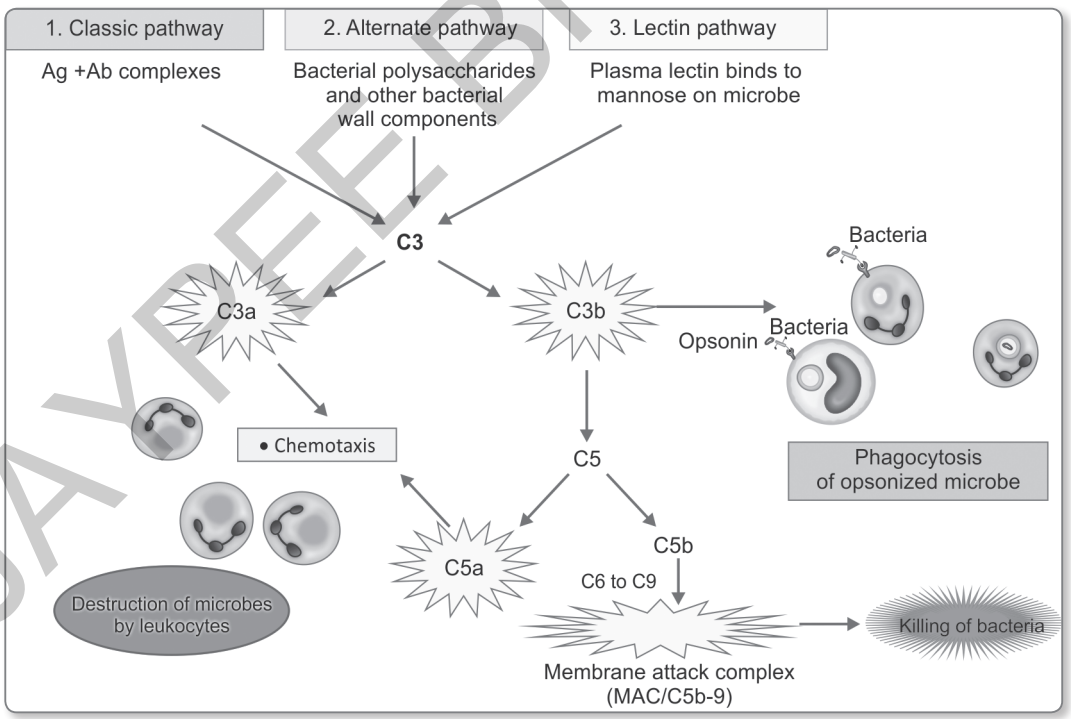


Fig. 3.6: Different pathways of activation and functions of the complement system. All pathways of activation lead to cleavage of C3

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