Pathology of

INFLAMMATION

CH 2: Lecture I

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Introduction:

- **Inflammation** is **"dynamic response of vascularised tissue to injury."**
- It is **physiologic**, protective response.
- Serves to bring **defense** & **healing** mechanisms to the site of injury.

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Inflammation:

- **Inflammation** occurs in the vascularized connective tissue.
- **Inflammation** is followed by repair process:
  - damaged tissue is replaced by the regeneration of parenchymal cells,
  - and/or by filling of any residual defect with fibrous scar tissue.
- **Inflammation** *has considerable potential to cause harm.*

e.g. life-threatening anaphylactic reactions to insect bites or drugs.

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Inflammation Causes: ..Injury

- **Physical agents** – Trauma, radiation
- **Infection** – microbial agents
- **Chemical agents** – acid, alkali, toxins
- **Ischemia**
- **Immune reaction**

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Patterns of inflammation:

- **Acute inflammation:** **immediate** and early response to injury, characterized by fluid and plasma protein exudation and a predominant neutrophilic accumulation. It lasts only for few minutes to few days.

- **Chronic inflammation:** **delayed** response, characterized by influx of macrophages and lymphocytes with associated vascular proliferation and scarring.

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Components for inflammation:

1. **The vascular wall cells** include the endothelial cells in direct contact with the blood, and the underlying smooth muscle cells that control the vessels tone.
2. **The circulating cells** include bone marrow-derived polymorphonuclear leukocytes (neutrophils), eosinophils, & basophils; lymphocytes & monocytes; and platelets
3. **The circulating proteins** include clotting factors, kininogens, & complement
4. **The connective tissue cells** include mast cells & macrophages, in addition to the fibroblasts that synthesize the extracellular matrix and can proliferate to fill in a wound.
5. **The connective tissue (extracellular matrix)** consists of fibrous structural proteins (e.g., collagen and elastin), gel-forming proteoglycans, and adhesive glycoproteins (e.g., fibronectin) that are the cell-ECM and ECM-ECM connectors

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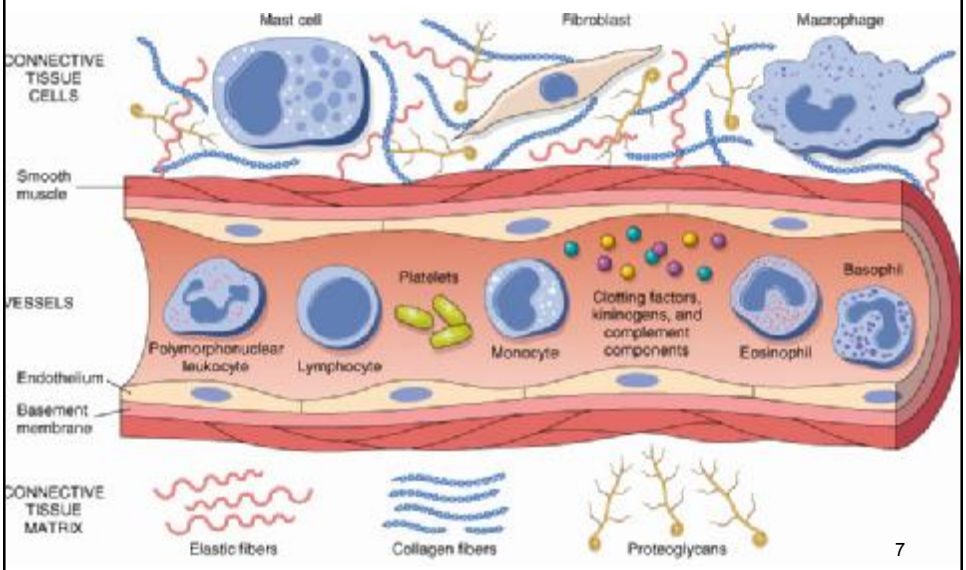
Components for inflammation



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Acute inflammation:

- **Acute** – up to days.
  - Vascular changes : Hyperemia & exudation.
  - Neutrophils, pus/suppuration.
- Immediate and early response to injury aiming at delivery of leukocytes to the site of injury.
- Clinically has 5 local signs: **heat, redness, swelling, pain and loss of function.**

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Cardinal Signs of Inflammation

- **Calor** : Warm, heat – Hyperaemia.
- **Rubor** : Redness – Hyperaemia.
- **Dolor** : Pain – Nerve, Chemical mediators
- **Tumor** : Swelling – Exudation
- **Functio laesa**: Loss of function

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Nomenclature and etiology of common types of inflammation

Tissue	Acute inflammation	Typical causes
Meninges	Meningitis	Bacterial and viral infections
Brain	Encephalitis	Viral infections
Lung	Pneumonia	Bacterial infections
Pleura	Pleurisy	Bacterial and viral infections
Pericardium	Pericarditis	Bacterial and viral infections, MI
Oesophagus	Oesophagitis	Gastric acid reflux, fungal infections
Stomach	Gastritis	Alcohol abuse, *Helicobacter pylori* infection
Colon	Colitis	Bacterial infections, ulcerative colitis
Rectum	Proctitis	Ulcerative colitis
Appendix	Appendicitis	Faecal obstruction
Liver	Hepatitis	Alcohol abuse, viral infections
Gallbladder	Cholecystitis	Bacterial infections, chemical irritation
Pancreas	Pancreatitis	Pancreatic enzyme release
Urinary bladder	Cystitis	Bacterial infections
Bone	Osteomyelitis	Bacterial infections
Subcutaneous tissues	Cellulitis	Bacterial infections
Skin	Sunburn	UV radiation
Joints	Arthritis	Bacterial & viral infections, immune complex deposition
Arteries	Arteritis	Immune complex deposition

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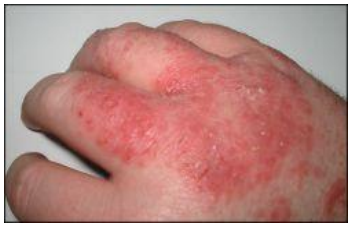
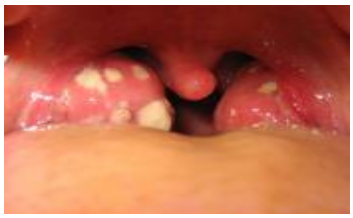
Inflammation - Examples

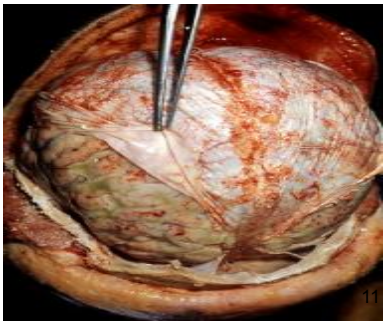


Dermatitis

Appendicitis



Tonsillitis



Meningitis

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Acute inflammation:

Two major components:

- ***Vascular***: with alteration of the vessels caliber (vasodilation), and increased vascular permeability to allow delivery of plasma proteins into the focus of inflammation.
- ***Cellular***: emigration of the WBCs from the microcirculation into the focus of inflammation.

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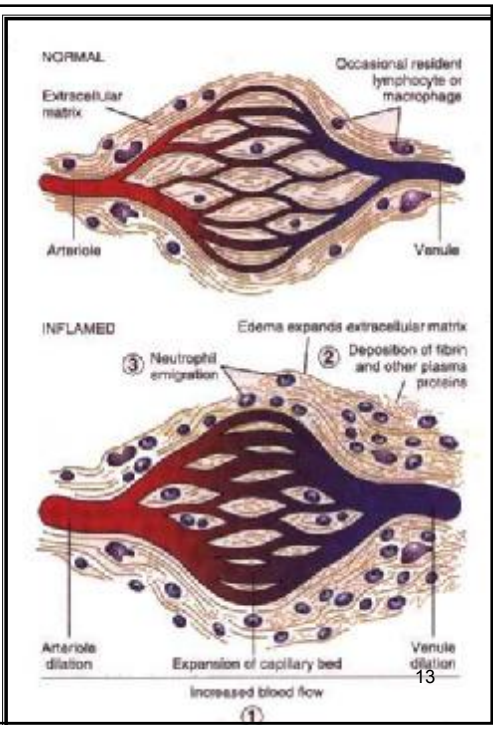
Mechanism

1. Vasodilatation
2. Exudation - Edema
3. Emigration of cells
4. Mediator release
5. Phagocytosis



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Acute inflammation: 5 cardinal signs

- **The major <u>local</u> manifestations:**

(1) vascular dilation (causing erythema and warmth), heat *(**calor**)*, redness *(**rubor**)*,

(2) extravasation of plasma fluid and proteins (edema) swelling *(**tumor**)*.

(3) leukocyte emigration and accumulation in the site of injury.

(4) local release of *chemical mediators, causing* pain *(**dolor**)* and loss of function *(**functio laesa**)*

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Acute inflammation:

Vascular changes:

1. **Changes in vascular flow**

2. **Increased vascular permeability**

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Vascular changes:
1. Changes in vascular flow

- Transient vascular constriction
- Arteriolar vasodilation causing "**redness, erythema, rubor**"; leading to increase in the local blood flow "**heat, warmth, calor**"
- Increased vascular permeability, leading to extravasation of inflammatory cells and proteins into the interstitial tissue "**swelling, edema, tumor**"
- Slowing of the circulation due to increased viscosity and stasis.

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Vascular changes: 2. Increased vascular permeability

- **Increased vascular permeability** leading to the escape of a protein-rich fluid (**exudate**) into the extravascular tissue.
- The loss of protein from the plasma reduces the intravascular osmotic pressure and increases the osmotic pressure of the interstitial fluid.
- Together with the increased hydrostatic pressure owing to increased blood flow through the dilated vessels, this leads to a marked outflow of fluid and its accumulation in the interstitial tissue.
- The net increase of extravascular fluid results in **edema**

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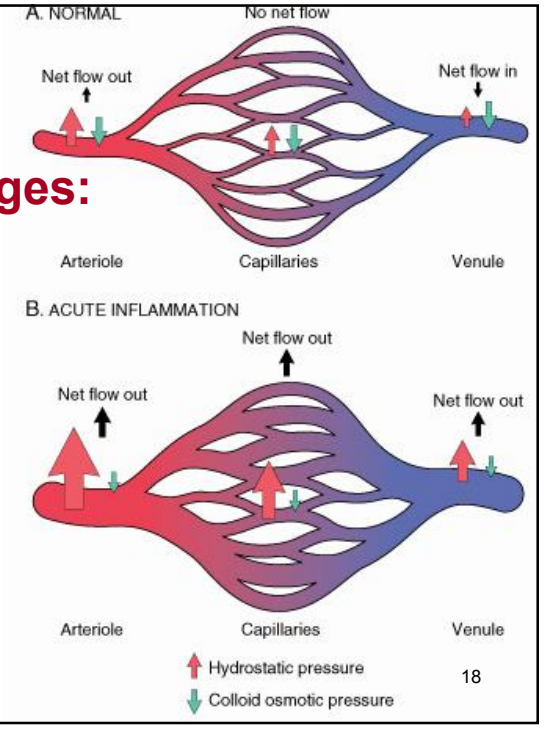
- **Vascular changes:**
  2. Increased vascular permeability



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Vascular changes:
2. Increased vascular permeability

Two types of fluids can be seen:

1) **Transudation:** Ultrafiltration of blood plasma which contains little protein under the effect of increased hydrostatic pressure due to arteriolar vasodilation and increased blood flow.
2) **Exudation:** the move of protein rich fluid from the blood into the extravascular tissue due to increased vascular permeability.

This fluid accumulation is called **edema**.

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Vascular changes:
2. Increased vascular permeability

What are the mechanisms:

1. Endothelial cell contraction
2. Direct endothelial injury
3. Leukocyte dependent endothelial injury
4. Increased transcytosis
5. Leakage from new blood vessels

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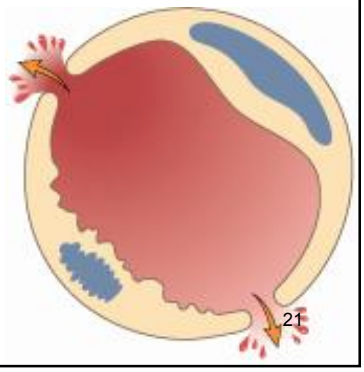
Increased vascular permeability:

Mechanism

1. Endothelial cell contraction:

- the most common cause of increased vascular permeability
- leading to intercellular gaps
- resulting in "*the immediate transient response*"
- mediated by histamine, bradykinins, leukotrienes.
- seen only at the **venules**

This to be differentiated from endothelial cell retraction, in which the cytoskeleton proteins are rearranged, and thus the response is delayed. Retraction is mediated by other inflammatory mediators like TNF/IL-1.
Both processes are completely reversible.



Increased vascular permeability:

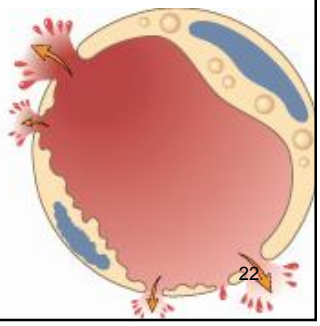
Mechanism

2. Direct endothelial injury

- "**immediate sustained response**" if the injury is severe, involves venules, capillaries & arterioles
- "**delayed prolonged response**" if the injury is mild, involves venules & capillaries only.

Direct injury

- Arterioles, capillaries, and venules
- Toxins, burns, chemicals
- Fast and may be long-lived (hours to days)



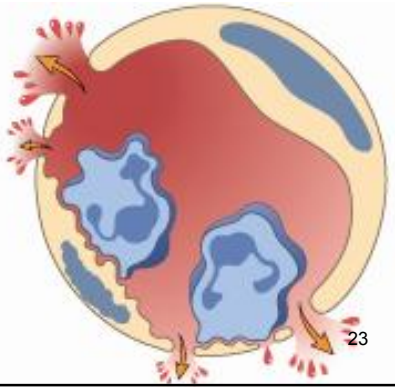
Increased vascular permeability: Mechanism

3. Leukocyte dependent endothelial injury:

This occurs in the systemic **venules** and in the pulmonary capillaries.

Leukocyte-dependent injury

- Mostly venules
- Pulmonary capillaries
- Late response
- Long-lived (hours)



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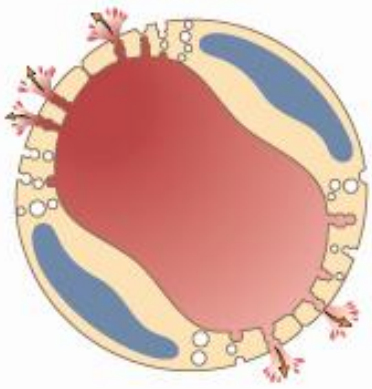
Increased vascular permeability: Mechanism

4. Increased transcytosis:

- occurs through vesicles in the cytoplasm of the endothelial cells in **venules** and is induced by VEGF

Increased transcytosis

- Venules
- Vascular endothelium–derived growth factor **(VEGF)**



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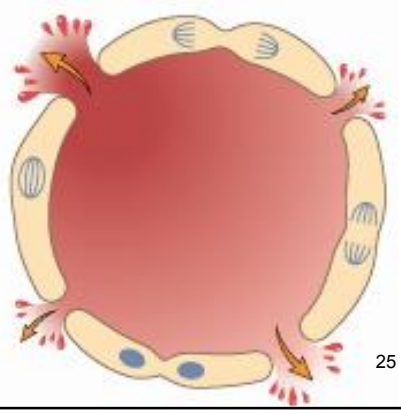
Increased vascular permeability:
Mechanism

5. Leakage from new blood vessels

New blood vessel formation

- Sites of angiogenesis
- Persists until intercellular junctions form



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Cellular reaction:
Acute Inflammatory Cells: Neutrophils

- Accumulation of **neutrophils** in extracellular space
- In severe cases, accumulation of neutrophils, cellular debris, bacteria and edema fluid forms **pus**
- Neutrophils:
  - Produced in bone marrow
  - Commonest white cell in blood ~ **65%**
  - **Increase in acute inflammation**
  - **Motile**, can move into tissues
  - Directional chemotaxis
  - **Short lifespan** (hours in tissues)

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Cellular reaction:

Acute Inflammatory Cells: Neutrophils

- **Neutrophil activation**

– expression of **adhesion** molecules causes neutrophils to adhere to endothelium

– increased motility allows **emigration** from vessels into surrounding tissues

– increase capacity for **bacterial killing**.

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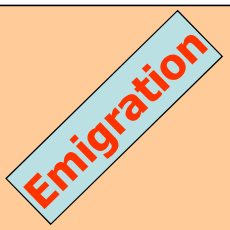
Cellular events

Cellular response of leukocytes:

1. Margination
2. Rolling
3. Adhesion
4. Transmigration by diapedesis.



5. Chemotaxis
6. Activation
7. Phagocytosis and degranulation

These events are facilitated by certain **chemical mediators and adhesion molecules** that are induced on the cells.

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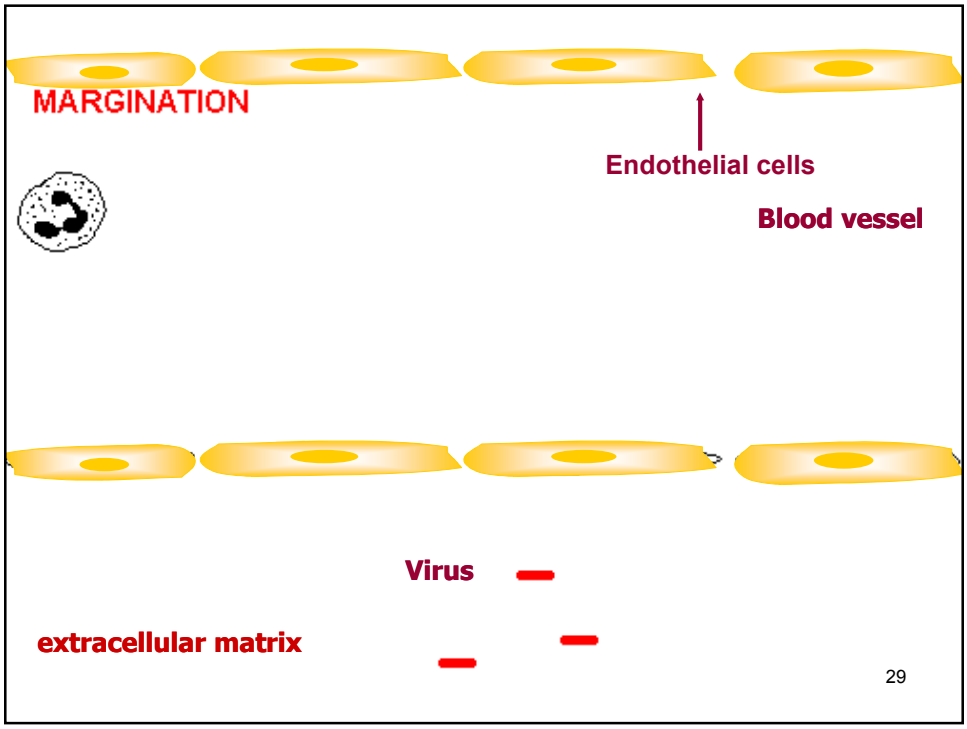
MARGINATION
Endothelial cells
Blood vessel
Virus
extracellular matrix
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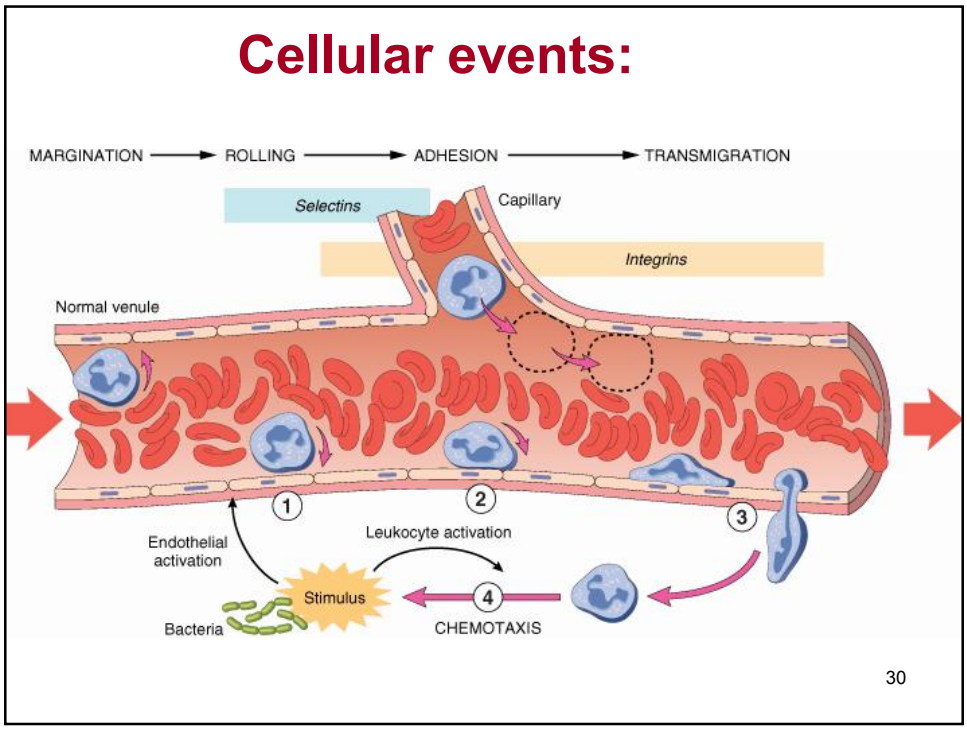
Cellular events:
MARGINATION
ROLLING
ADHESION
TRANSMIGRATION
Selectins
Capillary
Integrins
Normal venule
1
2
3
4
Endothelial activation
Leukocyte activation
Stimulus
Bacteria
CHEMOTAXIS
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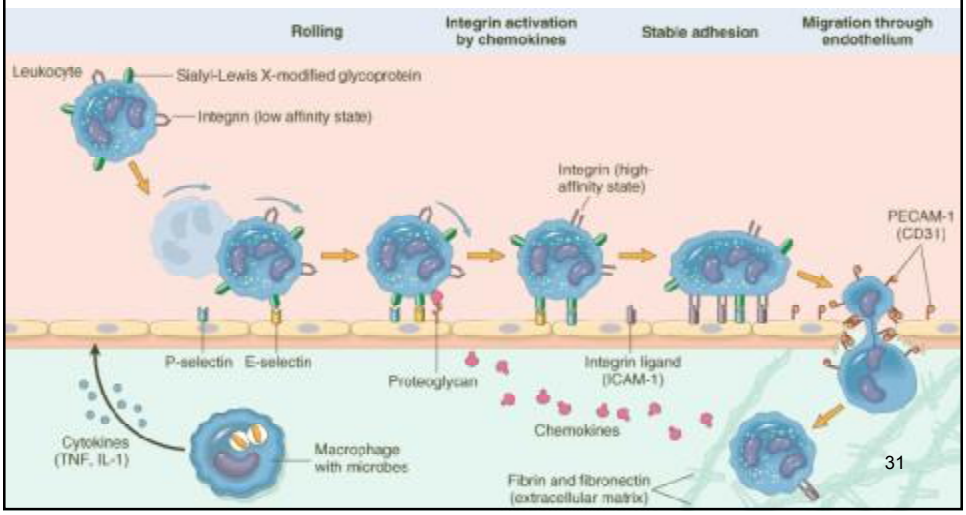
Adhesion molecules:

- **Selectins**
- **Integrins**
- **Immunoglobulin family** (e.g. ICAM-1, ICAM-2, VCAMs)



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Cellular events: Margination & rolling

1) **Margination**: the process by which leukocytes accumulate at the periphery of vessel. This is augmented by increased vascular permeability and stasis.
2) **Rolling**: tumbling of the leukocytes and transient sticking on the endothelial surfaces.

- Margination and rolling: Mediated through molecules called **selectins** which are receptors expressed on endothelial cells, platelets, and leukocytes.
- **Types of selectins:**

1. **E-selectins**: confined to **Endothelial cells**, induced after stimulation of the endothelial cells by inflammatory mediators, like IL-1 &TNF.
2. **P-selectins**: **endothelial cells** and **Platelets**. In endothelial cells they are found within the Weibel-Palade bodies and under the influence of histamine and thrombin, they are redistributed to the cell surface.
3. **L-selectins:** always expressed on the surface of **Leukocytes**.

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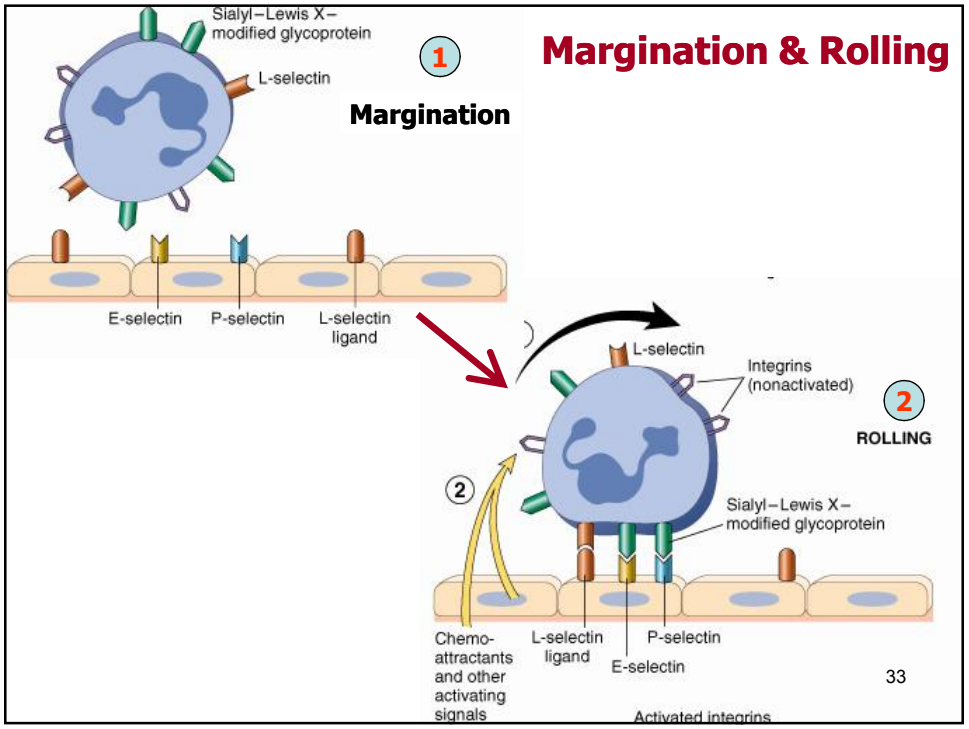

Cellular events: Adhesion

3) Adhesion: firm sticking of the leukocytes to the endothelial cells

- Mediated through **Integrins**: Transmembrane glycoproteins that are normally expressed on the **leukocyte** plasma membrane.
- Integrins affinity is increased after stimulation by chemical mediators like chemokines, complement C5a and PAF.
- Once activated, they undergo conformational changes that allow them to interact with their ligands, which are immunoglobulins that are normally expressed on the endothelial plasma membrane (ICAM-1, VCAM-1), and which are induced by TNF and IL-1
- **Types of integrins:**

1. LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18), both bind to ICAM-1 on endothelial cells.
2. VLA-4: this binds to VCAM-1.

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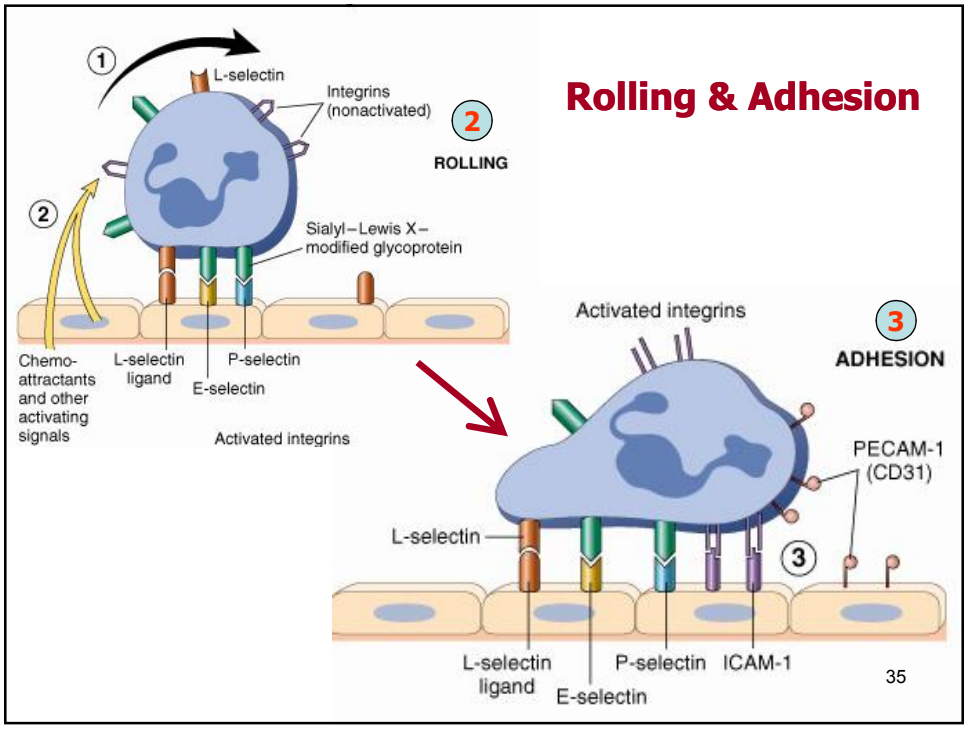

Cellular events: Transmigration

4) Transmigration: crawling of the leukocytes between the endothelial cells and through the basement membrane into the extravascular space, by diapedesis.

- Occurs mainly in the venules of the systemic circulation.
- Mediated through **PECAM-1 (CD-31)**, present on both the endothelial cells and leukocytes.
- **Collagenases** elaborated from leukocytes degrade the basement membrane.

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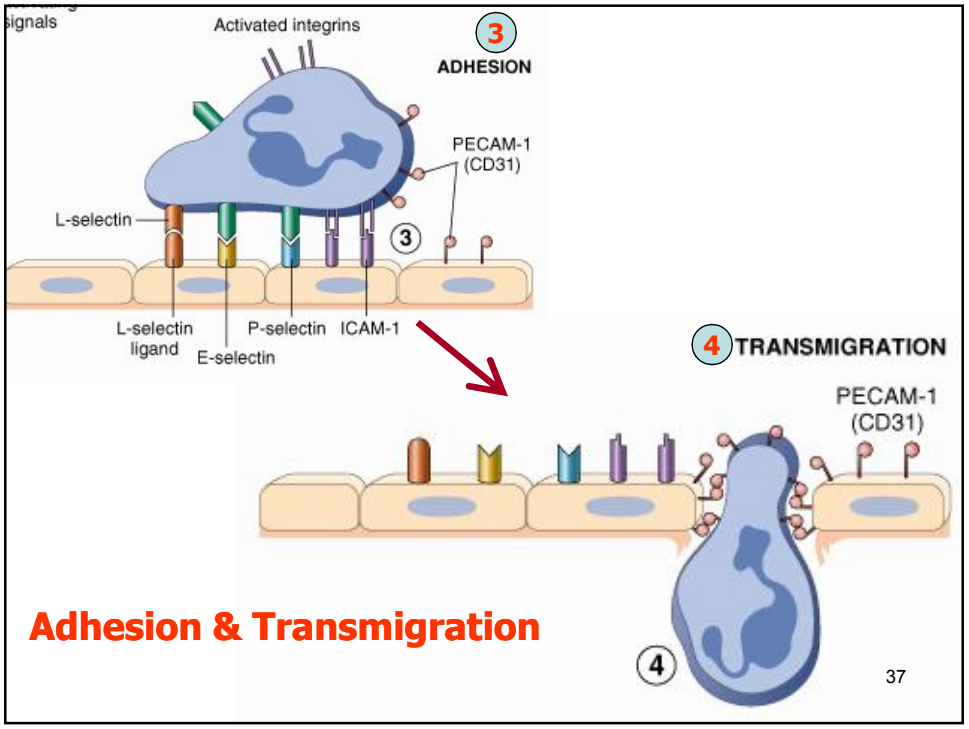

Cellular events: Chemotaxis

5) Chemotaxis: migration of the leukocytes toward the site of injury along a chemical gradient.

- Chemotactic substances to leukocytes:

1. Soluble bacterial products
2. Complement, e.g. C5a complement factor
3. Arachidonic acid, e.g. Leukotriene B4 (LTB 4)
4. Chemokines, especially IL-8 for neutrophils, eotaxin for eosinophils, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α) for monocytes and the RANTES for lymphocytes & monocytes

- **The type of inflammatory cells depends on the nature of stimulus:**
  - Neutrophils predominate in acute inflammation in the 1st 24 hours, and then are replaced by macrophages and lymphocytes.
  - For allergic reactions and parasitic infestations eosinophils predominate.
  - For viruses lymphocytes are the main cells.

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Cellular events: Activation,

6) Activation involves:

1. binding of the chemoattractant molecule with a G-protein-coupled receptor on the surface of the inflammatory cell.
2. Activation of phopholipase A2, with generation of AA metabolites.
3. Modulation of adhesion molecules by increasing Calcium levels.
4. Degradation and secretion of lysosomal enzymes.
5. Generation of oxidative burst.

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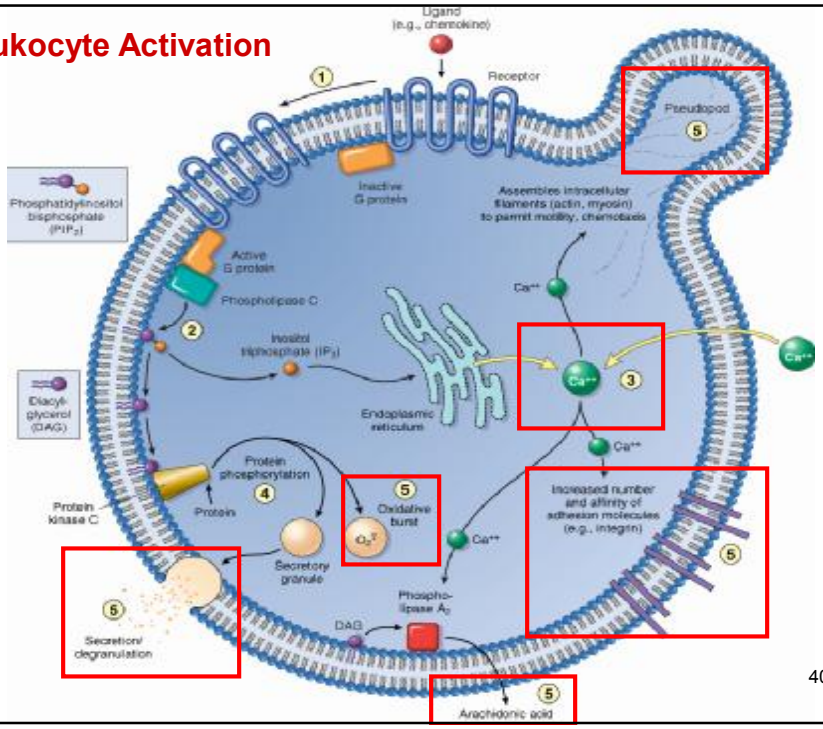
Leukocyte Activation



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Cellular events: Phagocytosis & degranulation

7) Phagocytosis:

1. Opsonization: A Recognition and attachment of leukocytes to the micro-organism

2. Engulfment: a pesudopod is extended around the object to form a phagocytic vacuole

3. Fusion of the phagocytic vacuole with lysosomes to form a phagolysosome leading to **degranulation**:

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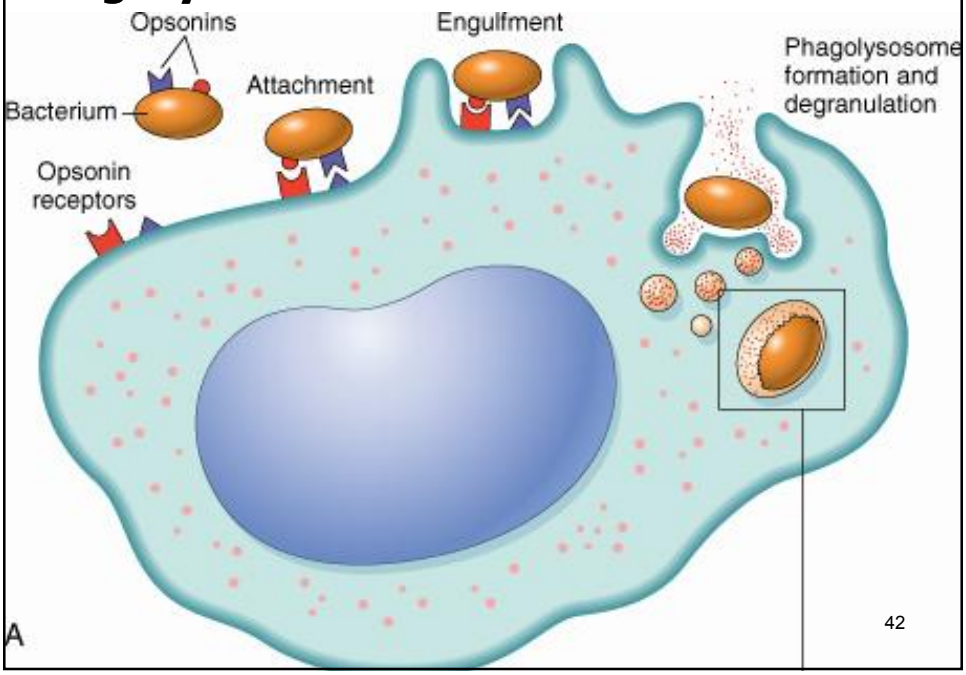
Phagocytosis:



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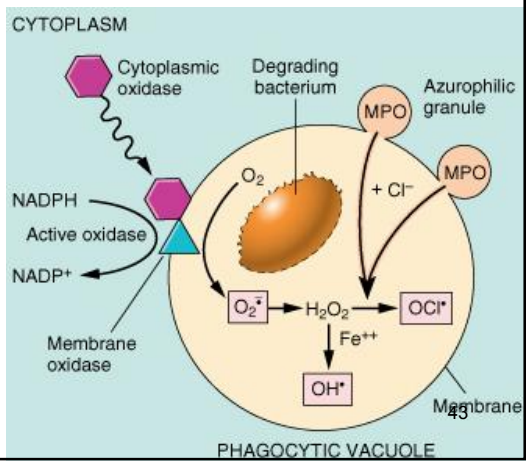
4. Microbial killing: the final step in the process, involve

A) Oxidative burst: the generation of reactive oxygen species through activation of the NADPH oxidase.

B) Myeloperoxidase (MPO), present within the lysosomes (azurophilic granules) in neutrophils. MPO in the presence of Cl, will convert H2O2 into HOCl (hypochlorous radical), powerful free radical , that will degrade the microorganism.

5. **Degradation**:

through acid hydrolases.



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Defects of leukocyte function

- **Defects of adhesion:**
  - Integrins LFA-1 and Mac-1 subunit defects lead to impaired adhesion, leukocytes adhesion deficiency (**LAD-1**)
  - Absence of sialyl-Lewis X, that binds to E- and P-selectin (**LAD-2**)
- **Defects of chemotaxis/phagocytosis:**
  - Microtubule assembly defect leads to impaired locomotion and lysosomal degranulation (Chediak-Higashi Syndrome)
  - Autosomal recessive, characterized by repeated infection

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Defects of leukocyte function

- **Defects of microbicidal activity:**
  - Deficiency of NADPH oxidase that generates superoxide, therefore no oxygen-dependent killing mechanism (chronic granulomatous disease) – X-Linked disorder

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