Inflammation
↳ Respone of VASCULARIZE TISSUE.
↳ TO 1. Infections 2. Tissue damage

STEPS of Inflammation ?
1. Recognition
2. Recruitment
3. Activation
4. Termination
5. Repair

Inflammation
Acute — Chronic

Table 3.2 Features of Acute and Chronic Inflammation

Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	Often severe and progressive
Local and systemic signs	Prominent	Less

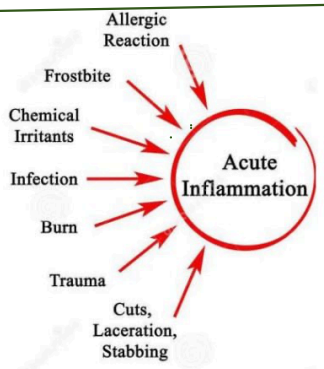
If the initial response fails to clear the stimulus,

Manifestation of Inflammation:-
1. Heat (calor) 2. Redness (Rubor)
3. Swelling (Tumor) 4. Pain (dolor)
5. Loss of function (Functio laesa)

Disorders	Cells and Molecules Involved in Injury
Acute	
Acute respiratory distress syndrome	Neutrophils
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, monocytes
Septic shock	Cytokines
Chronic	
Arthritis	Lymphocytes, macrophages; antibodies?
Asthma	Eosinophils; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes
Pulmonary fibrosis	Macrophages; fibroblasts

- هل الالتهاب دايماً كويس؟
1. Auto-Immune diseases ← طبيّ
2. Allergies → Against normally Harmless enviro. substance
3. Common chronic disease

لماذا العلاجات شغالة بزيادة مع طبيب لو نقصت؟
↓ Leukocytes, How ?
By Replacement of bone marrow
↳ Cancer
↳ Bone marrow Supressive therapies for ↳ Cancer ↳ Grafts



Phases →

Recognition

mediated by

1. Cellular Receptors for Microbes

Toll like Receptors (TLRs).

بس يتم التعرّف على المايكروب من خلالهم

ليتم فرز بروتينات

- Cytokines → Induces Inflammation
- Interferons → Antiviral Cytokines
- Cytokines & membrane Proteins → ↑ Lymphocyte Activation → ↑ Immune Response

2. Sensors For Cell Damage

- Cytosolic
- NOD-Like Receptors
- Recognize:
  - Uric Acid → A Product of DNA Damage
  - ATP → Released from damaged mitochondria
  - ↓ Intracellular K^+ → loss of ions because of Plasma membrane Injury
  - DNA

→ Activates Inflammasome ***
→ ↑ Production of (IL-1) → ↑ Recruitment of leukocytes → ↑ Inflammation

3. Circulating proteins

Complement system

Reacts against microbes

- Mannose binding lectin → Recognizes microbial sugars → ↑ Ingestion of microbes + ↑ Activation of Complement System
- Collectin → bind to microbes → ↑ microbes Phagocytosis

*** لقوا أنه ال Inflammasome موجود بكثير أمراض:

Inflammatory reactions to →

1. Urate crystals → Gout
2. Cholestrol crystals → Atherosclerosis
3. Lipids → Metabolic syndromes + Obesity Associated Diabetes
4. Amyloid → Brain Alzheimer
5. Calcium Pyrophosphate dihydrate → Pseudogout "Rhomboid"

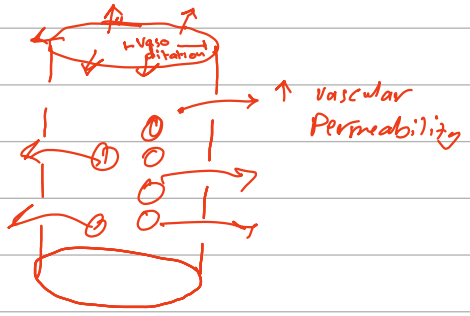
+ احيانًا بكونوا ال Cystosolic شغالين

بطلع spontaneous inflammation

الحل؟ IL-1 Antagonists

Reaction of Blood vessels in Acute Inflammation

Normal Blood vessel

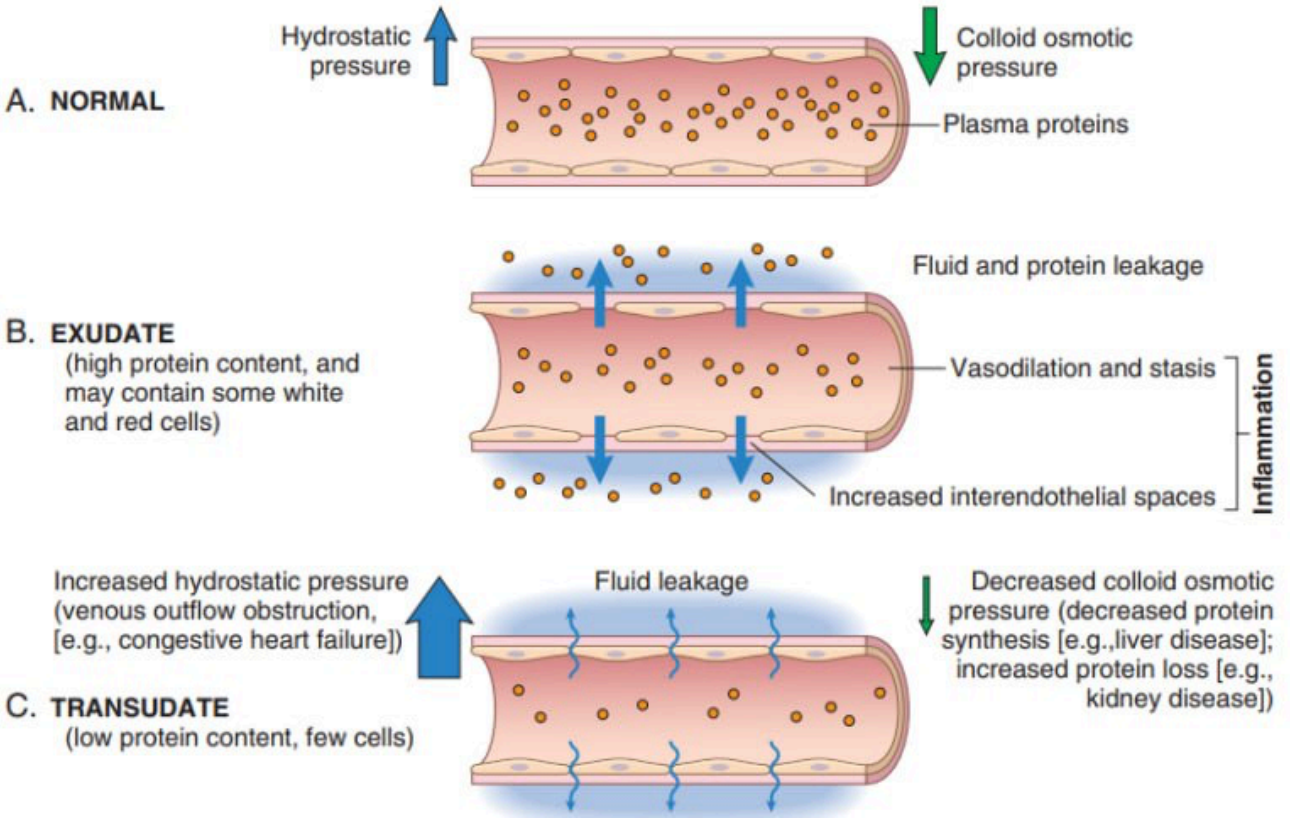


In inflammation

✓ Vasodilation by histamine acting on vascular smooth muscle
↳ ↑ blood flow → Heat + Redness (Erythema)

✓ ↑ permeability

✓ Slower blood flow → Vascular Congestion

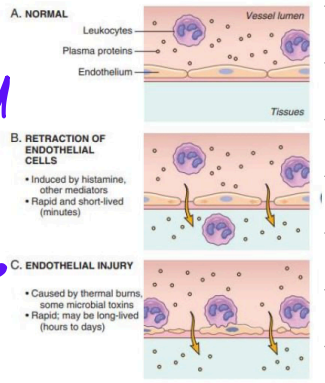


متذكرين الـ Permeability وانها تزيد؟ طيب كيف؟

3 Causes:

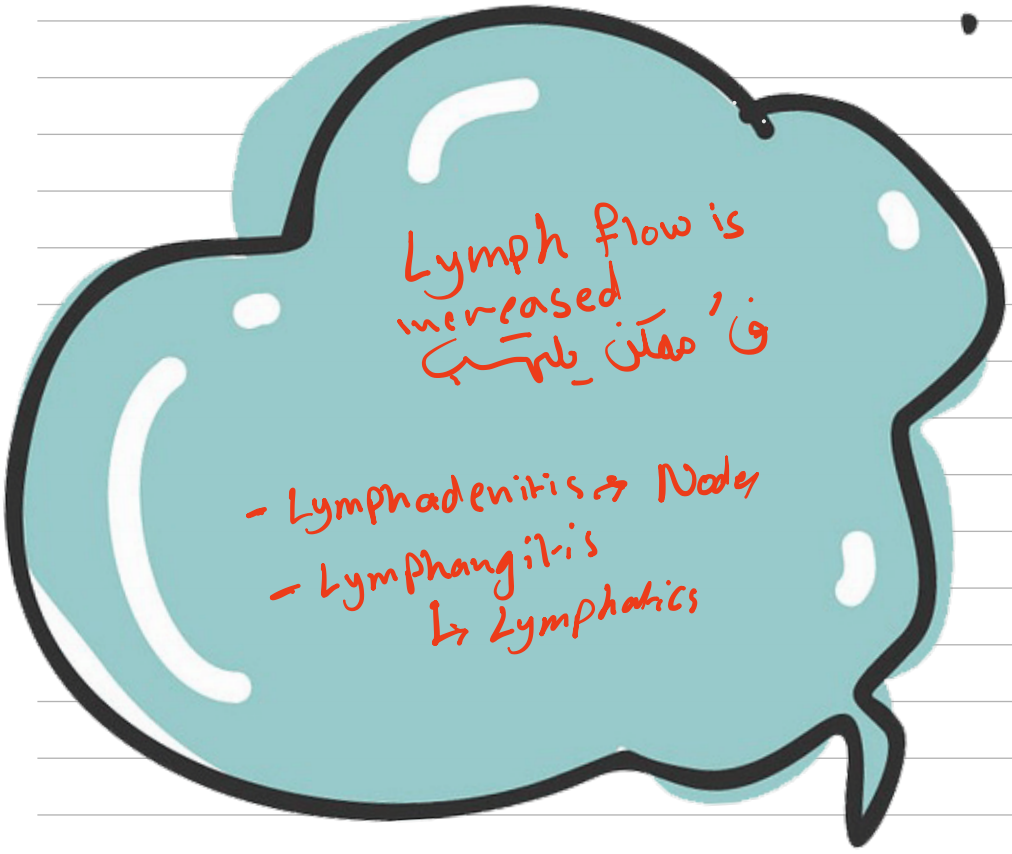
1. Retraction of endothelial cell → Transient & immediate

Histamine
Bradykinin
Leukotriens



2. Endothelial injury.

3. Transcytosis → ↑ transport of fluid and proteins

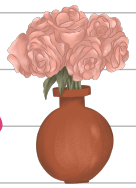


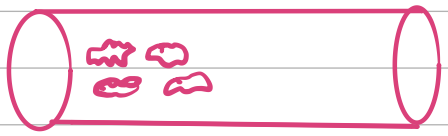
Recruitment → Mainly cells that are capable of phagocytosis

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	HSCs in bone marrow (in inflammatory reactions) Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Lifespan in tissues	Several days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
Cytokine production	Low levels or none	Major functional activity; requires transcriptional activation of cytokine genes
NET formation	Rapidly induced, by extrusion of nuclear contents	No
Secretion of lysosomal enzymes	Prominent	Less

why in Acute? → More Numerous
↳ They Respond Rapidly to Chemokines
↳ They may attach more firmly to adhesion molecules such as P & E selectin

Adhesion
Migration
Movement





Normal

1. Adhesion

Migration

Movement toward offending agent

1. Adhesion
   - A. Margination (Assume peripheral position)
   - B. Rolling (Bind & detach)
   - C. Adhere firmly

Adhesion molecules

Selectin

- Weak interaction
- Found on both: A. Leukocytes B. Endothelium
- 3 members
  - E-selectin → CD62E → on Endothelial cells
  - P-selectin → CD62P → Platelets & Endothelium
  - L-selectin → CD62L → Leukocytes

The endothelial selectins are expressed at low levels on unactivated endothelium, they are upregulated after stimulation by cytokines and other mediators.

- Therefore, binding of leukocytes is largely restricted to the endothelium at sites of infection or tissue injury (where the mediators are produced).
- These weak selectin-mediated rolling interactions slow down the leukocytes and give them the chance to recognize additional adhesion molecules on the endothelium

Integrin

→ Leukocyte surface proteins.

بالعادة بكونوا ع الـ Leukocytes بـ
شكل Low affinity وما بمسكوا
بالـ Ligands ولكن عند الـ Rolling بصيرلهم
Conformational changes وبتحولوا
لـ High affinity وبصيروا يمسكوا
بالـ Endothelial cells، طيب الـ Endothelial
شو وين تتجيب الـ Ligands ؟
يُفرز بفعل الـ IL-1 & TNF

INTEGRIN WITH THEIR LIGANDS:

- Intercellular adhesion molecule-1 (ICAM-1), which binds to the integrins (LFA-1)
- Macrophage-1 antigen (Mac-1): ICAM-2.
- VCAM-1 which binds to the integrin : VLA-4.
- The leukocytes stop rolling, and engagement of integrins by their ligands delivers signals leading to cytoskeletal changes that arrest the leukocytes and firmly attach them to the endothelium

Migration

→ Driven by chemokines produced in extravascular tissues

- Squeezing between cells at intercellular junctions.
- Platelet endothelial cell adhesion molecule-1 (PECAM-1)*

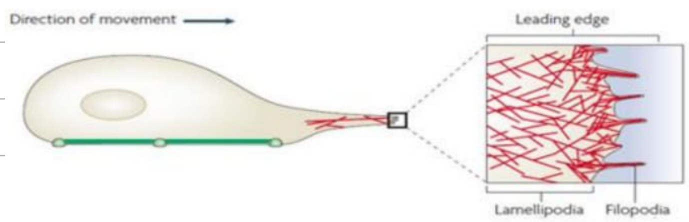
→ After traversing the endothelium → They pierce the basement membrane BY Collagenases

Chemotaxis

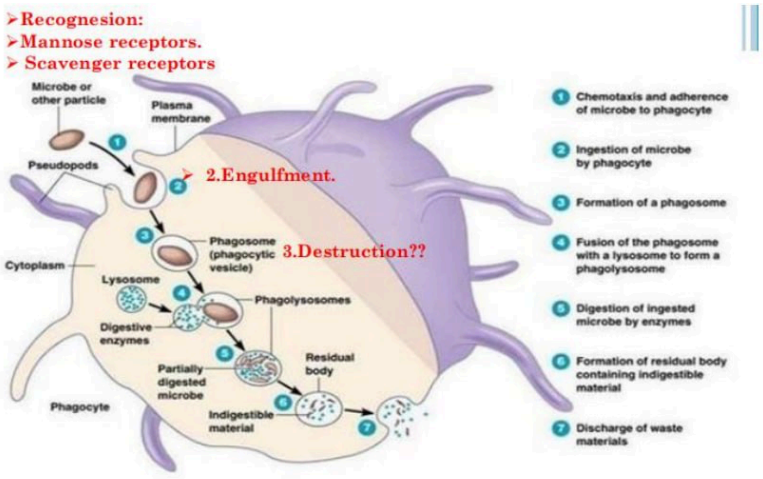
→ بعد ما يطلعوا من الأوعية لازم يروحوا للنسيج المتضرر. وتسحبهم الـ Chemical gradient يعني بدهم Chemoattractant

Exogenous and endogenous substances can act as chemoattractants, including the following:

1. Bacterial products.
2. Cytokines, especially those of the chemokine family.
3. Components of the complement system, particularly C5a .
4. Products of the lipoxygenase pathway of arachidonic acid (AA) metabolism, particularly leukotriene B4 (LTB4)



Activation → Phagocytosis
→ Intracellular killing

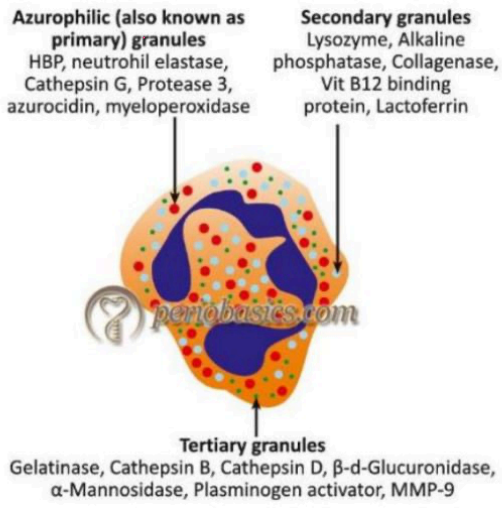


Destructive mechanisms

1. Respiratory burst → Rapid release of
   - → ROS (Reactive Oxy. Species)
   - → Superoxide Anion
   - → H_2O_2 (Hydrogen peroxide)

2. Nitric oxide
   - → eNOS → Endothelial → Maintain Vascular tone
   - → nNOS → Neuronal → Neurotransmitter
   - → iNOS → Microbial killing → Expressed when macrophages are activated by cytokines (IFN-γ) or microbial products.

3. Granule enzyme → Neutrophils → Antimicrobial proteins + Enzymes



- Protease are Controlled by Anti-Proteases in the serum & tissue fluids
- α1-anti-trypsin inhibits neutrophil elastase

1. Pseudomonas → Neutrophils ← ستشلات !
for days

2. Viral → Starts with Lymphocyte,

3. Allergy → Eosinphils

Leukocytes are important causes of injury to normal cells and tissues under several circumstances:

- As part of a normal defense reaction against infectious microbes, in some infections that are difficult to eradicate, such as TB, hepatitis.
- In certain autoimmune diseases.
- In allergic diseases, including asthma

Termination

1. Degradation of mediators.
2. Neutrophils apoptosis.
3. Stop signals:

- A switch in the type of arachidonic acid metabolite produced, from proinflammatory leukotrienes to anti-inflammatory lipoxins.
- Liberation of anti-inflammatory cytokines, including transforming growth factor-β (TGF-β) and IL-10, from macrophage