RECOGNITION OF MICROBES AND VASCULAR CHANGES OF ACUTE INFLAMMATION

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Learning objectives:

- By the end of this lecture student should be able to
- Describe recognition of microbes and damaged tissues by different cells.
- Describe vascular events of acute inflammation
- Discuss pathogenesis of vascular changes
- Discuss factors responsible for these changes

Recognition of Microbes and Damaged Cells

- Initiating step in inflammatory reactions.
- Different cellular and circulating proteins are responsible for recognition process.

1. **Toll-like receptors (TLR)**

- Present on epithelial cells, dendritic cells, macrophages an other leukocytes.

- These receptors can be present at different levels.

a. Cell surface

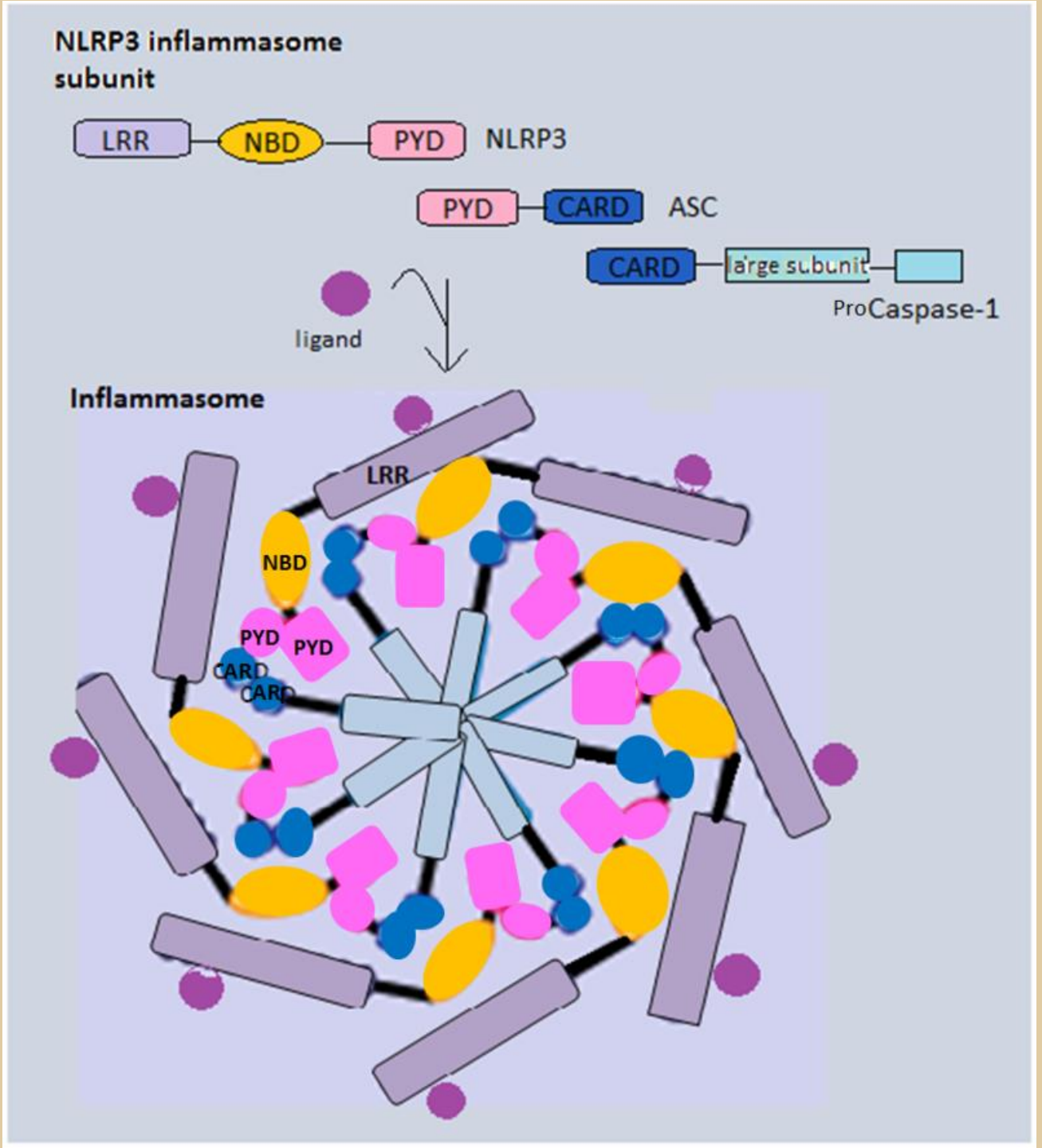
b. Endosomes

c. Cytosol

- On attachment with microbes these receptors initiate production of different cytokines and mediators.

2. **Sensors of cell damage.**

- All cells have cytosolic receptors, such as NOD-like receptors (NLRs), that recognize molecules liberated as a result of cell damage.
- Molecules include uric acid, ATP, even DNA itself.
- These molecules after attachment with NOD like receptors activate a protein complex Inflammasome.


NLRP3 inflammasome subunit
LRR
NBD
PYD
NLRP3
PYD
CARD
ASC
CARD
large subunit
ProCaspase-1
ligand
Inflammasome
LRR
NBD
PYD
PYD
CARD
CARD

- Inflammasome causes production of IL1.
- IL1 recruits leukocytes to the site of damage.

3. **Other cellular receptors**

- Present at the surface of leukocytes which recognize the organisms coated by antibodies or complement fragments (C3b).
- It is called opsonization.

4. **Circulating proteins**

- They attach to certain molecules of microorganisms.
- Manose binding lectin binds with manose residues (sugar residues) of microorganisms and thus activate complement system.

Vascular changes of inflammation

- Vascular changes are increase in blood flow and increase in vascular permeability.
- Meant to deliver leukocytes and proteins to the site of inflammation.

A. **Vascular Changes:**

a) **Changes in Vascular Caliber and Flow:**

- Changes in blood vessels begin rapidly after infection or injury.

i. **Transient vasoconstriction:**

- First there is vasoconstriction (lasting only for seconds).

- Occurs in mild skin injury
- Due to neurogenic and chemical mediator systems.

ii. **Arteriolar vasodilation:**

- After that arteriolar vasodilation occurs, resulting in locally increased blood flow.

- Opening up of new capillary beds (proliferation)
- Expansion of vascular bed.
- Vasodilation occurs under the influence of histamine, bradykinin and leukotriens(mainly histamine).

- This vascular expansion is the cause of the redness (erythema) and warmth seen in acute inflammation.
- Vasodilation immediately followed by increased vascular permeability.

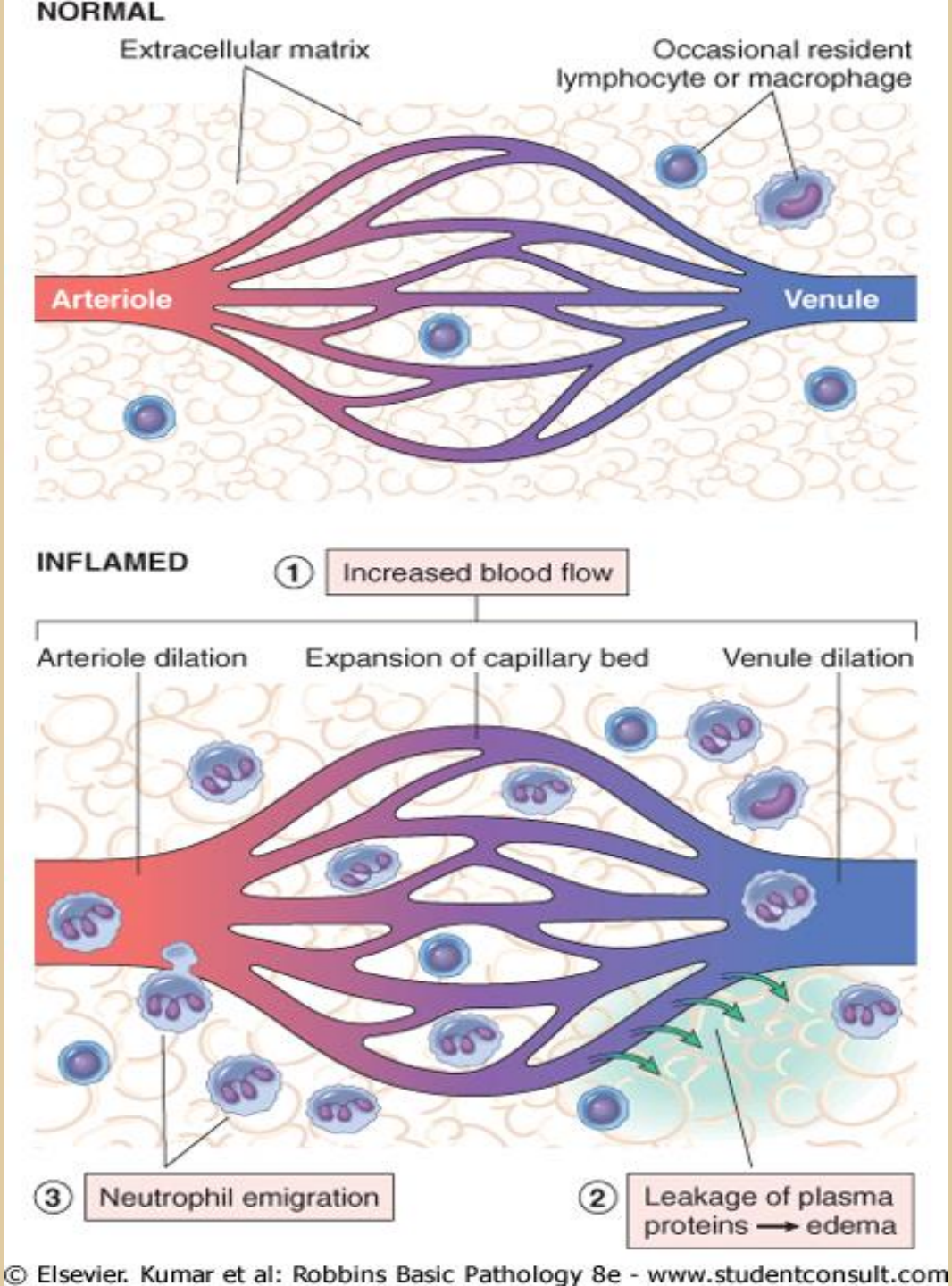
- Small blood vessels/microvasculature (vennules). become more permeable
- Protein-rich fluid moves into the extravascular tissues.
- This increases blood viscosity and slowing the circulation, a process called **stasis.**

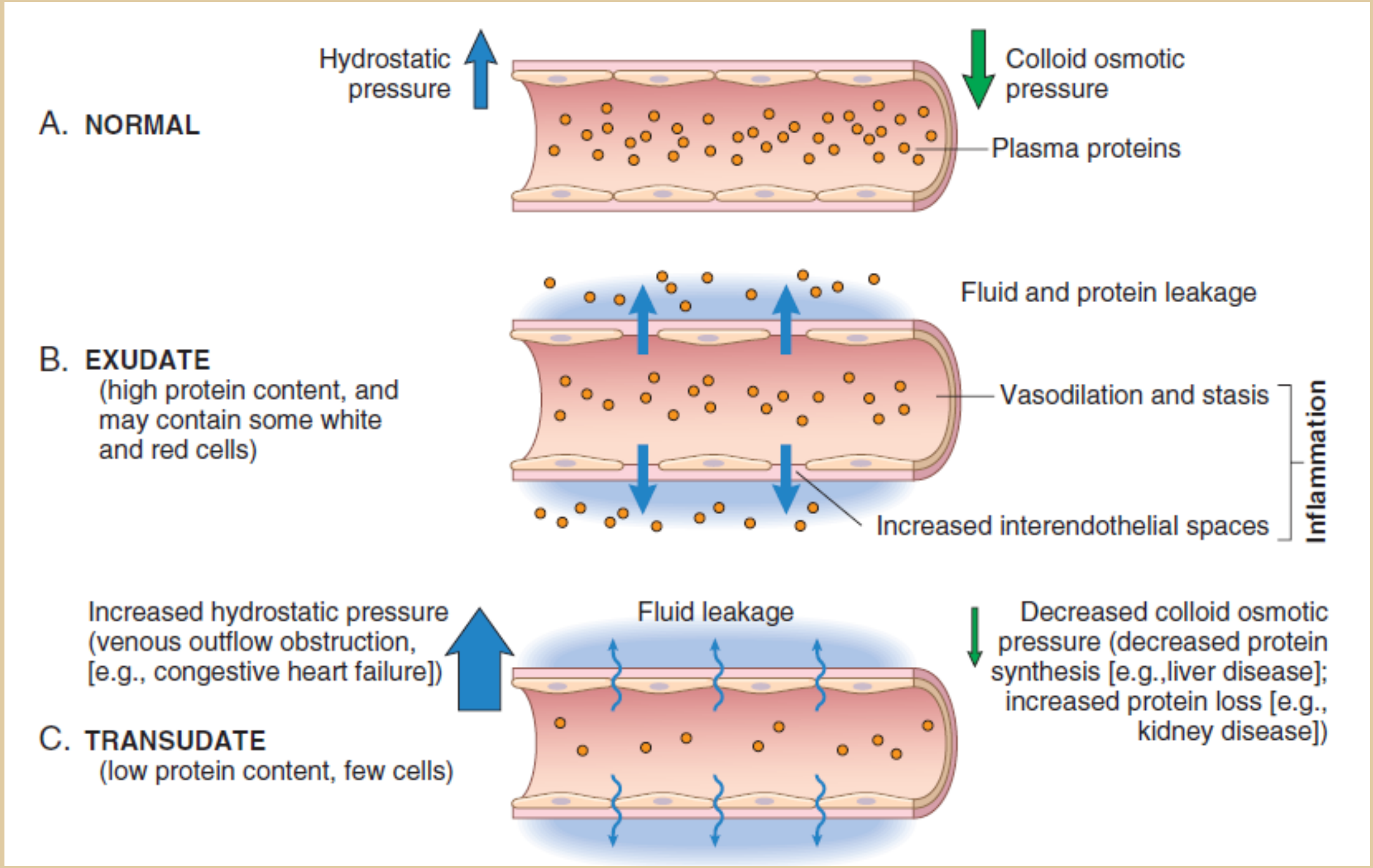
- Stasis leads to congestion and local redness in the tissue.
- Stasis also helps the leukocytes to migrate outwards.

b) **Increased Vascular Permeability**

- In the early phase of inflammation, arteriolar vasodilation and increased volume of blood flow lead to a rise in intravascular hydrostatic pressure.
- This results in movement of fluid from capillaries into the tissues.

- This fluid is called a transudate.
- It is an ultrafiltrate of blood and contains little protein.
- Later on when vascular permeability increases it allows the movement of protein-rich fluid and even cells.
- This is called an exudate.




A. NORMAL
Hydrostatic pressure
Colloid osmotic pressure
Plasma proteins
B. EXUDATE
(high protein content, and may contain some white and red cells)
Fluid and protein leakage
Vasodilation and stasis
Increased interendothelial spaces
Inflammation
C. TRANSUDATE
(low protein content, few cells)
Increased hydrostatic pressure (venous outflow obstruction, [e.g., congestive heart failure])
Fluid leakage
Decreased colloid osmotic pressure (decreased protein synthesis [e.g.,liver disease]; increased protein loss [e.g., kidney disease])

- Later on due to increase in vascular permeability protein and leukocytes migrate outward.
- The loss of protein-rich fluid reduces the intravascular osmotic pressure and increases the osmotic pressure of the interstitial fluid.

- The net result is outflow of water and ions into the extravascular tissues.
- Fluid accumulation in extravascular spaces is called edema; the fluid may be a transudate or exudate

Properties	Transudate	Exudate
Main causes	1. Increased hydrostatic pressure. 2. Decreased colloid osmotic pressure	Inflammation
Appearance	Clear	Cloudy
Specific gravity	<1.012	>1.020
Protein content	High	Low
WBCs	Not present	Present
Examples	Tuberculous peritonitis	Heart failure

- Two mechanisms are responsible for increased vascular permeability.

i. **Contraction of endothelial cells:**

- It is the most important mechanism
- Occurs due to histamine, bradykinin and leukotriens.
- Occurs immediately after mediator release.

- Lasts for 15-30 minutes.
- In some mild injuries permeability increases after 2-12 hours and may last for even days.
- Sunburn is a classic example

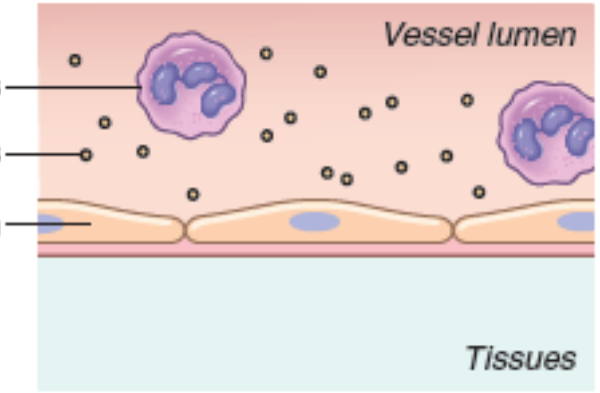
ii. **Endothelial injury:**

iii. Endothelial injury leads to endothelial cell necrosis and detachment.

- Occurs in injuries caused by burns, microorganisms and their toxins.
- Leakage of fluid starts immediately and lasts for hours until vessel repaired by thrombosis.

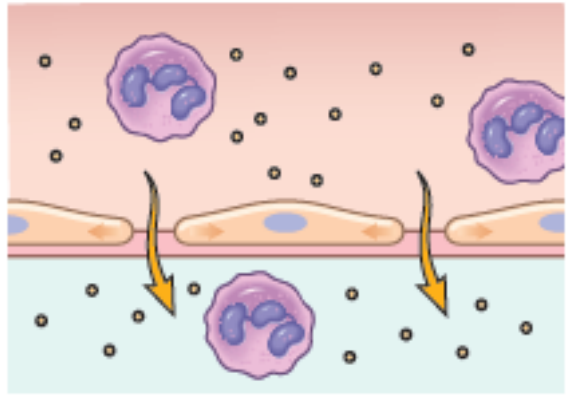
- Neutrophils that adhere to the endothelium during inflammation may also injure endothelial cells.
- Usually both mechanisms operate at the same time.

A. **NORMAL**



B. **RETRACTION OF ENDOTHELIAL CELLS**

- Induced by histamine, other mediators
- Rapid and short-lived (minutes)



C. **ENDOTHELIAL INJURY**

- Caused by thermal burns, some microbial toxins
- Rapid; may be long-lived (hours to days)

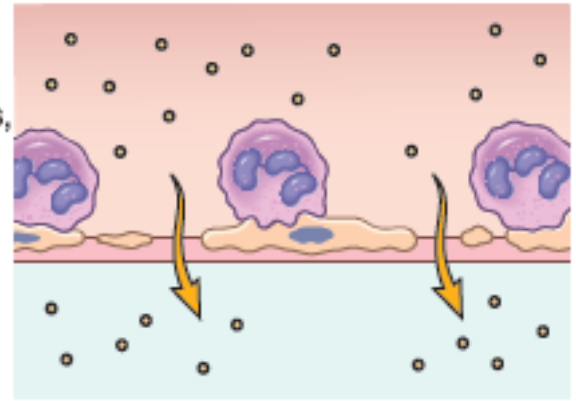
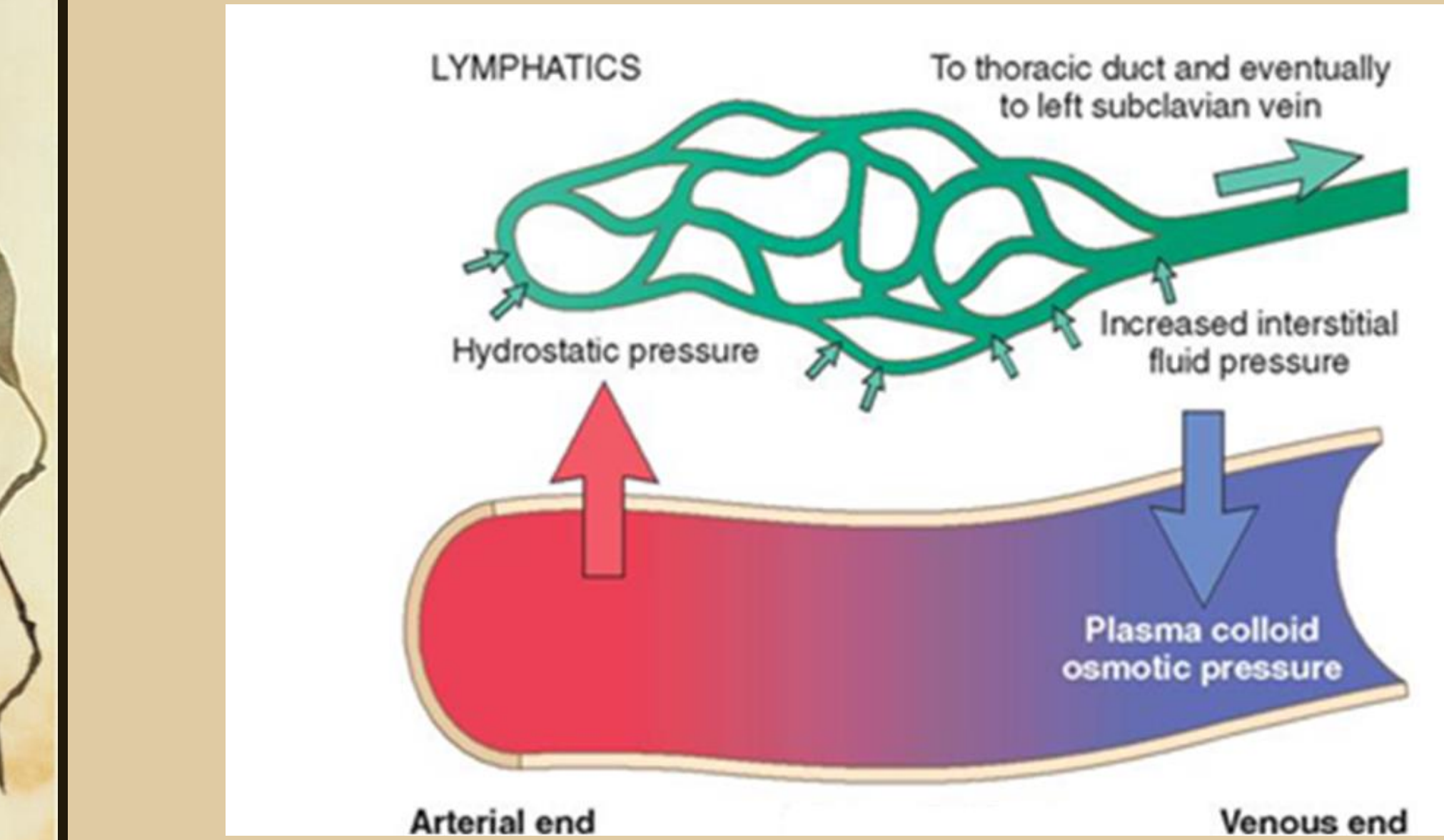


Figure 3.3 Principal mechanisms of increased vascular permeability in inflammation and their features and underlying causes.

- Lymphatic vessels also take part in inflammation.
- Normally lymphatics drain the small amount of extravascular fluid that seeps out of capillaries.
- In inflammation, lymph flow is increased and helps drain edema fluid accumulated due to increased vascular permeability.


LYMPHATICS
To thoracic duct and eventually to left subclavian vein
Hydrostatic pressure
Increased interstitial fluid pressure
Plasma colloid osmotic pressure
Arterial end
Venous end

- Lymphatic vessels, like blood vessels, proliferate during inflammatory reactions to handle the increased load.
- The lymphatics may become inflamed due to extension of inflammatory process (lymphangitis).

- Draining lymph nodes may also become inflammed(lymphadenitis).
- Also known as reactive or inflammatory lymphadentis.
- The presence of red streaks near a skin wound in a bacterial infection represent inflamed lymphatics (lymphadenitis).

THANK YOU