Pathology

Second Year - First Semester Course

Rahma Marie

Lecture 8

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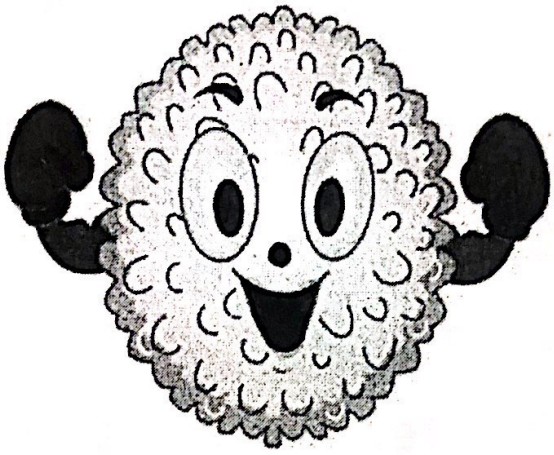
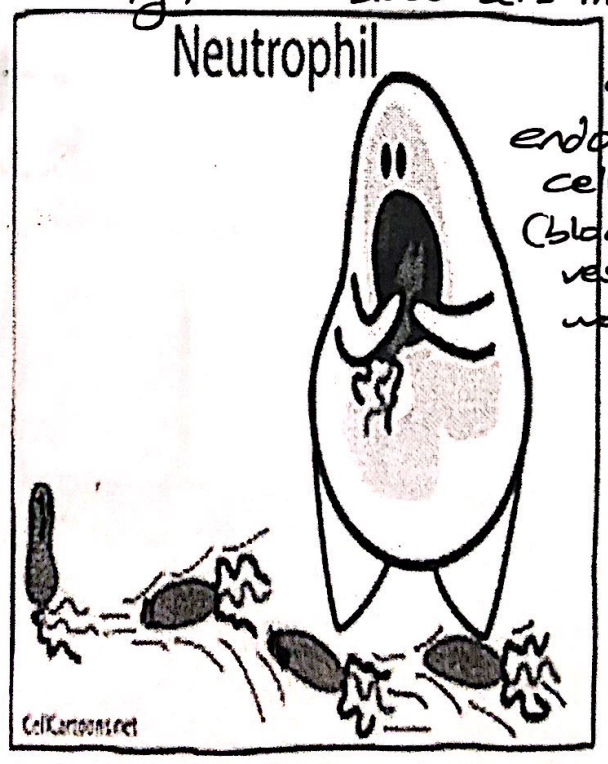
Acute Inflammation 2



① Vasular events (at capillery level)

② Cellular Events : interaction and movement between cells, mainly, white blood cells in the blood and endothelium cells (blood vessel walls)

- An important function of the inflammatory response is to deliver leukocytes to the site of injury and to activate them.
- Leukocytes ingest offending agents, kill bacteria and other microbes, and eliminate necrotic tissue and foreign substances. Tissue repair follows.



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Leukocyte Recruitment

WBC (blood vessels) → site of inflammation

The sequence of events in the recruitment of leukocytes consists of :

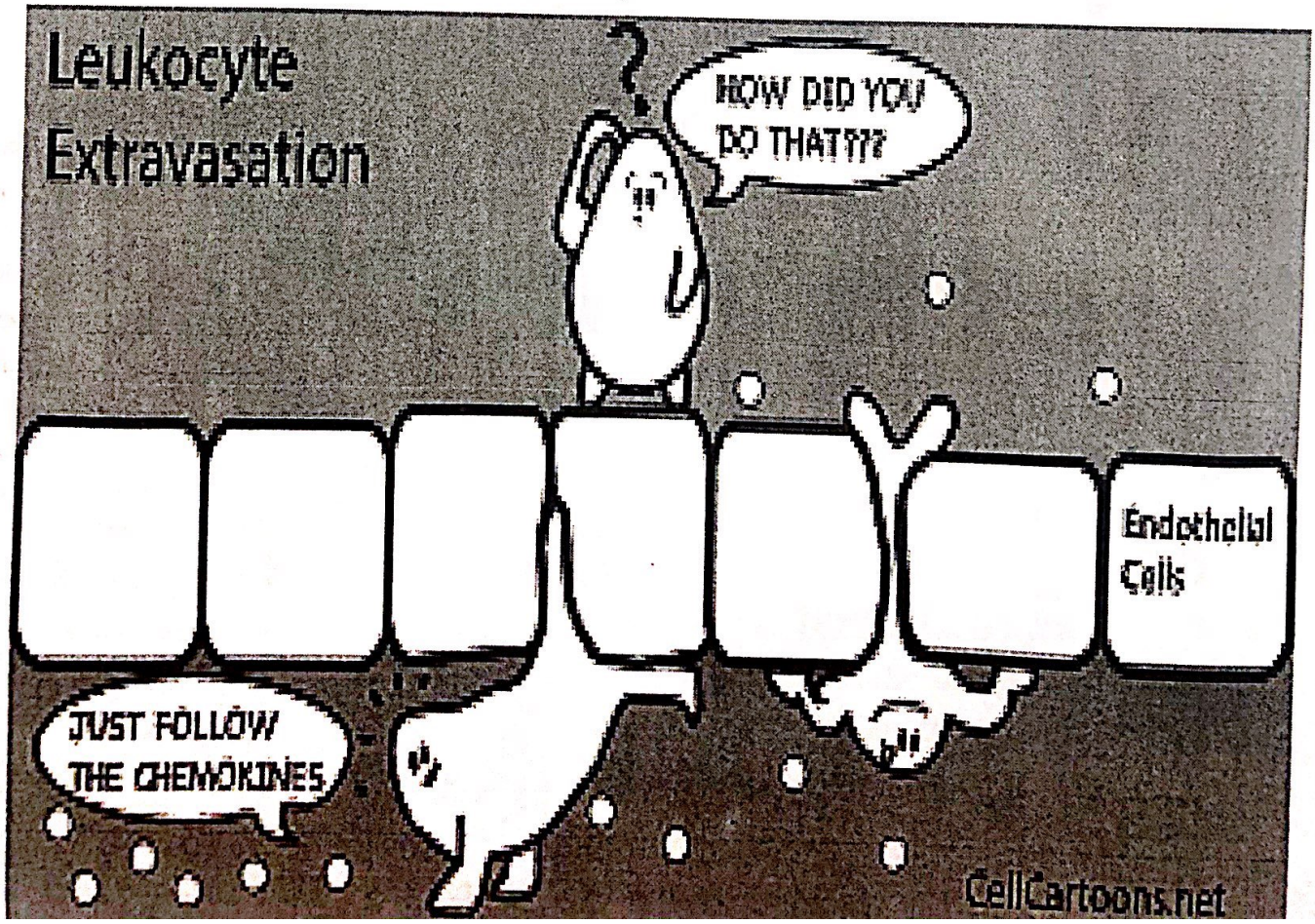
(1) Margination and rolling along the vessel wall.

(2) Firm adhesion to the endothelium. mainly through integrins.

(3) Transmigration between endothelial cells

(4) Migration in interstitial tissues toward a chemotactic stimulus

Blood slows down by vasodilation, allowing these cells to exit through the walls to the site of injury. Slowing down of the blood in the vessels leads to margination (leukocytes along the margin of the blood vessel try to migrate to the site of inflammation/tissue). They attach themselves firmly to the blood vessel. They leave the vessel to head to the site of injury.



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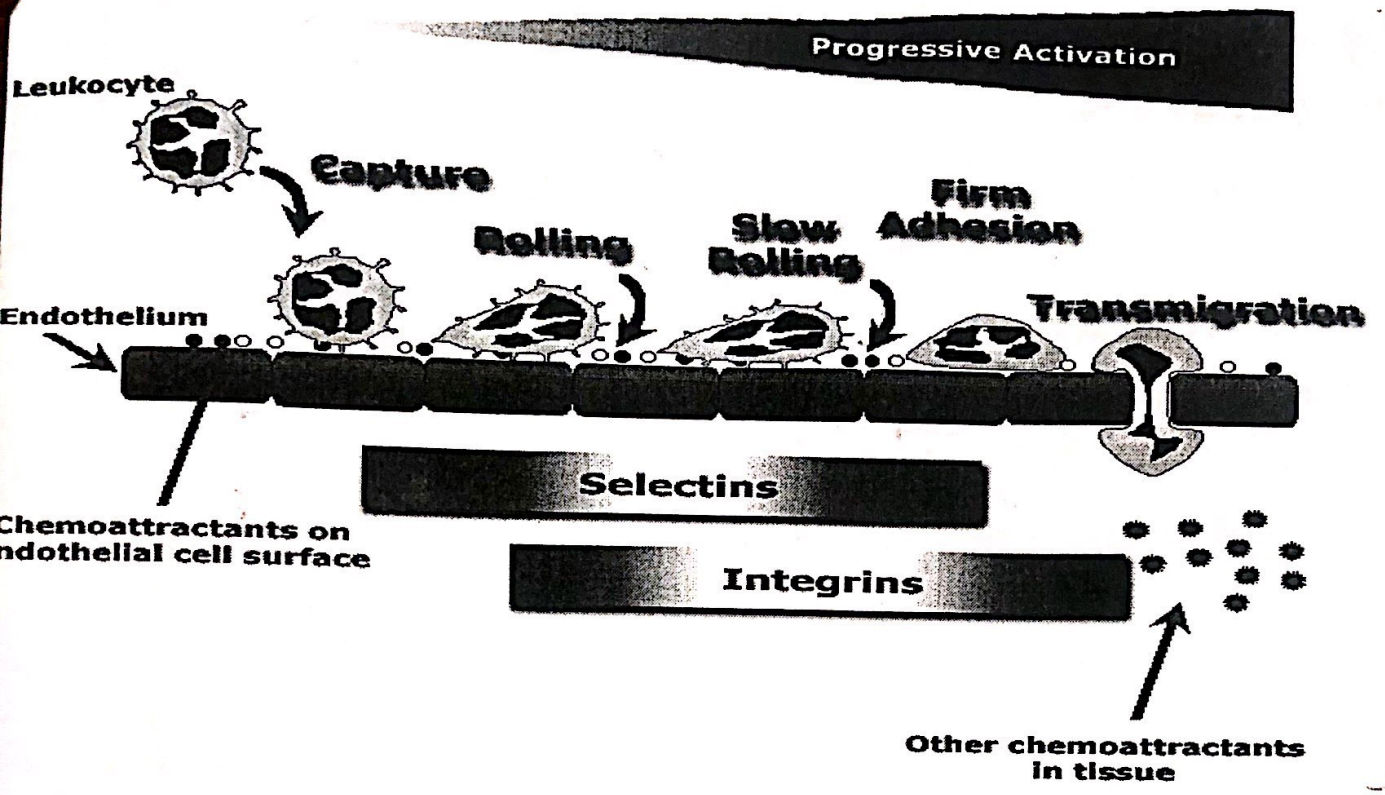
The Process of Extravasation of Leukocytes



- Different molecules play predominant roles in different steps of this process:

- Selectins in rolling.
- Integrins in firm adhesion.
- CD31 (PECAM-1) in transmigration

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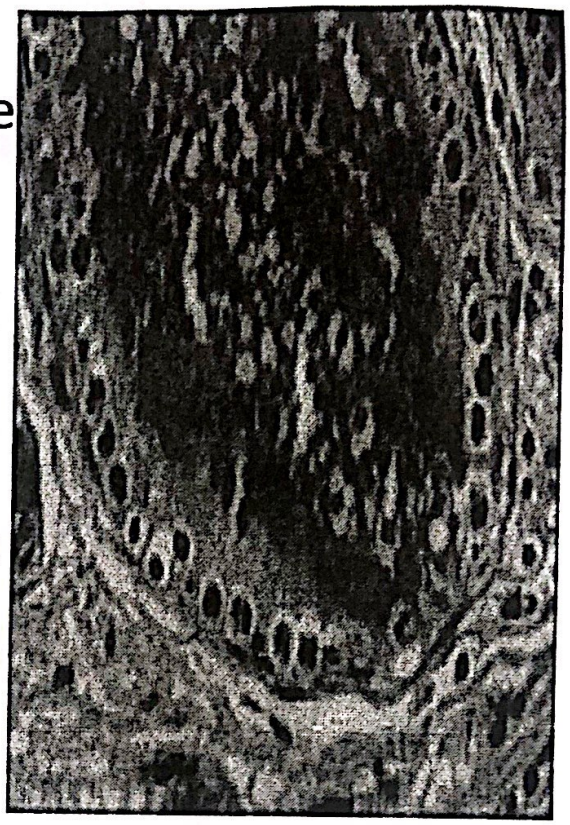
1- Margination and Rolling

- ***Margination:*** The process of **leukocyte accumulation** at the (edges) periphery of vessels
- Subsequently, leukocytes tumble on the endothelial surface, **transiently loose (bonding) sticking** along the way, in a process **called *rolling*.** receptors attach and let go repeatedly = rolling
- The weak and transient adhesions involved in rolling are mediated by **the *selectin*** family.



Rolling : by selectins , Adhesion : by integrins , Integrins : by chemokines

(selectins)

The three members of this family are:

present on endothelial cells
- **E-selectin :** expressed on endothelial cells
- **P-selectin** : present on endothelium and platelets
- **L-selectin:** on the surface of most leukocytes

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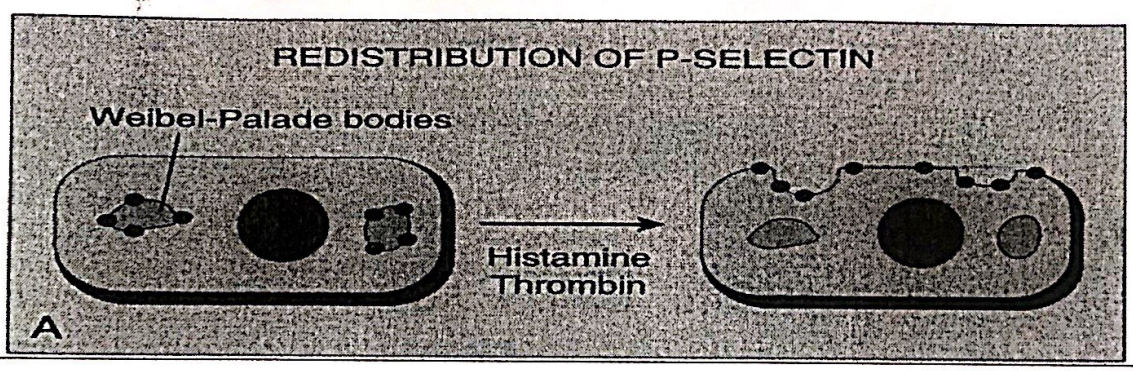
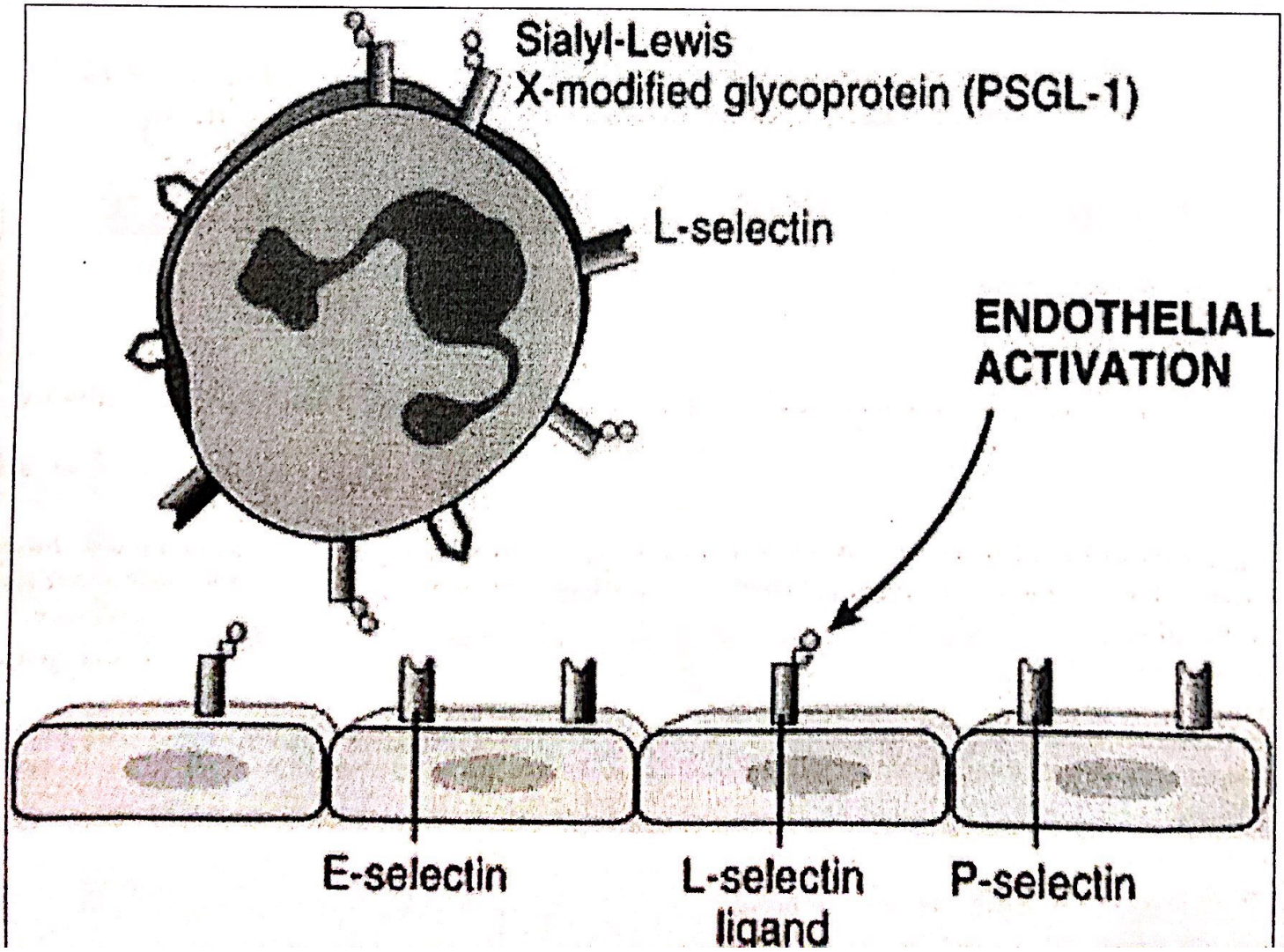
Selectins

- E- selectins are typically expressed at low levels or not present at all on normal cells.

- They are up-regulated after stimulation by specific mediators such as IL-1 and TNF.

- **P-selectin** In **nonactivated endothelial cells** is found primarily in intracellular **Weibel-Palade bodies**. Within minutes of exposure to chemokines, P-selectin is distributed to the cell surface.





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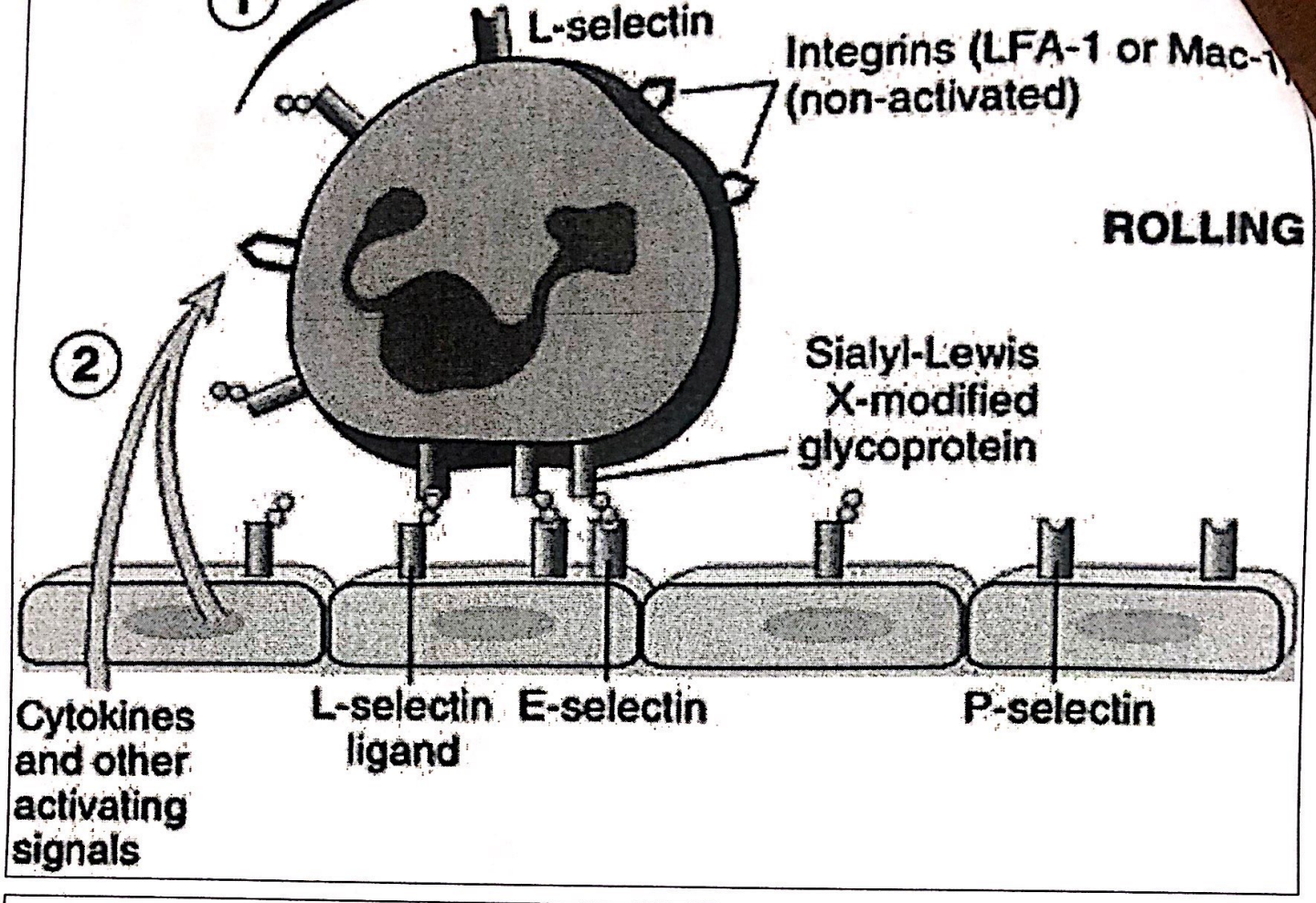


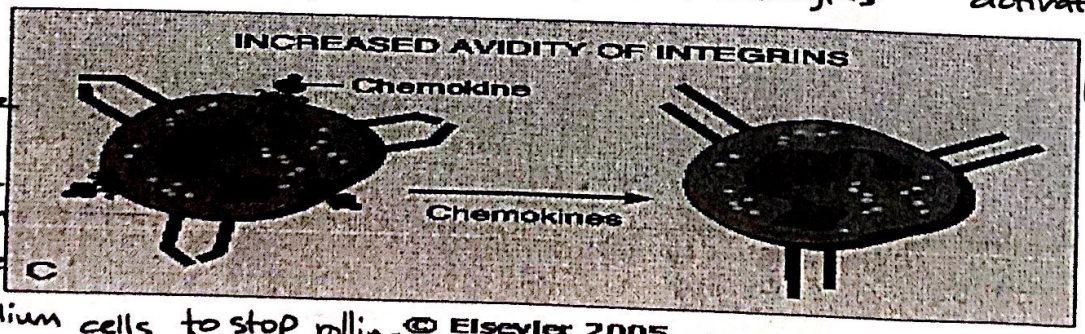
2- Firm *adhesion* : stops WBC rolling

- Mediated by **integrins** expressed <u>on leukocyte cell surfaces interacting with their ligands on endothelial cells</u>.
  - cells stop moving and go through the spaces between endothelial cells

- Integrins are activated by chemokines. → released at site of injury

chemokines bind to receptors on leukocytes and they alter the shape of the proteins on surface of leukocytes. → stimulate integrins' activation on the surface of leukocytes

Integrins bound to the surface of WBC bind to the receptors on the surface of endothelium cells to stop rolling.



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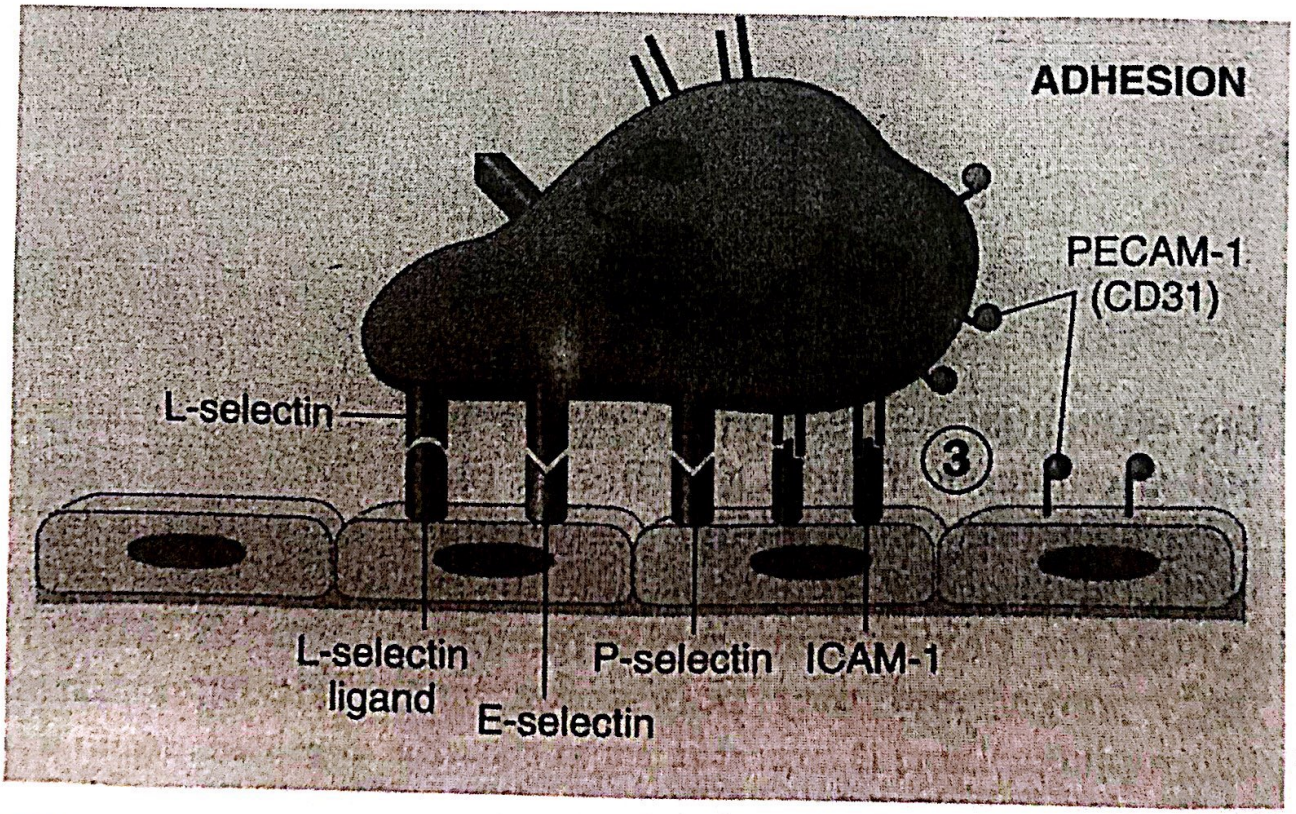
- The ligands for integrins found on endothelial cell surface include:
- **ICAM-1** (intercellular adhesion molecule 1)
- **VCAM-1** (vascular cell adhesion molecule 1)

- ***The net result is stable adhesion of leukocytes to endothelial cells.***

not transient anymore!

Firm Adhesion via Integrin -ICAM Interactions



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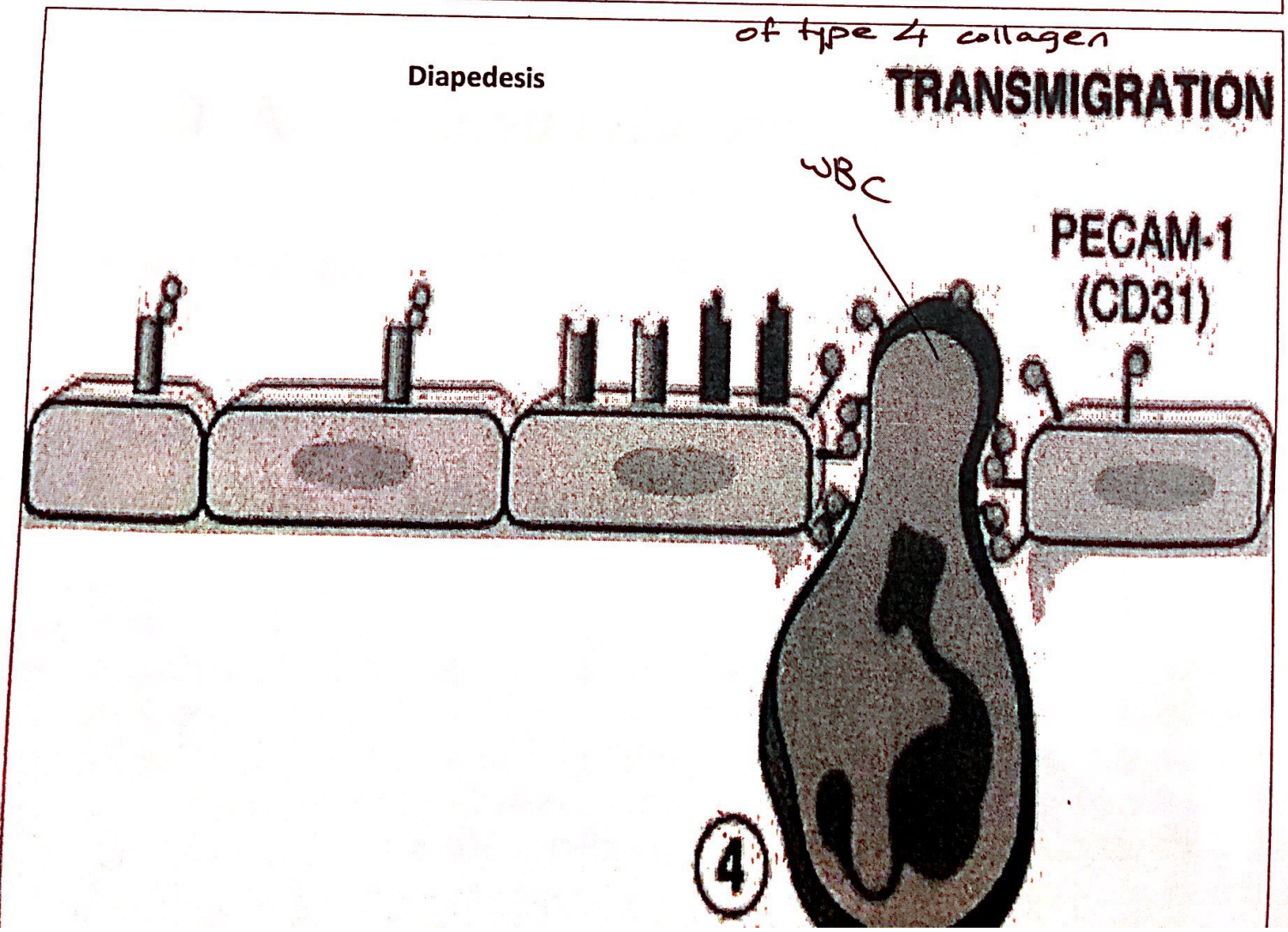
3- Transmigration of leukocytes

- leukocytes migrate through the vessel wall primarily by squeezing between cells at intercellular junctions (**diapedesis**). → like bacteria/ movement. they form foot like structures
- **PECAM-1 (**platelet endothelial cell adhesion molecule 1, also **called CD31)**, mediates the binding events needed for leukocytes to traverse the endothelium. through the cytoskeleton
- Leukocytes secrete collagenase that enable them to cross vascular basement membranes.

CD31 : one of the receptors on endothelium cells
collagenase : causes lysis of the basement membrane that is formed of type 4 collagen



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Endothelial and Leukocyte Adhesion Molecule Interactions

ENDOTHELIUM	WBC	FUNCTION
• P & E-selectins	Sialyl-Lewis X	Rolling
• GlyCAM-1, CD34	L-selectin	Rolling
• VCAM-1, ICAM1	Integrin	Adhesion
• CD31 (PECAM-1)	CD31(PECAM1)	Transmigration

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WBC → interstitial space chemotaxis → site of injury

4- Migration in interstitial tissue toward chemotactic stimulus

- Chemotaxis: leukocytes move toward sites of infection or injury along a chemical gradient .

chemokines released at time of inflammation

- Both **exogenous and endogenous substances** can be chemotactic for leukocytes:
  - (1) **bacterial products,** particularly peptides with *N*-formyl-methionine termini
  - (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 B_4 (**LTB_4**)

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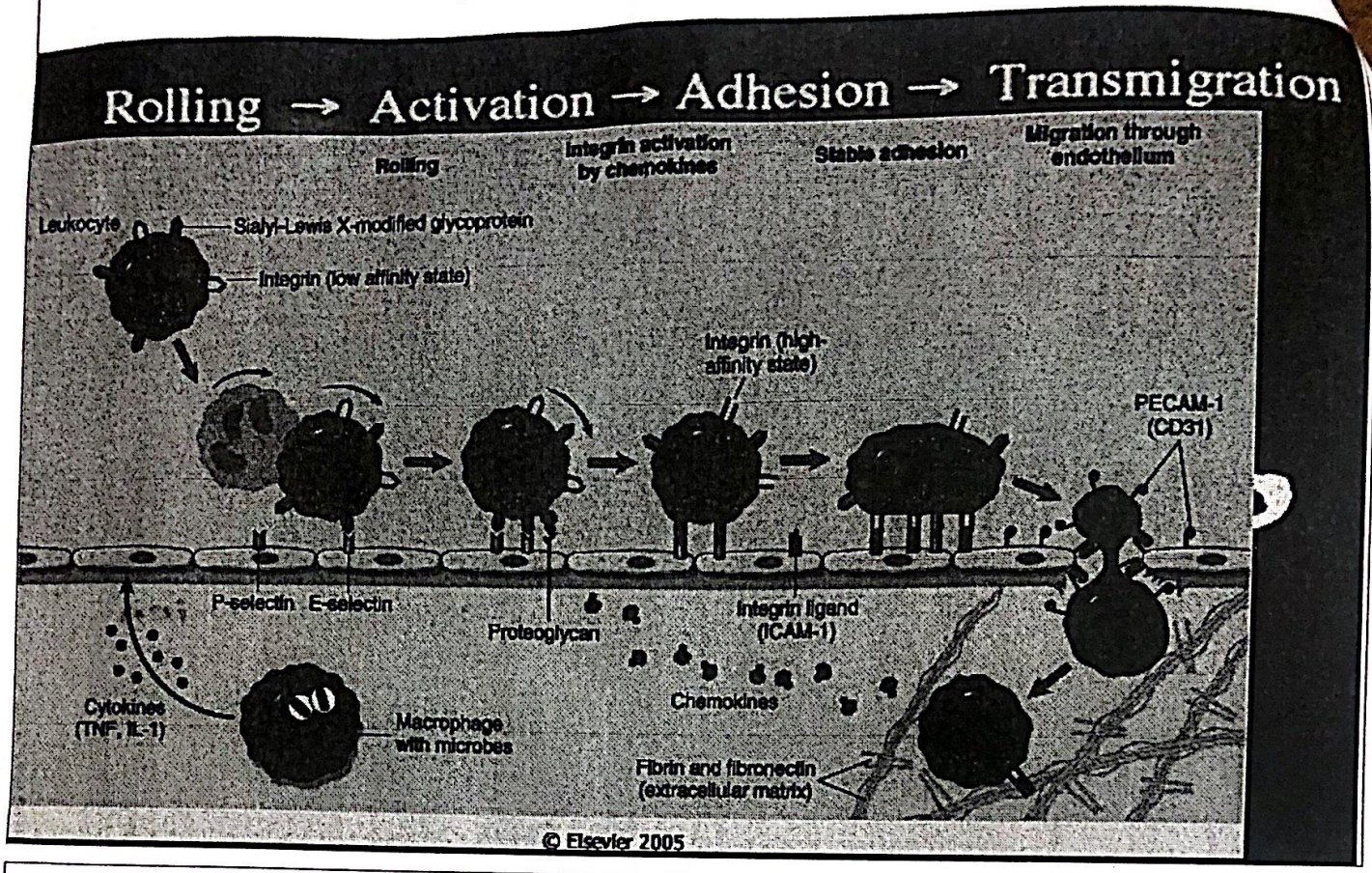
Leukocyte Cellular Events



Nature of leukocyte infiltrates in acute inflammatory reactions

- In **most forms of acute inflammation,** ***neutrophils*** *predominate in the inflammatory infiltrate during the first 6 to 24 hours and are replaced by monocytes in 24 to 48 hours.*

  → as macrophages to engulf the debri

- Neutrophils are short-lived-they die by apoptosis and disappear within 24 to 48 hours-while monocytes survive longer. , more efficient

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