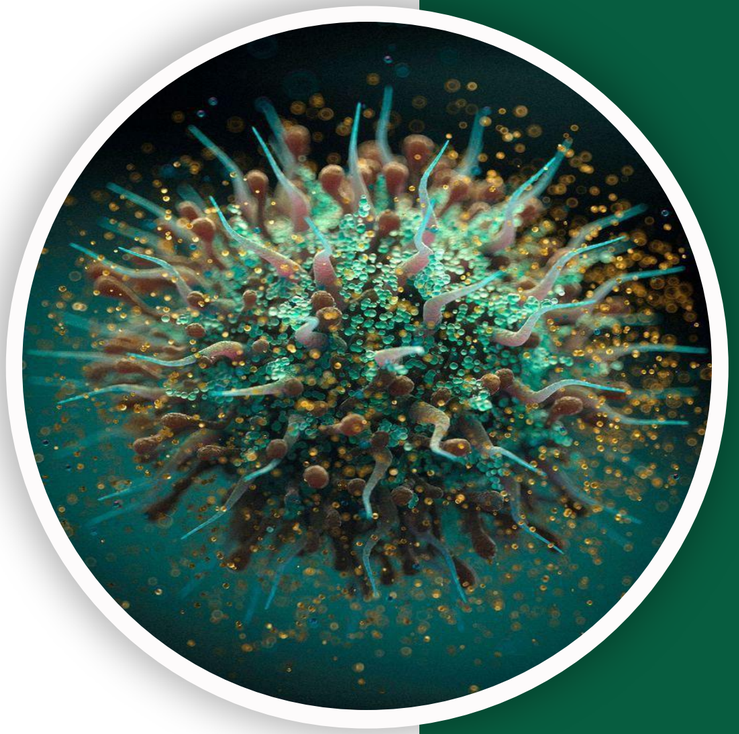
بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pathology | Lecture 7

Inflammation Pt.2



Written by : Rama Ejueidi
Malak Mksosi

Reviewed by : Lana Alyaseen

Inflammation and Repair

Mousa Al-Abbadi, MD, FCAP,CPE, CPHQ,FIAC
Professor of Pathology & Cytopathology
University of Jordan
College of Medicine
2024

Lecture 2

ACUTE INFLAMMATION

Generally, it is called the initial vascular phase ; it happens after the recognition of the offending agents either through DAMPs (Damage-Associated Molecular Patterns) or PAMPs (Pathogen Associated Molecular Patterns – through Toll-like R receptors (TLRs))

- 3 major components (multiple things happen to the blood vessels)

B V dilatation

Increased V permeability

Emigration of WBCs

B V dilatation

Blood vessel dilatation, in the book it is mentioned that when you are for example pricked by a pin (تتعرض لوخزة دبوس) the first few seconds there will be immediate , transient and quick vasoconstriction – ignore these few seconds –

Dilation happens through multiple mediators, the most significant one is Histamine that explains why when you have a cold you take antihistamine to reduce the symptoms

Histamine is the most important blood vessel dilator in the vascular (initial) phase

Serotonin is also a mediator specifically in brain but mainly in animals

Increased V permeability

If it is a mild inflammation there will be transient with a slight swelling . However, if the offending agents last longer there will be more damage to the blood vessel wall and the vascular permeability will increase.

Increasing in permeability depends on the severity of the offending agent and the nature of inflammation

So the (BV dilatation) phase and (increased V permeability) phase are called the initial vascular phase followed be (recruitment/emigration of WBCs) phase

Emigration of WBCs

Recruitment of white blood cells from the intravascular compartment to the extra vascular component (interstitial)

NOTE: each phase (step) has many mediators but there are important mediator foe each phase

Summary

General Features and Causes of Inflammation

- Inflammation is a beneficial host response to foreign invaders and necrotic tissue, but also may cause tissue damage.
- The main components of inflammation are a vascular reaction and a cellular response; both are activated by mediators that are derived from plasma proteins and various cells.
- The steps of the inflammatory response can be remembered as the five Rs: (1) recognition of the injurious agent, (2) recruitment of leukocytes, (3) removal of the agent, (4) regulation (control) of the response, and (5) resolution (repair).
- The causes of inflammation include infections, tissue necrosis, foreign bodies, trauma, and immune responses.
- Epithelial cells, tissue macrophages and dendritic cells, leukocytes, and other cell types express receptors that sense the presence of microbes and necrotic cells. Circulating proteins recognize microbes that have entered the blood.
- The outcome of acute inflammation is either elimination of the noxious stimulus followed by decline of the reaction and repair of the damaged tissue, or persistent injury resulting in chronic inflammation.

Lumen contains fluids (blood) , white blood cells and proteins

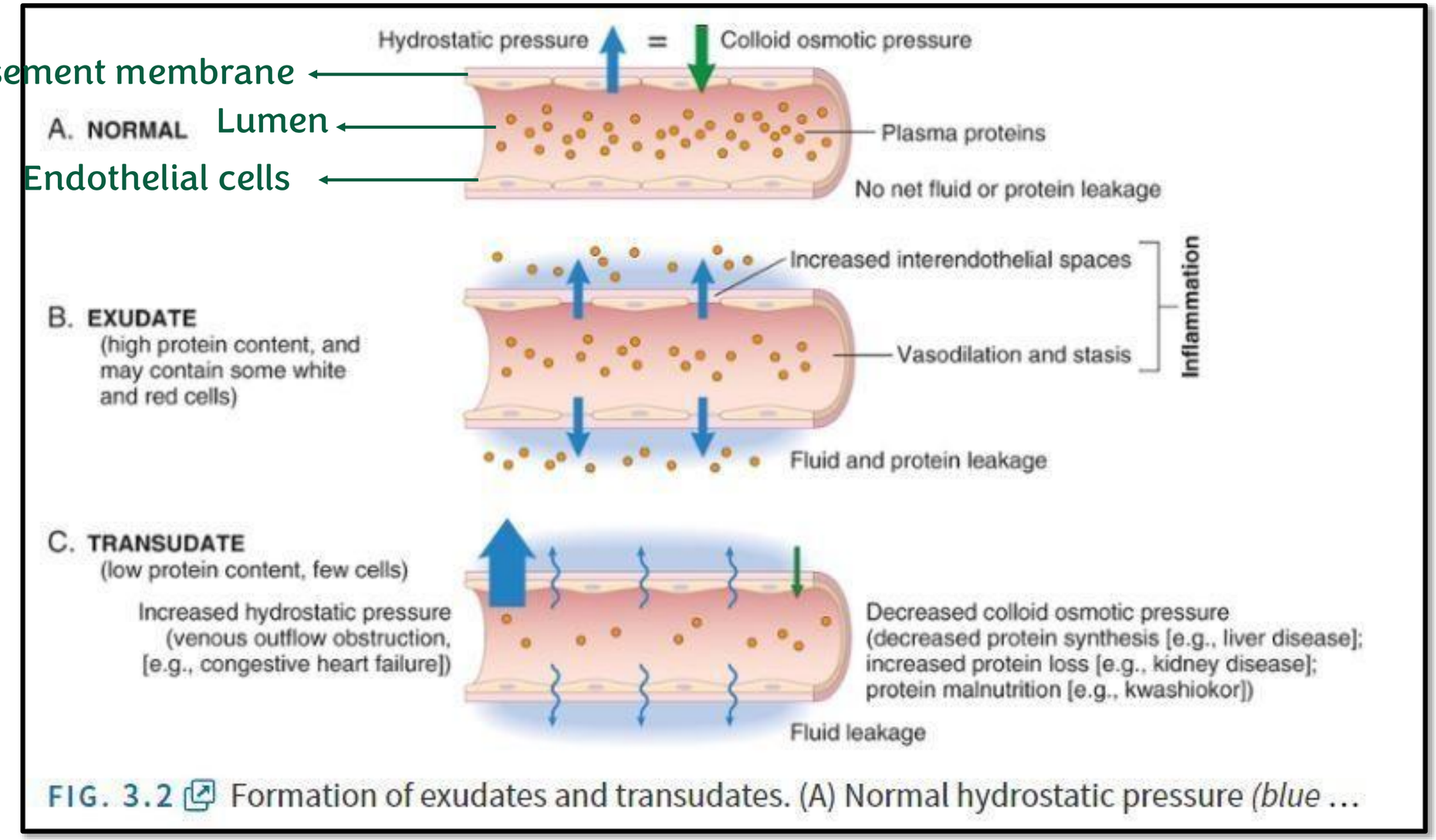


FIG. 3.2 Formation of exudates and transudates. (A) Normal hydrostatic pressure *(blue …*

Colloid osmotic pressure (oncotic pressure) depends on the concentration of plasma proteins within the blood vessels.
When plasma protein concentration increases, fluid is drawn into the blood vessels from the surrounding tissues, whereas when it decreases, fluid moves out of the blood vessels into the interstitial space.

Hydrostatic pressure depends on fluids, it is the force exerted by the fluid within the blood vessels.
When hydrostatic pressure increases, it pushes fluid out of the blood vessels into the surrounding tissues.
When it decreases, less fluid is pushed out, allowing fluid to remain inside the vessels.

Hydrostatic pressure and colloid osmotic pressure are in equilibrium, disturbance of this equilibrium leads to process in which sometimes fluids pushed out causing swelling . This process has two types : transudate and exudate.

Transudate	Exudate
Low protein	High protein
Low cell content	Many cells & debris
Low specific gravity Too much fluids	Higher specific gravity
Caused by osmotic/hydrostatic pressure imbalance Congestive heart failure Chronic renal failure Hepatic failure	Caused by increased vascular permeability and denotes inflammatory reaction Severe injury , bad diseases like cancer and TB

EDEMA & PUS:

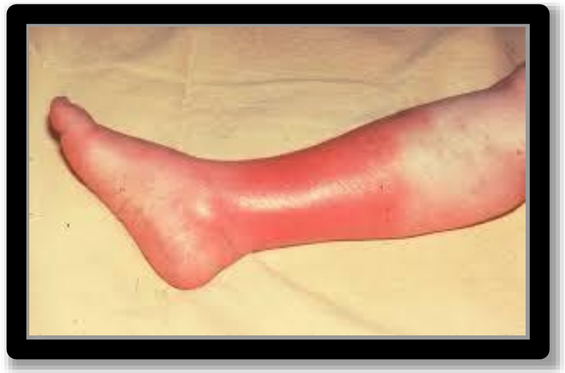
- **Edema: excess fluids in interstitium or serous cavities (either transudate or exudate)**
- **Pus: purulent exudate; inflammatory exudate rich in WBCs, debris, and microbes**

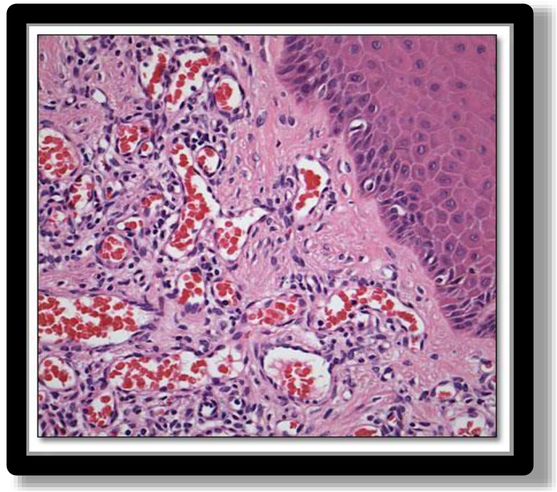
When fluid accumulation in the body, it's essential to distinguish between edema(وذمة) and pus(قيح), as they differ in both origin and content.

- **Edema** refers to an excess of fluid that builds up within interstitium (tissues) or body cavities . This fluid is typically a transudate – meaning it's low in protein and cellular content – and often results from imbalances in pressure gradients, such as increased hydrostatic pressure or decreased oncotic pressure, commonly seen in conditions like heart , kidney or liver failure. However, in certain pathological conditions, edema can be an exudate, which is richer in proteins and cells due to increased vascular permeability commonly seen in Pneumonia (الالتهاب الرئوي) and cancer .

- **Pus** indicates severe acute inflammation that causes severe tissue damage,It's a classic example of an **exudative** fluid and is specifically categorized as purulent (قيح او صديد) or suppurative , meaning it contains a high concentration of inflammatory cells, especially white blood cells (WBCs),neutrophils along with microbial, cellular debris, and proteins. This type of fluid forms as part of the body’s immune response to infection or tissue injury. Pus typically accumulates within an abscess, and small abscesses are often managed by draining — either by squeezing or surgical rupture.

Vascular changes (early events)





- **Vasodilatation: histamine; increased blood flow causing redness (erythema) and heat**
- **Followed by increased permeability (exudate)**
- **Stasis; congestion and erythema**
- **PMNs accumulate and adher to endothelium then migrate outside the vessel into the interstitium**

Erythema means redness , as in erythrocytes (red blood cells). Therefore, erythema means redness of the skin due to increased blood flow.

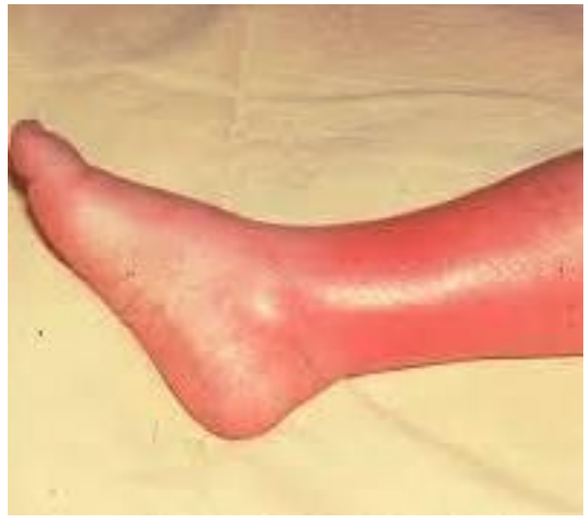
erythro = red · erythrocyte = redcells · erythema = redness

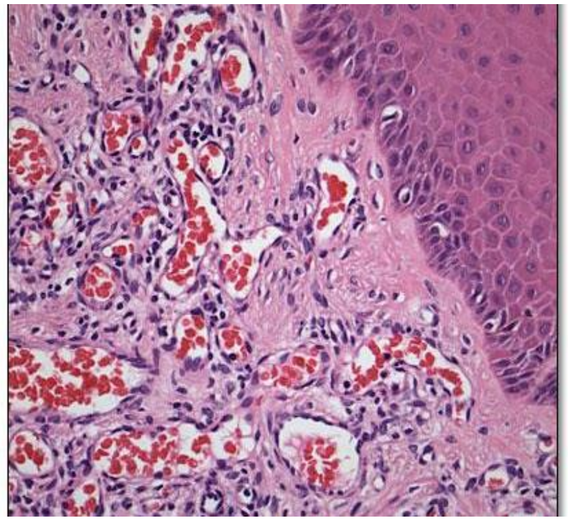
A CLINICAL CAUSE :
Cellulitis

- We can observe the cardinal signs (main signs) of inflammation: redness, swelling and pain . This condition is called cellulitis, which is a severe acute inflammation of the skin and subcutaneous tissue.

- f you were to look at a microscopic section from an affected area, you would see
the squamous epithelium and the submucosal tissue.This area would be filled with numerous engorged and congested blood vessels packed with red blood cells.

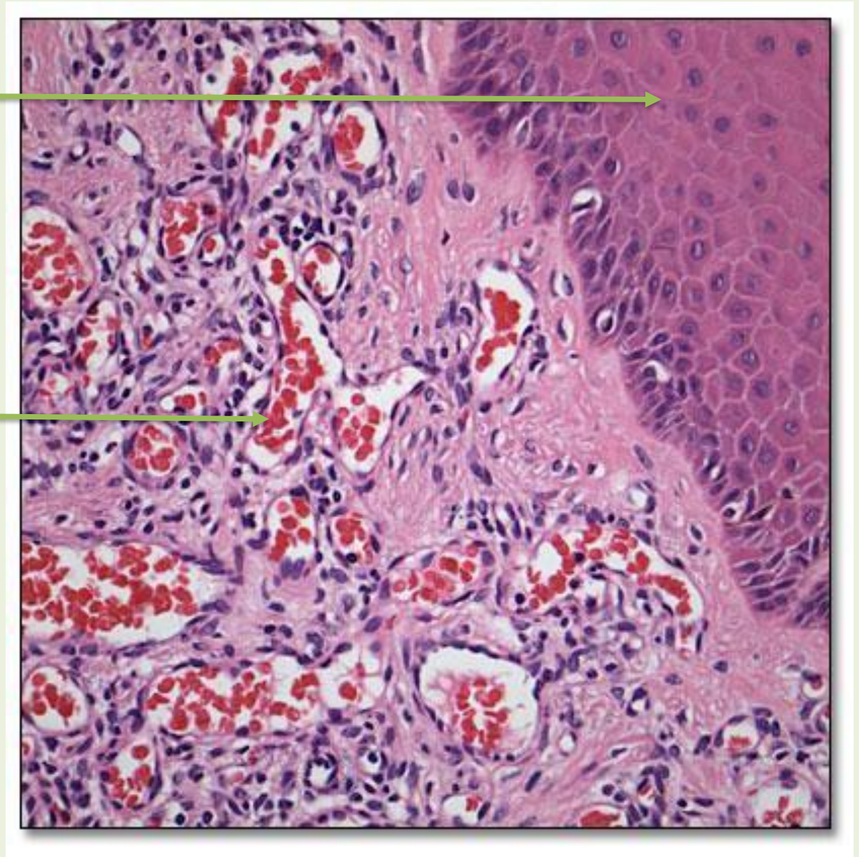
- This massive accumulation of blood in the vessels is what gives
the skin its characteristic redness (also known as erythema)
that you observe when examining the patient.





Squamous Epithelium

The redness observed due to engorged blood vessels in the submucosal epithelium.



Important question the doctor asked in the lectuer

The engorged blood vessels in the subcutaneous tissue is mediated mainly by?

Answer is histamine

Remembare the majo combonents of Basal Lamina :
1-collagen IV
2-laminin

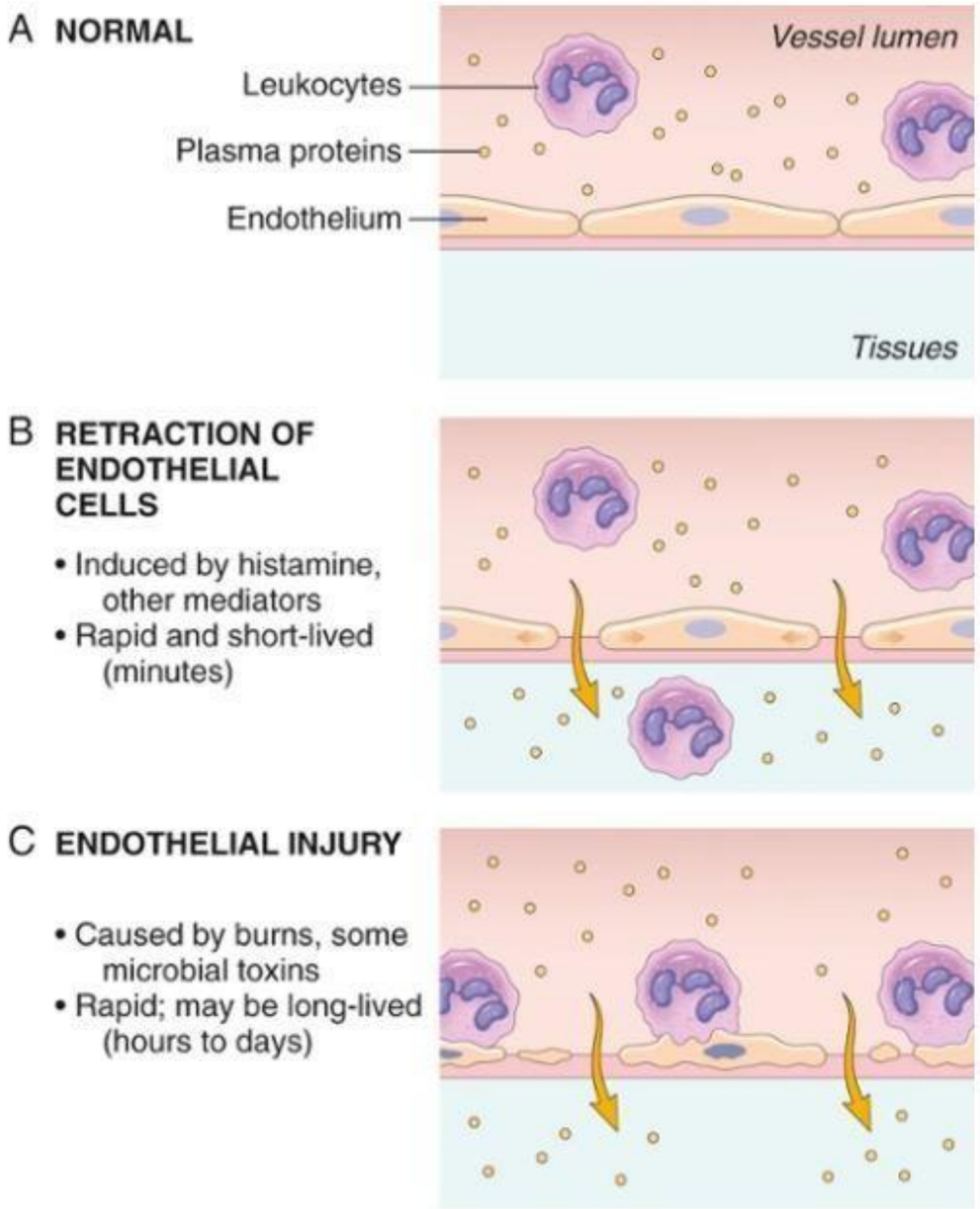


FIG. 3.3 Principal mechanisms of increased vascular permeability in inflammation and …

Explanation of the previous picture:

After the recognition of the offending agent, the initial vascular phase begins. This phase is induced by multiple chemical mediators, the most important of which is histamine.
Under normal conditions, endothelial cells rest on the basement membrane, which is composed mainly of type IV collagen and laminin. These proteins provide structural support, and both endothelial and epithelial cells attach to them.

When histamine is released, it binds to specific receptors on endothelial cells, triggering an active process that causes retraction (contraction) of these cells. As the endothelial cells contract, the spaces between their edges widen, allowing fluids to pass from the blood vessels into the surrounding tissues according to hydrostatic and osmotic pressure gradients.

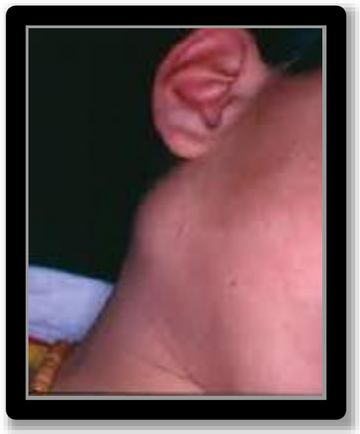
If the inflammation becomes more severe, additional tissue damage occurs. In such cases, components of the basement membrane, such as type IV collagen and laminin, undergo enzymatic degradation, and enzymes may also damage the endothelial cells themselves. The resulting endothelial injury further increases vascular permeability, allowing more proteins and cells to escape into the interstitial space.

This leads to the formation of exudate—an indicator of severe acute inflammation.

Remember: Histamine causes endothelial retraction. In severe injury, there is direct damage to both the endothelium and the basement membrane, resulting in greater leakage of proteins and cells.

Lymphatic vessels and lymph nodes:

- **Lymphangitis: inflammation and proliferation of lymphatic vessels to drain fluids and other elements**
- **Drainage to nearby lymph nodes; hence causing lymphadenitis (reactive lymphadenitis or inflammatory lymphadenitis)**



During inflammation, lymphatic vessels and lymph nodes play a critical role in clearing excess fluid, cellular debris, and infectious agents from tissues. Lymph Nodes locations (cervical, axillary, inguinal, para-aortic....) are immune-filtering stations.

They help trap microorganisms, inflammatory products, and even malignant cells

. **Lymphadenopathy** ·

Definition: Lymphadenopathy refers to enlargement of lymph nodes (e.g., cervical or axillary lymphadenopathy).

Enlarged lymph nodes that do not improve with initial treatment (such as antibiotics) are considered a warning sign. In such cases, further evaluation is needed to identify the cause.

Causes of Lymph Node Enlargement

1- Reactive / Inflammatory Lymphadenitis Due to ongoing infection or inflammation. Lymph nodes enlarge as immune cells multiply and fight pathogens.

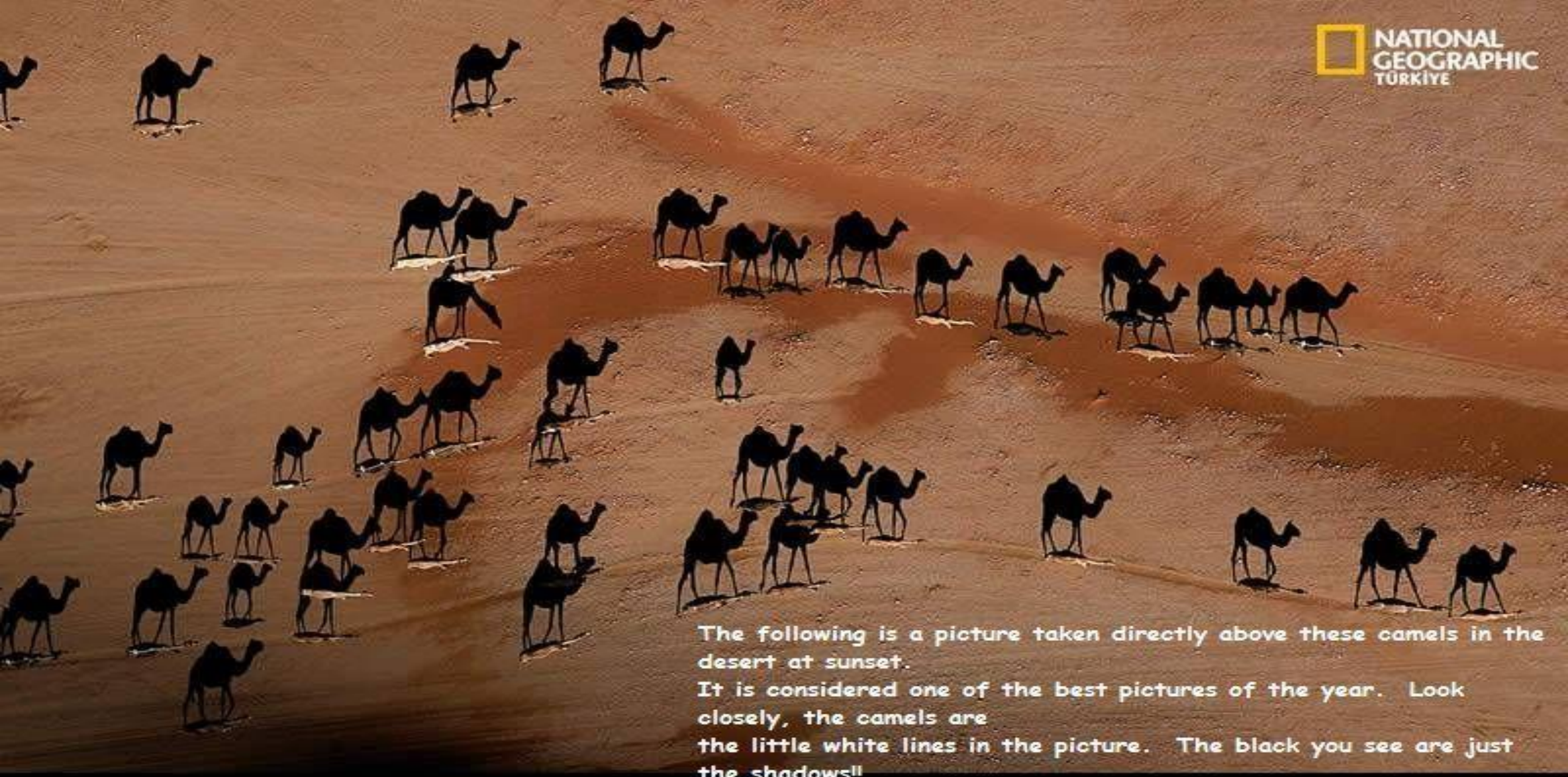
2-Malignancy Node enlargement due to cancer, either primary or metastasis (spread from another organ).

- **Lymphangitis**
- **Definition: Inflammation of lymphatic vessels themselves (which drain into the nodes) . The inflamed lymphatics become more active and start draining increased fluid and inflammatory material toward lymph nodes which may lead to lymph node enlargement. If lymph node swelling continues without resolution, it must be fully investigated to rule out malignancy or other serious causes.**

Summary

Vascular Reactions in Acute Inflammation

- Vasodilation is induced by inflammatory mediators such as histamine (described later), and is the cause of erythema and stasis of blood flow.
- Increased vascular permeability is induced by histamine, kinins, and other mediators that produce gaps between endothelial cells, by direct or leukocyte-induced endothelial injury, and by increased passage of fluids through the endothelium.
- Increased vascular permeability allows plasma proteins and leukocytes, the mediators of host defense, to enter sites of infection or tissue damage. Fluid leak from blood vessels (exudation) results in edema.
- Lymphatic vessels and lymph nodes also are involved in inflammation, and often show redness and swelling.



The following is a picture taken directly above these camels in the desert at sunset.
It is considered one of the best pictures of the year. Look closely, the camels are
the little white lines in the picture. The black you see are just the shadows!!

Fotoğraf: George Steinmetz

Dev Develer

© 2005 National Geographic Society. Her hakkı saklıdır.

National Geographic Türkiye, Şubat 2005

Leukocytes role:

- PMNs(ploymorphonuclear)"neutrophils" & Macrophages
- Recruitment and migration to tissue
- Eliminate the enemy (phagocytosis)
- Migration of leukocytes from BV to tissue is multistep process: adhesions; transmigration then movement toward the enemy area

Leukocytes play a central role in the inflammatory response, mainly by identifying and eliminating harmful agents. In acute inflammation, the key cells involved are **neutrophils (PMNs) and macrophages**.

Function: Their primary role is to eliminate microbes and enemies through phagocytosis. They also secrete mediators to recruit more inflammatory cells.

Neutrophils vs. Macrophages Lifespan: Neutrophils have a very short lifespan. Significance: Because their lifespan is short, seeing neutrophils in a tissue sample indicates an acute process (meaning a couple of days old), not a chronic one.

Response: Neutrophils have a more rapid response to stimuli, while the response in macrophages is more prolonged.

Important

TABLE 3.3 Properties of Neutrophils and Macrophages

	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)
Life span in tissues	1–2 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

HSC, Hematopoietic stem cells; *iNOS*, inducible nitric oxide synthase; *NET*, neutrophil extracellular traps.

This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, ability to migrate through blood vessels into tissues, and chemotaxis.

ADHESION (WBCs to endothelium)

- **Steps:**
  - **1. Margination**
  - **2. Rolling**
  - **3. Adhering**
- **Selectins (initial weak adherence) and integrins (firm strong adherence)**

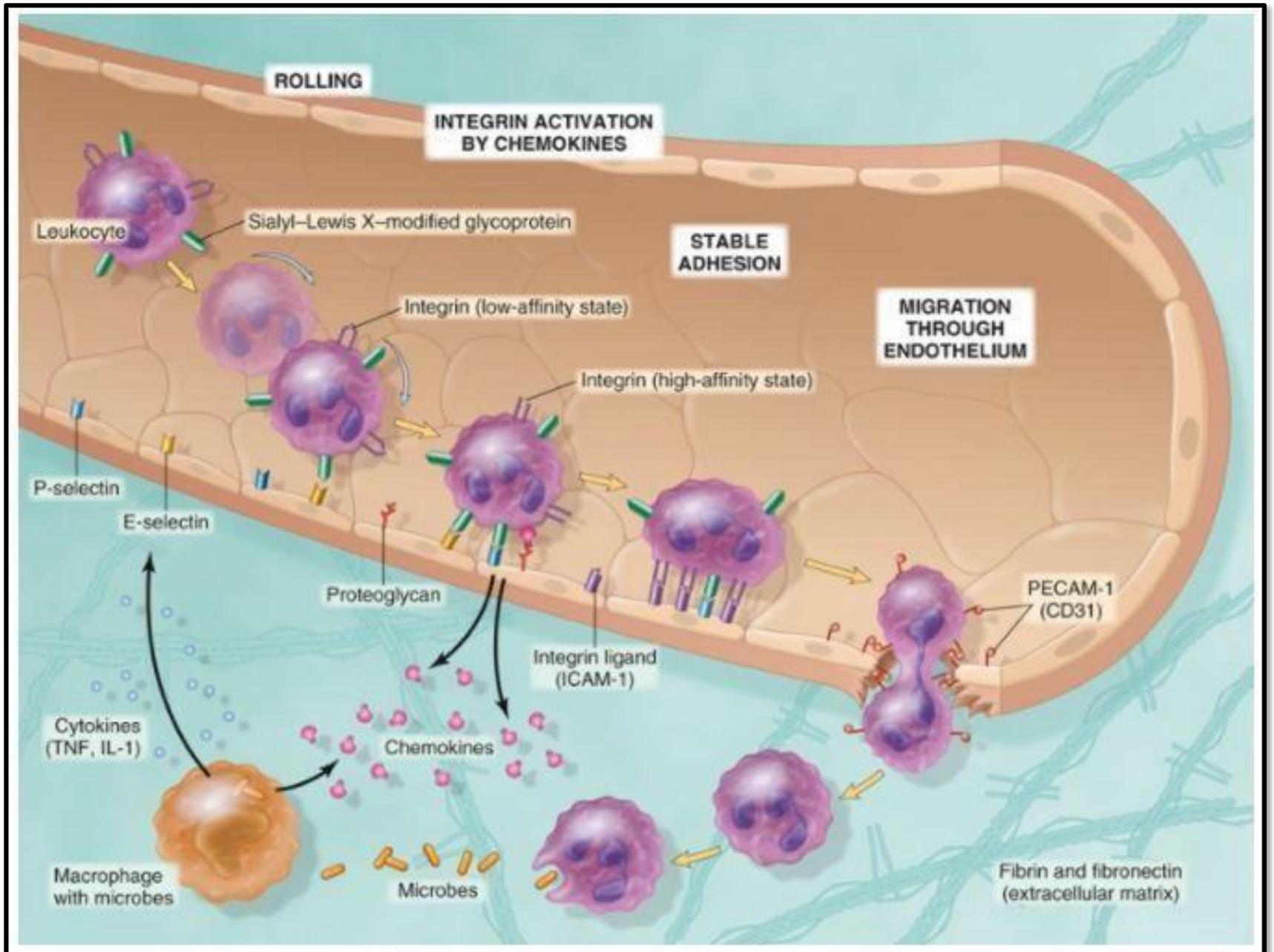


FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he…

Leukocyte Migration, Adhesion & Transmigration

The movement of leukocytes from the bloodstream to the site of inflammation is an active multi-step process.

This process allows neutrophils to exit the vessel and enter tissues to fight infection.

Steps of Leukocyte Migration

1- **Margination** With slowed blood flow (stasis), leukocytes move from the center of the vessel lumen toward the endothelial wall.

2- **Rolling** Leukocytes begin to roll along the endothelium (initially fast). This weak interaction is mediated mainly by Selectins (e.g., E-selectin).

3- **Adhesion** (Weak)Rolling slows down due to light sticking to the vessel wall — still mediated by Selectins.

- 4-**Adhesion** (strong)Attachment becomes strong, causing the cells to stop rolling. This step is mediated by Integrins (e.g., **ICAM-1**).
- 5-**Transmigration (Diapedesis)** Leukocytes actively squeeze through endothelial junctions and exit the blood vessel. This step requires **CD31(Cluster Designation 31) which also known as (PECAM-1)** (the main mediators). Once in the tissues, leukocytes release inflammatory mediators and perform functions like phagocytosis and intracellular killing.

When a leukocyte wants to exit the blood vessel, its main obstacle is the basement membrane, which is mainly composed of type IV collagen. To cross it, the leukocyte stimulates "collagenases" enzymes that break down type IV collagen and create a small passage in the membrane. This allows the leukocyte to squeeze through the vessel wall into the interstitium. This process is supported by CD31 (PECAM-1), which helps activate collagenases and guide these leukocytes during transmigration.

You don't need to memorize every single adhesion molecule the important thing is understanding their roles.·

Selectins: Responsible for the initial weak attachment between leukocytes and endothelium, allowing rolling to occur.

Integrins: Mediate the strong and firm adhesion, stopping the rolling and firmly attaching the leukocyte to the vessel wall.

· **CD31 (PECAM-1):** Essential for the final step of transmigration (diapedesis), helping leukocytes squeeze through endothelial junctions and exit the vessel.

TABLE 3.4 Endothelial and Leukocyte Adhesion Molecules

Family	Molecule	Distribution	Ligand
Selectin	L-selectin (CD62L)	Neutrophils, monocytes T cells (naïve and central memory) B cells (naïve)	Sialyl-Lewis X/PNAd on GlyCAM-1, CD34, MAdCAM-1, others; expressed on endothelium (HEV)
	E-selectin (CD62E)	Endothelium activated by cytokines (TNF, IL-1)	Sialyl-Lewis X (e.g., CLA) on glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory)
	P-selectin (CD62P)	Endothelium activated by cytokines (TNF, IL-1), histamine, or thrombin; platelets	Sialyl-Lewis X on PSGL-1 and other glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory)
Integrin	LFA-1 (CD11aCD18)	Neutrophils, monocytes, T cells (naïve, effector, memory)	ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium)
	MAC-1 (CD11bCD18)	Monocytes, DCs	ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium)
	VLA-4 (CD49aCD29)	Monocytes T cells (naïve, effector, memory)	VCAM-1 (CD106); expressed on endothelium (upregulated on activated endothelium)
	α4β7 (CD49DCD29)	Monocytes T cells (gut homing naïve effector, memory)	VCAM-1 (CD106), MAdCAM-1; expressed on endothelium in gut and gut-associated lymphoid tissues
Ig	CD31	Endothelial cells, leukocytes	CD31 (homotypic interaction)

CLA, Cutaneous lymphocyte antigen-1; *GlyCAM-1,* glycan-bearing cell adhesion molecule-1; *HEV,* high endothelial venule; *ICAM,* intercellular adhesion molecule; *Ig,* immunoglobulin; *IL-1,* interleukin-1; *MAdCAM-1,* mucosal adhesion cell adhesion molecule-1; *PSGL-1,* P-selectin glycoprotein ligand-1; *TNF,* tumor necrosis factor; *VCAM,* vascular cell adhesion molecule.

Summary

Leukocyte Recruitment to Sites of Inflammation

- Leukocytes are recruited from the blood into the extravascular tissue where infectious pathogens or damaged tissues may be located, migrate to the site of infection or tissue injury, and are activated to perform their functions.
- Leukocyte recruitment is a multistep process consisting of loose attachment to and rolling on endothelium (mediated by selectins); firm attachment to endothelium (mediated by integrins); and migration through interendothelial gaps.
- Various cytokines promote the expression of selectins and integrin ligands on endothelium (TNF, IL-1), increase the avidity of integrins for their ligands (chemokines), and promote directional migration of leukocytes (also chemokines). Tissue macrophages and other cells responding to the pathogens or damaged tissues produce many of these cytokines.
- Neutrophils predominate in the early inflammatory infiltrate and are later replaced by monocytes and macrophages.

GOOD

LUCK

Additional Resources:

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	• **Slid(23)** • **slide (29)** • **NEW SLIDE ADD(31) describing collagenases** • **New summery slide add (22)**		We clarify what do PMN(slide23) and CD31(slide 29) means
V1 → V2			