PATHOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 7

Inflammation 2

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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Ensure you have got Lecture 6 well by checking out this quiz ☺

Click on the image above

ACUTE INFLAMMATION

➔ Vascular Phase + Cellular Phase

- 3 major components

B V dilatation

Increased V permeability

Emigration of WBCs

The initial phase after enemy recognition is called the **vascular phase**, which has some overlap with the **cellular phase**, and they together constitute the acute inflammation (3 main components).

It starts with

(1) **Blood vessels dilatation**, and then if the situation is sustained and the body couldn't tackle it (due to age factors or weak immunity), BV's (endothelial cells and basement membrane) will be damaged.

(2) **Increasing the permeability**, and allowing proteins and fluids to exit into the interstitium followed by

(3) **chemotaxis**, which is the movement of leukocytes (WBCs) from the intravascular compartment to the interstitium, where the inflammation occurs.

Mediators released in an inflammatory response:

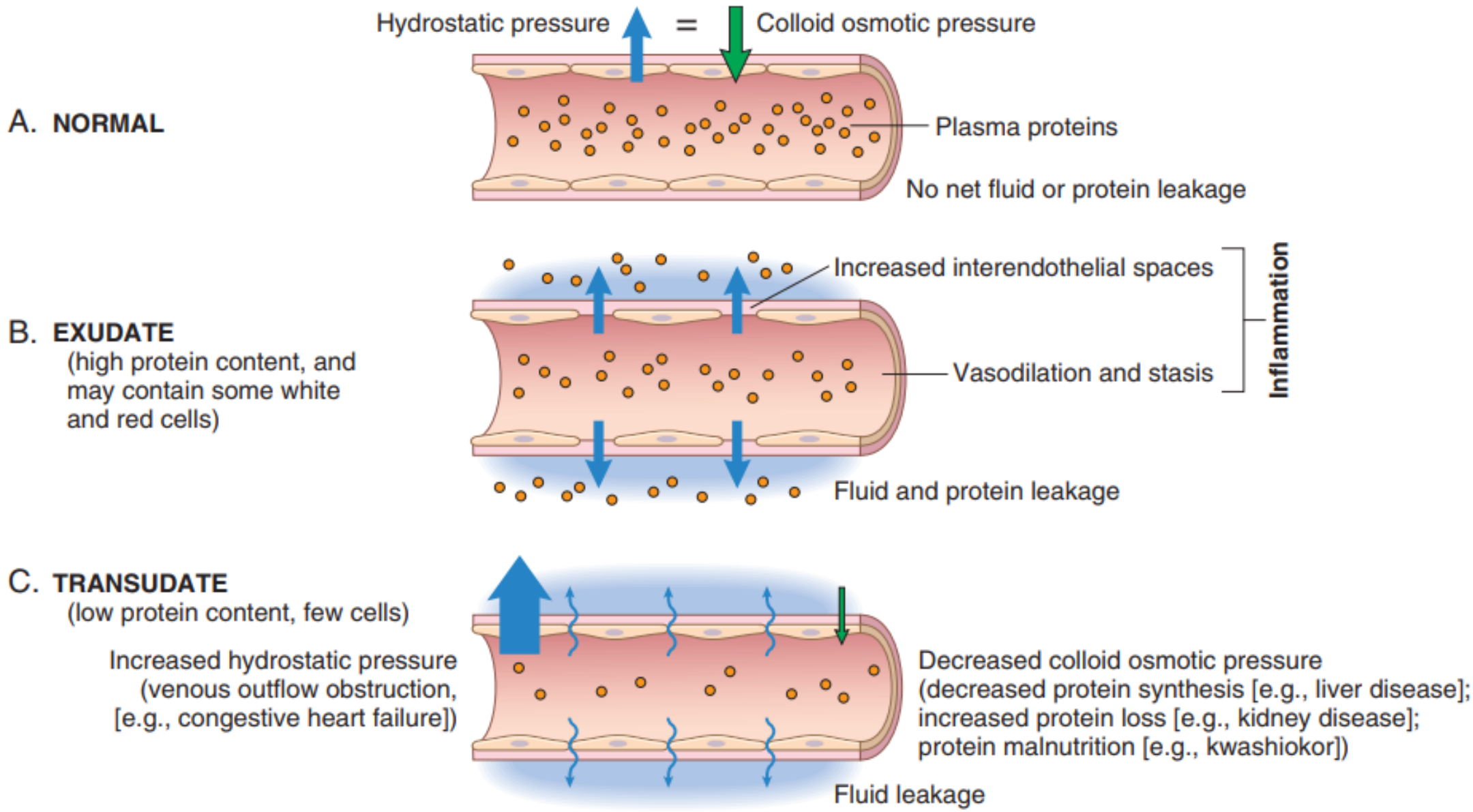
1. **Local** (cardinal signs of inflammation observed)
2. **Systemic** (fever, muscle weakness, etc.)

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.

See *next slides* for explanation



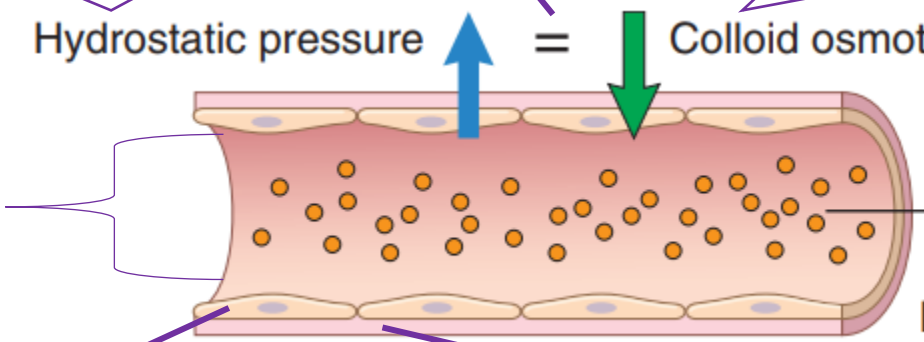
Explanation of Slide 5 (A ⇔ Normal)

A) Longitudinal section of a blood vessel:

Both forces **normally** balance each other ➔ no net fluid movement (equilibrium)

Induced by intravascular fluids (mainly water)

Due to [proteins mainly albumin] in the vessels



Lumen:
1) Plasma (fluids + proteins)
2) Cells

Endothelial Cells

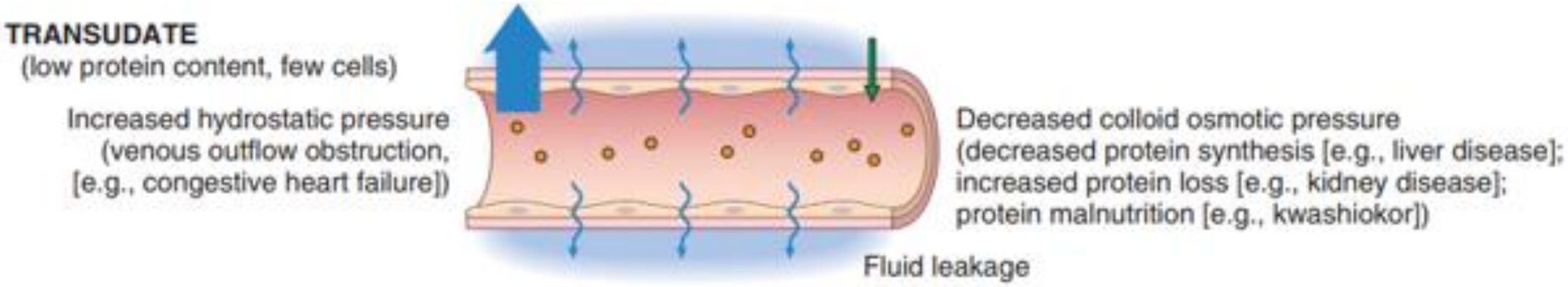
Basement Membrane
Composed mainly of
1) Type IV Collagen
2) Laminin

Explanation of Slide 5 (B & C – Part 1)

- In the case of inflammation ⇔ abnormal case: the 2 forces (hydrostatic and colloid osmotic pressures) are no longer balanced, equilibrium is disturbed, and there will be net movement of fluids and other stuff from the intravascular compartment (lumen) into the extravascular compartment (interstitium).
- We have 2 cases (exudate and transudate):
- Both represent leakage of components to the interstitium.
- They have different causes (etiology) and mechanisms (pathogenesis).
- Understanding the difference between the 2 is crucial.
- The first question that should be asked clinically when encountering a case with any form of edema, such as pulmonary edema (fluids in the lung itself), pleural effusion (fluids in the pleura), ascites (fluids in the peritoneum), etc., is: is this edema caused by transudate or exudate leakage?

Explanation of Slide 5 (B & C – Part 2)

- In **transudate**, leakage is mainly water as well as little amounts of cells and small plasma proteins, such as albumin, due to **increased hydrostatic pressure** or **decreased colloid osmotic pressure.**
- Usually transient and due to vascular phenomena. It does not include real endothelial damage ➔ less severe than exudate (next slide).



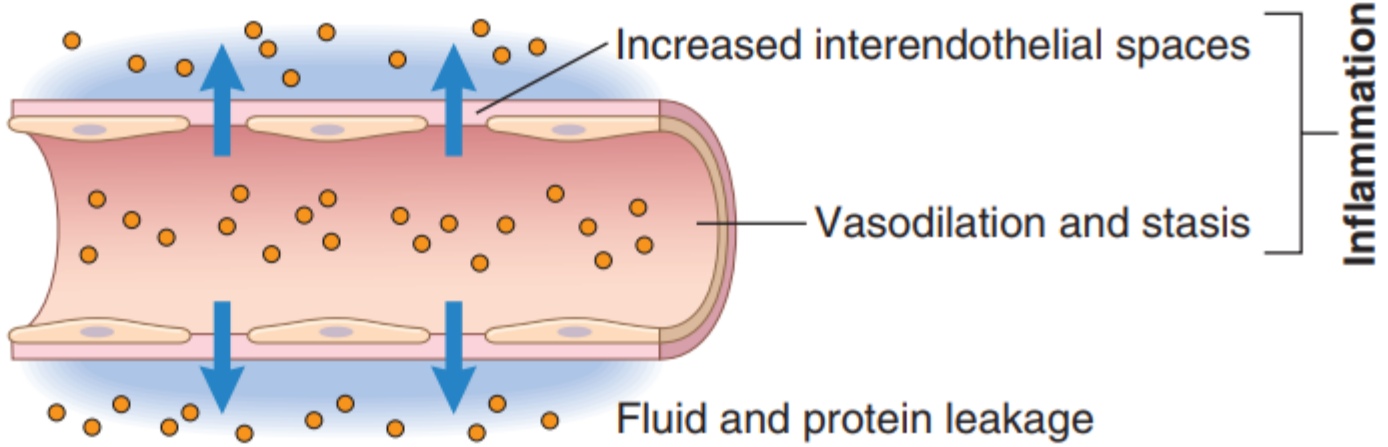
Possible reasons for transudate:

- Congestive heart failure → high hydrostatic pressure
- Chronic renal failure → protein leakage → low osmotic pressure
- Chronic liver disease → low protein synthesis → low osmotic pressure

Explanation of Slide 6 (B & C – Part 3)

- In exudate, a lot of proteins, cells, and neutrophils leak from the intravascular compartment to the interstitium.

EXUDATE
(high protein content, and may contain some white and red cells)



- This is usually present in severe cases such as severe bacterial pneumonia in the lungs.
- It is pathogenically more severe than transudate; aggressive pathogenic agent is usually present.

Very Important

	Transudate	Exudate
	Low protein	High protein
	Low cell content	Many cells & debris
SG (recall Phy-105) Average density Depends on protein concentration	Low specific gravity	Higher specific gravity
High Hydrostatic Or Low Osmotic	Caused by osmotic/hydrostatic pressure imbalance	Caused by increased vascular permeability and denotes inflammatory reaction

We mean excess fluids since normal fluids are always there

EDEMA & PUS:

Trans- or Exu- date?

Clinical symptoms such as
1. Severe Fever
2. Dyspnea (shortness of breath)
3.Lobar pneumonia

Indicate exudate

In some cases, a biopsy or fluid sample may be needed for microscopic examination to analyze the specific components of the fluid and confirm whether it is exudate or transudate.

- **Edema: excess fluids in interstitium or serous cavities (either transudate or exudate)**
  - Pleura
  - Peritoneum
  - CSF cavity

  Edema mainly occurs in the first two
- **Pus: purulent exudate; inflammatory exudate rich in WBCs, debris, and microbes**

  Suppurative process

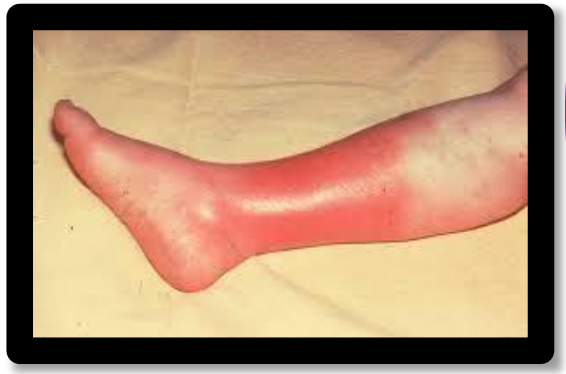
  Especially neutrophils

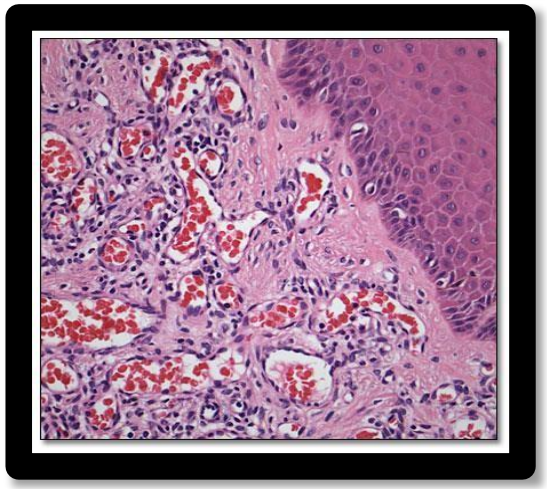
  Mainly bacteria

Vascular changes (early events)

Cellulitis ←
Skin and subcutaneous inflammation

Severe bacterial infection that must be treated with antibiotics





Erythro = Red ⇔ Erythrocytes = RBCs

- **Vasodilatation: histamine; increased blood flow causing redness (erythema) and heat**
- **Followed by increased permeability (exudate)**
- **Stasis; (1) congestion and (2) erythema**
- **PMNs accumulate and adhere to endothelium then migrate outside the vessel into the interstitium**

Major dilator of the vessels (vasoactive amine)

Can be used in other contexts such as urinary blockage or intracranial fluids

Inflammations in general can start as a transient transudate. If the pathogenetic agent is persistent, several mediators will induce damage in the endothelium and basement membrane switching to exudate.

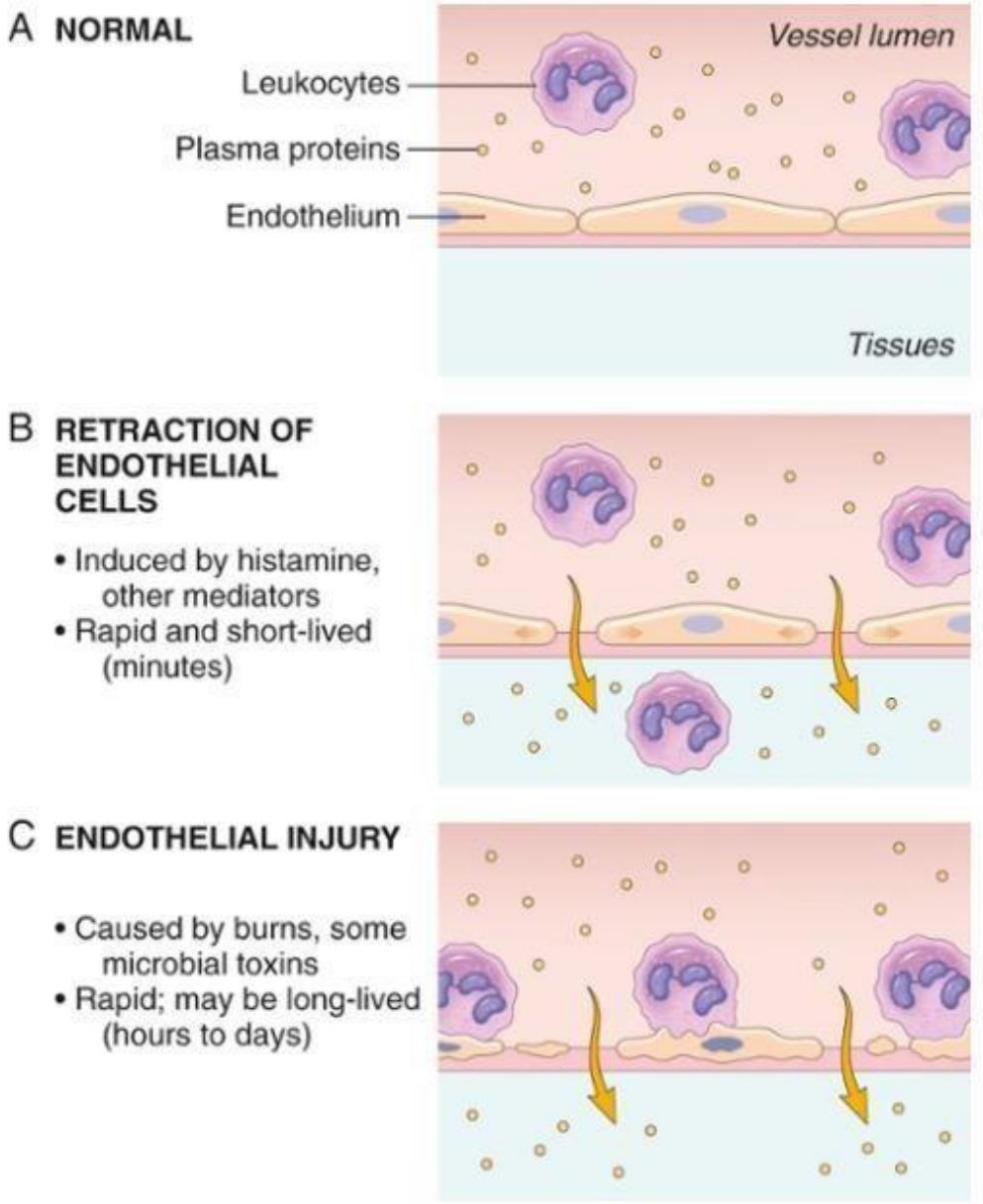
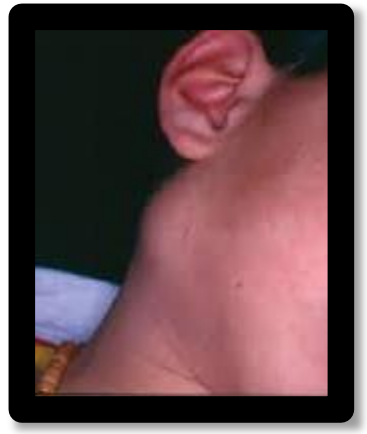


FIG. 3.3 Principal mechanisms of increased vascular permeability in inflammation and …

Further notes regarding the previous slide

- **Our blood vessels** are composed of:
  - The vascular lumen which contains the circulating cells and proteins.
  - Endothelial cells lining the lumen of the vessels.
  - A basement membrane that supports these endothelial cells.
- **Normally,** a state of equilibrium is present between the intravascular and the extracellular compartments.
- **In case of inflammation,** the initial phase which is induced by histamine will cause a mild, transient change by retracting the endothelial cells making pores through which fluids and small proteins can go, the accumulated fluid is transudate as the injury is mild and not severe.
- **If the inflammation is severe,** such in case of cancer or severe injury more damage will happen to the endothelial cells and the basement membrane, leading to the flow of bigger proteins (**exudate fluid**).
- **The accumulation of fluids** could happen in different sites of the body such as:
  - In the lungs (plural effusion).
  - In the abdomen (ascites).
- **We could check the composition** of the accumulated fluid to determine if the fluid is transudate or exudate.

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)**

- Anatomically, lymph nodes are present in certain areas inside the body such as, cervical, periaortic, peribronchial and inguinal lymph nodes.
- Any blockage or inflammation in the lymph nodes will lead to the enlargement of them.
- Most of the time, the enlargement of the lymph nodes is due to a self-limiting viral or bacterial infections (self-limiting: a disease that is resolved spontaneously without a treatment).
- In a patient with a viral infection in a lymph node, antiviral drugs are usually not needed because viral lymphadenitis (inflammation of the lymph node) often resolves on its own. Instead, simple treatments to relieve symptoms, like reducing fever and pain, are usually enough. However, if the lymph node remains swollen and painful without improvement after these basic treatments, further evaluation may be needed. This persistent inflammation could suggest a bacterial infection, such as tuberculosis in the lymph node (tuberculosis lymphadenitis). In such cases, antibiotics are often prescribed based on the suspected bacterial cause, and for tuberculosis lymphadenitis specifically, a longer course of multiple antibiotics is required. If the lymph node does not improve with treatment, a biopsy may be performed to investigate the cause of inflammation more thoroughly.

Lymphadenitis is also known as lymphadenopathy

Lymphangitis refers to the inflammation of the lymph vessels

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.

Leukocyte's role:

- Leuko: white, cyte: cell (white blood cell).

- **PMNs & Macrophages**
  - **PMNs** stands for polymorphonuclear neutrophils, referring to neutrophils that have a single, multi-lobed nucleus with 3–5 lobes connected by thin strands.
  - The origin of **macrophages** is circulating **monocytes.** Once the circulating **monocytes** leave the intravascular compartment to the tissues, they get activated to become **macrophages** with a long lifetime.
  - **Macrophages** have different names depending on the specific tissue where they reside.
- **Recruitment and migration to tissue**
  - **PMNs** and **macrophages** are involved in the migration and recruitment of other types of leukocytes.

- **Eliminate the enemy (phagocytosis)**
- **Migration of leukocytes from BV to tissue is multistep process: adhesions; transmigration then movement toward the enemy area**

- The movement of WBCs from the BV towards the tissues is called chemotaxis as the cells move in response to chemical signals.
- Diapedesis is sometimes used to refer to the whole process of migration or to only the shift of the cells through the vessel wall.

Notice the long lifespan of macrophages, in contrast to neutrophils that have a short life span.

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)

SEE NEXT TWO SLIDES FOR EXPLANATION

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

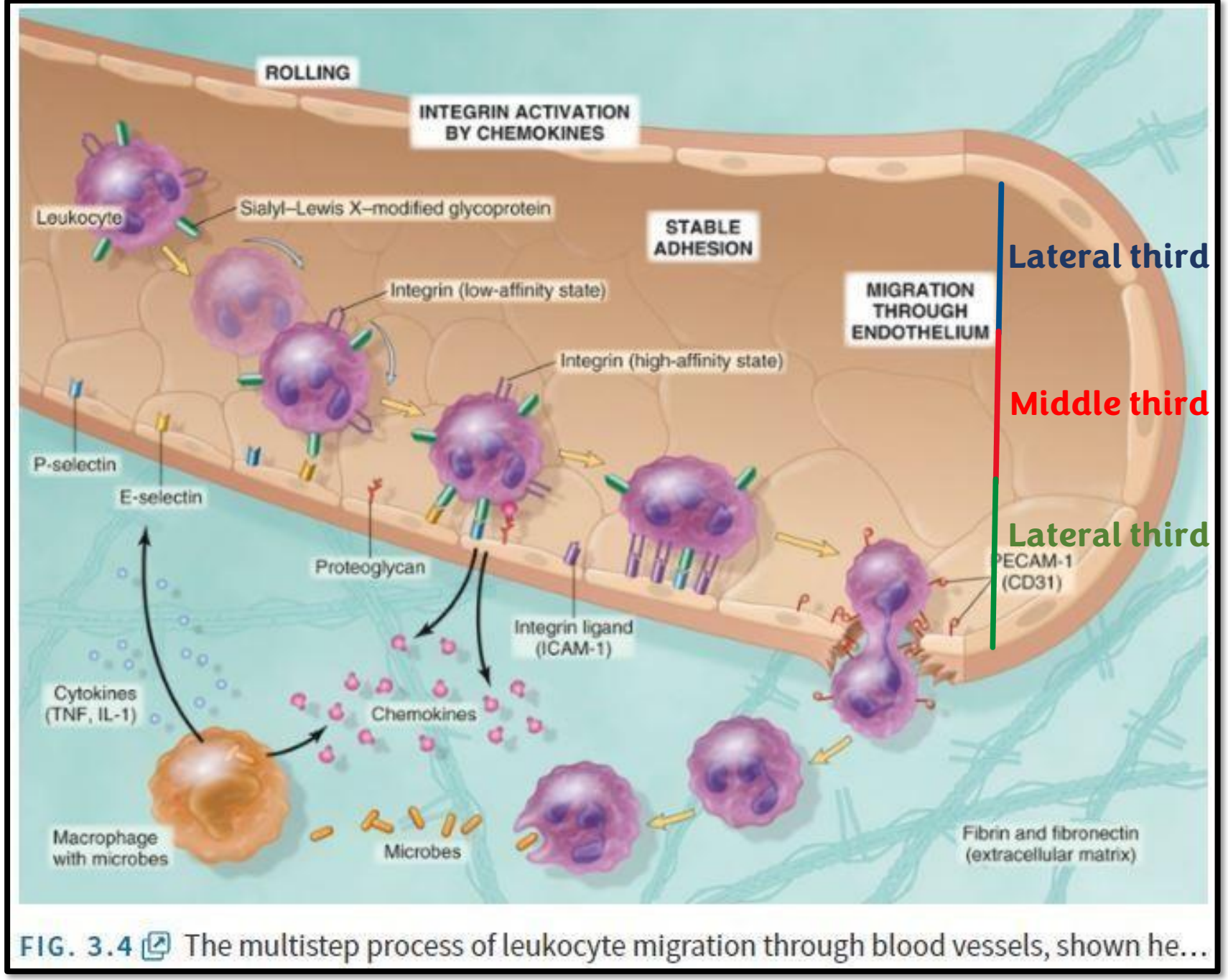


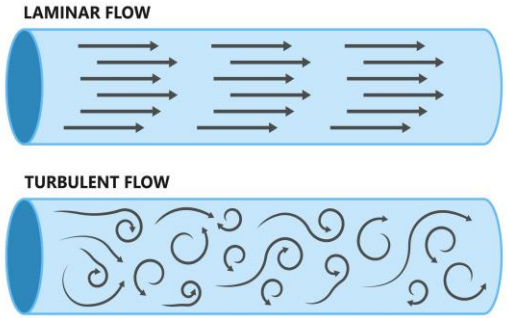
FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he…

Let's divide the blood vessel into three thirds.

Further notes regarding the previous slide

Let's discuss how the leukocytes move from the blood vessels to the tissues.

Physics 105 recall



- The flow in blood vessels is laminar flow, this means that most of proteins and cells flow in the middle third (see the figure in the previous slide).
- The first step is called **margination** which is the process in which the leukocyte moves from the middle third to the lower lateral third close to the vessel's wall.
- When the leukocyte touches the endothelial cells, it will start rolling, the initial rolling is fast, then it will start to slow down, this process is called **rolling**.
- After that, a **process of adhesion** between the leukocyte surface proteins and endothelial cells surface proteins will start with two major types:
  - Initial weak adhesions by the interaction of **selectins** proteins with the endothelial cells.
  - Stronger adhesions mediated by **integrins** proteins.
- Finally, this leukocyte will squeeze itself from inside the vessel towards the tissue, this process is mediated by **PECAM-1** or **CD31** (cluster designation 31) which is a certain protein marker on the surface of WBCs.
- The interaction of leukocyte with **PECAM-1** will induce the production of certain digestive enzyme such as **collagenase** and **lamininase** so it can digest the basement membrane and pass through it, this final process is called **transmigration**.

Margination → Rolling → Adhesion → Transmigration (diapedesis in some textbooks)

Don't memorize

Just know that selectin is for weak adhesion, integrin for strong adhesion, CD31 the mediator of transmigration.

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.

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	2 21	Migration → Rolling →	Added the QUIZ Margination → Rolling →
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

Robbins & Kumar Basic Pathology,
11th edition, pg. 27-30

قال رسول الله صل الله عليه وسلم (مثل المؤمنين في توادهم وتراحمهم وتعاطفهم مثل الجسد؛ إذا اشتكى منه عضو تداعى له سائر الجسد بالسّهر والحمّىّ)
رواه مسلم

اللهم أنج المستضعفين من المسلمين في كل مكان
اللهم انصرهم على عدوك وعدوهم
اللهم عليك باليهود وأعوانهم يا عزيز