SHEET NO. 7

PATHOLOGY

DOCTOR 2019 | MEDICINE | JU

DONE BY : Elaf Al-Sqour

SCIENTIFIC CORRECTION : Noor Shahwan

GRAMMATICAL CORRECTION : Noor Shahwan

DOCTOR : Mousa Al-Abbadi

ملاحظه :أي جملة باللون الأزرق هي اضافه ليس من كلام الدكتور ولكنها للتوضيح وللفهم اكثر

Acute Inflammation

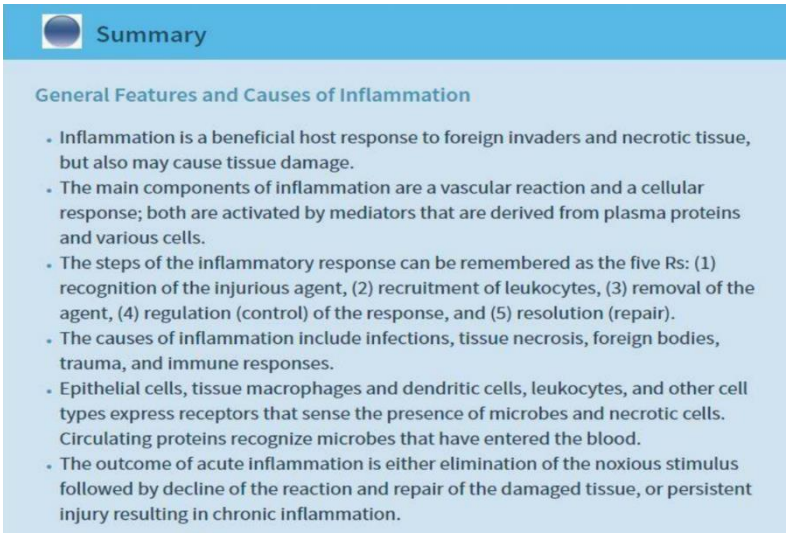
One of the initial important steps of acute inflammation is Acute Initial Vascular Phase of inflammation, that explains multiple cardinal signs seen on inflamed organ (swollen, redness, erythema, pain, a symptom, tenderness when you touch the site of pain, heat)

Acute vascular phase is also related to changes of the blood vessels at the site of inflammation.

Major components of acute inflammation in
nitial phases there are:

1. **Blood vessel dilatation** (Blood vessel dilation can be passive and active, passive and active mean that they require more energy and more work to happen).
2. **Increased vascular permeability** which is an active process.
3. And then the recruitment or the **emigration of white blood cells** from the intervascular compartment to the extravascular compartment.

This is the summary of the previous slides. (Note about the box above: the doctor advised us to read this summary (quoted from the book) for what we talked about last time.



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.

If you remember we're going to talk about:
The vascular phase of the initial vascular phase liquid inflammation, the blood vessels in the normal equilibrium state, there are intracellular fluid and proteins, there is also extracellular fluids and proteins and there's a balance between them.

Hydrostatic pressure: **which is responsible** mainly for pushing fluid from inside the blood vessels to outside
(Depends on the amount of the fluid inside the vessels)
Colloid osmotic pressure which depends on the plasma protein concentration sucks (absorbs) the fluid from the interstitium to the intravascular component)
(Depends on the amount of plasma proteins)

So during the phases of inflammation there can be two different processes which you have to really understand them very well.

1. **Exudate**
2. **Transudate**

And basically both of them are initial phases or process which occurs in the initial phase of accute inflammation.

Exudate: is the process where high protein content, sometimes inflammatory cells sneaks outside the blood vessel, so whatever it is whether in the interstitial fluids or in body fluids, it's always have high protein content and high cellular content.

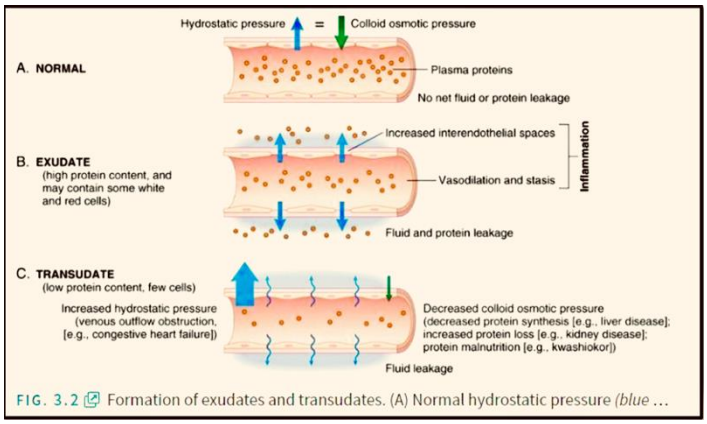


FIG. 3.2 Formation of exudates and transudates. (A) Normal hydrostatic pressure *(blue …*

Transudate it is completely opposite the protein content is low and the cellularity is low.
This is why when you are in the lab, you received a pleural fluid for examination or peritoneal fluid examination, we look at it if it's clear and **yellow** this is most likely a **transudate**,if it is **thick and creamy and maybe bloody** this'd probably an **exudate**,contains high protein content and cells and other one is opposite low protein content and Q cell .

The importance of the differentiated between those two, because the pathogeneses and the reasons and etiology of each one is different, the exudate is more serious and indicates severe acute inflammation or cancer and other severe conditions, the transudate is basically either problem the colloid pressure, hypoproteinemia due to liver disease or kidney disease or malnutrition so this is what happens during those processes.

This is the difference between normal exudate and transudate..

Transudate	Exudate
Low protein	High protein
Low cell content	Many cells & debris
Low specific gravity	Higher specific gravity
Caused by osmotic/hydrostatic pressure imbalance	Caused by increased vascular permeability and denotes inflammatory reaction

You're going to hear about these definitions in all your life as a physician.

Edema and **Pus**

Edema: is basically excess fluids in the interstitium or serous cavities, so you're going to see a lot of patients with heart failure or liver failure where they have severe lower edema, and a lot of translated fluid are moved from the intravascular compartment to the interstitium, causing for example severe swelling in the leg.

We're going to see a lot of patients with unilateral or bilateral pleural effusion or patients with the ascites and those can also be either transudate or exudate and this is why sometimes they remove some of these and send it to us (pathologist) to the lab to examine the protein content the cellularity content and also to look for malignancy in these fluids, especially if we are dealing with an older patient with bilateral pleural effusion or an older woman with severe ascites

Edema is just fluid and most of the time it's due to osmotic hydrostatic, oncotic pressure imbalance.

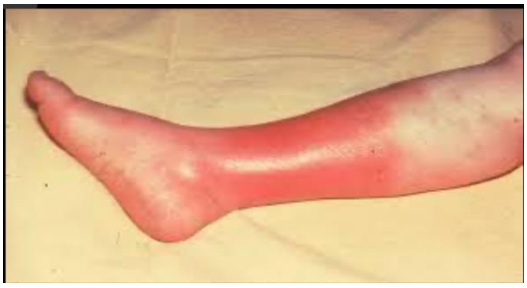
A **transudate** is a filtrate of blood. It is due to increased pressure in the veins and capillaries that forces fluid through the vessel walls or to a low level of protein in blood serum. **Transudate** accumulates in tissues outside the blood vessels and causes **edema** (swelling).

Pus indicates an exudative prosses which is purulent (mean increased numbers of inflammatory cells which is rich in red and white blood cells microbes debris and protein).

Advise: know the difference between edema and pus well.

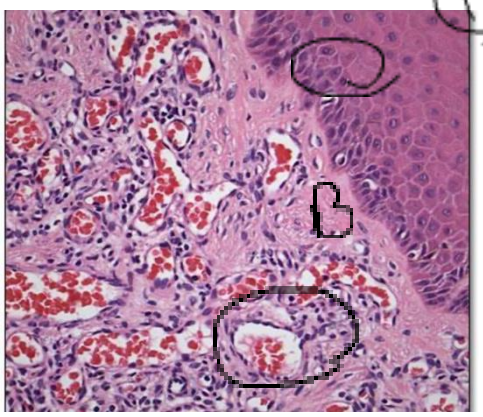
Simply pus is the content of an abscess, if you sometimes have injury and inflammation into your fingertip and it becomes real yellow and collects purely debris, sometimes you squeeze it to release it which is the treatment for small abscess and content is pus it is a purulent exudate.

Vascular changes (early events)



As you ***see*** in this picture, this is not a normal leg, this is mainly due to that patient has a disease called **cellulitis (acute cellulitis)**,where the infection is involving the skin and subcutaneous tissue and if you take section from this and you look at in the microscope.

A this is the squamous epithelium and ***B*** is the submucosal epithelium with numerous engorged and congested blood vessels with a lot of red blood cells which will give the color redness when you examine the patient by your eye.



So ,how the previous case happen ?

1) the initial phase of inflammation or vasodilation is mediated by multiple chemical mediators of inflammation.
The major mediator which is responsible for the vasodilatation effect is the histamine which will increase the major effect of histamine is increase blood flow causing the submucosa of validation, redness and heat, so initially there is immediate vasodilation due to the release of histamine, sometimes and certain books they will tell you that there is

actually a phase before that which is called that reflex transient vasoconstriction from the initial stimulus whether it's trauma or bacteria or heat or whatever, but for all practical purposes the first vascular phase of inflammation, is actually the vasodilation due to histamine release.

The initial phases is a little bit passive,this followed by more active process which will lead to leakage of more material from inside the blood vessel to the interstitium due to increased vascular permeability, both processes the initial vasodilatation followed by more an active process of increased vascular permeability will cause stasis which means the blood would stay over there does not move and this is what we call in pathology **congestion** and this will lead to the cutaneous changes termed erythema

Neutrophils or the Polymorph nuclear cells accumulate and adhere to the endothelial of the cell then try to migrate outside into the interstitium in the initial phases of acute inflammation in a process which we called ***Diapedesis***

Diapedesis: the movement of the neutrophils and other white blood cells from the intravascular compartment to the extravascular compartment in the initial phases of inflammation.

The main driver of the initial phase of vascular events is histamine, other amines, and mediator

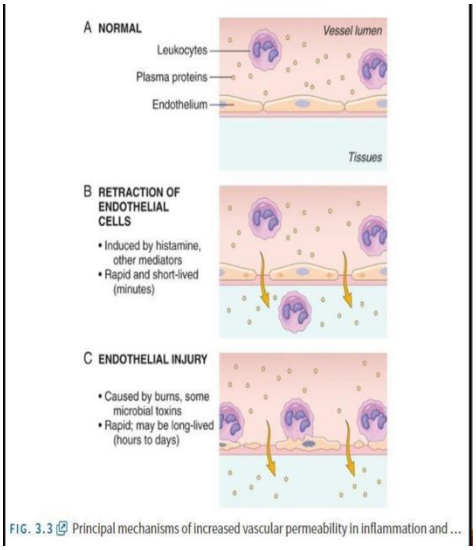


FIG. 3.3 Principal mechanisms of increased vascular permeability in inflammation and ...

What happens in an in these processes?

A normally you have the vascular wall, basement membrane lined by endothelial cells. Back to 12:23 of the video.
In normal equilibrium state, everything is moving smoothly, there is no movement in the blood vessels diameters, or movement of the cells or proteins from inside to the outside.

Vasodilation has 2 phases:

1) initial phases inflammation (quick, transient).
The initial change which happens due to histamine and also other chemical mediators of inflammation but the major one is histamine is there is retraction of the endothelial cells, there will be retracted movement, it will be more gaps in between those endothelial cells and this is basically the immediate rapid and short-lived process where are fluids can move cells and proteins and fluid can move from intravascular to extravascular compartment.

This will be followed by **phase 2 (severe)** as I mentioned a more active energy requiring step where will be really damage to the endothelial cells and there will be more gaps between the endothelial cells, sometimes the basement membrane where more cells and more proteins move out.

Basement membrane is a very important structure to epithelial cells. Laminin and collagen4 are the main components of the basement membrane.

this process either it is a short a short lived, for example
in burns or microbial toxin induced changes or it is a little bit more long lived.

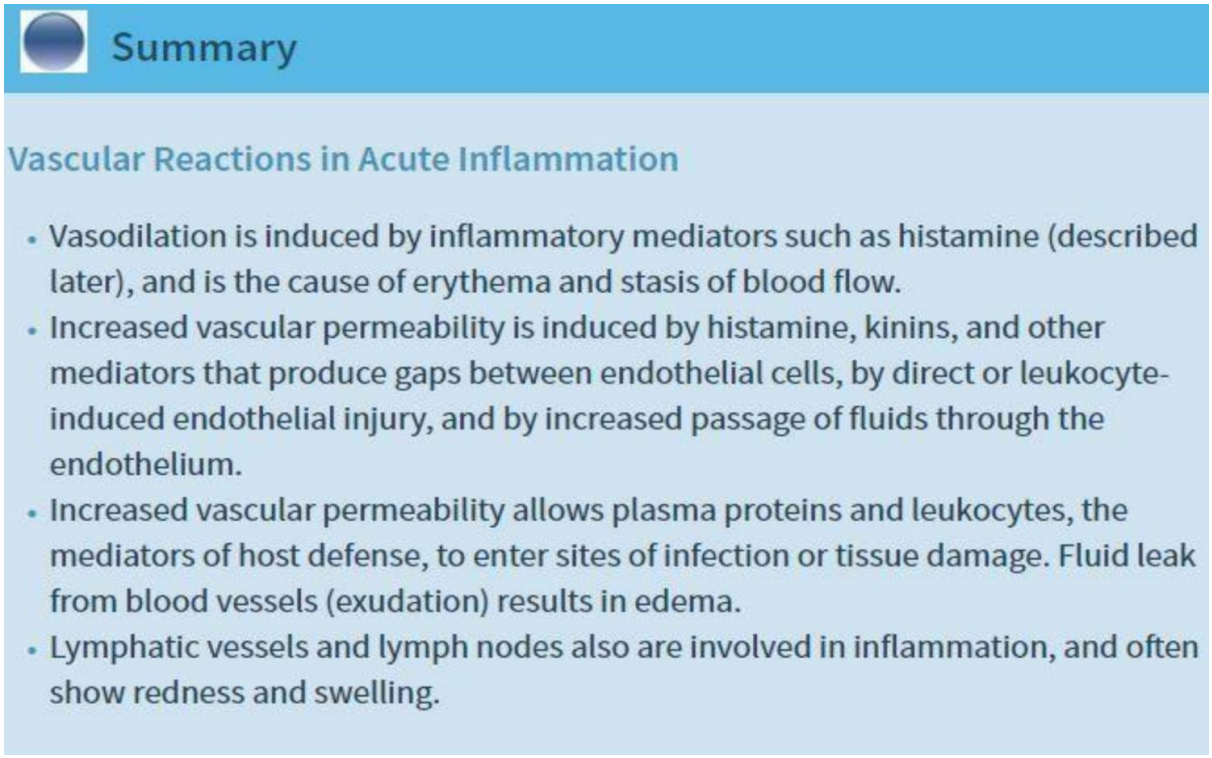
Lymphatic vessels and lymph nodes

What are the roles of lymphatic vessels and lymph nodes?

Remember we talked in anatomy that there are many groups of lymph nodes: cervical lymph nodes, axillary lymph nodes, inguinal lymph nodes, and para aortic lymph nodes.

Those are lymphatic tissues where they drained many of the active processes in your body where they drain a lot of changes, in addition to draining and the infiltration of cancer cells, this is why whenever we see somebody within enlarged lymph node what we call **lymphadenopathy..e.g** cervical ,auxiliary , and inguinal.
especially if it's not responding to a initial treatments, such as antibiotics this is the serous stations come back to the hospital for further investigation, where we try to figure out the major cause of lymph nodes enlargement whether it still inflammatory infectious, or we are dealing with stage 3 cancer, cancer from somewhere draining into those lymphnodes...

Sometimes there will be an inflammation of those lymphatic vessles which drain to the lymph nodes, we call it , lymphangitis and this will lead to a lymphatic vessel proliferation and drainage of fluids into these lymph nodes causing enlargement.
The presence of enlarged lymph nodes not responding to initial antibiotics or whatever, the treatment we give them we call it the ***persistent lymphadenopathy,*** always requires further investigation to make sure are we dealing with reactive inflammatory lymphadenitis or more serious process.
Again🤝 remember to summary of what we have explained



What is the leukocyte role in inflammation special in acute inflammatory process?

Almost all the leukocyte play role in inflammation

1) The main component Of acute inflammatory is the macrophages and neutrophils are responsible for **eliminating the microbes and the enemies** by the process of Phagocytosis.

2) They are also secrete mediators which will recruit mor inflammatory cells at the site of injury.

3) Remember that the migration of leukocytes from the intravascular compartment to the outside, but it is not a simple process, it's a multi-process which will require movement of those inflammatory cells toward the wall from inside and then adhesion then transmigration then movement toward the site of injury so we will talk about this process also in detail .

This table is extremely important and it gives you an overview of the differences between neutrophils and macrophages, their origin from where the life span of each remember that the lifespan of neutrophils is very short and this is why you see the more in the acute inflammatory process and if you see them in tissues and the microscopic examination this indicates an acute process rather than chronic process meaning couple days, response for activating stimuli which is more rapid in the neutrophils more prolonged in macrophages and the production of the reactive oxygen species, nitric oxide and degranulation all of them and there are difference between neutrophils and macrophages just **try to read say table in more details and memorize the differences between macrophages and neutrophils..**

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.

Now let's talk a little bit about the adhesions of white blood cells to the endothelium.
We mentioned before, that after the initial vascular phase of inflammation with retraction and damage to the endothelial cells, where proteins and cells can migrate from the intravascular compartment to the extravascular compartment, the white blood cells mainly, when they move from inside to outside there are multiple steps and this is an active process, where we have **margination**, followed by **rolling and adhering** of those cells to the vascular wall, and this process also requires some of the receptor **(selectins: initial weak adherence)** and then followed by **(integrins: firm strong adherence),** and then letting the cells to go out from the intravascular compartment to extravascular compartment.

It's better to go back to video 21:52.

This carton explains the steps of how neutrophils or a macrophage moves from inside the lumen into the extravascular compartment, so that they can perform their function.

Margination is the first step, which means the movement of WBCs (neutrophils and macrophage) from the center of lumen toward the wall of it.

Then **Rolling** on the wall, they will be initially fast because of the initial E-selectin process where the adhesion is weak, then it will slow down, followed by the stronger attachment by integrin ligand (ICAM-1) and it's really slow down the rolling process, to prepare the neutrophils to move from inside to outside of the blood vessel.

Then the cell will move out from inside the blood vessel into the outside by a more active process which is **utilizing the CD31,** (CD called cluster designation), but those are proteins mainly present on the surface of the cell and in each cell which is differentiated to the right side have specific types proteins.

So in the **transmigration** the PECAM-1 which is another name for CD31 will damage the endothelial cells and basement membrane, so that there will be a big hole in the wall, allowing to interfere to squeeze itself outside, (in some books they will say movement of neutrophils from inside to outside is diapedesis, other say the transmigration is called diapedesis), so those are the steps which you have to understand..

Quick summary:

Migration → Rolling → Selectins (weak attachment) → Integrins (strong attachment) → Transmigration or Diapedesis (movement of the cell itself outside through an active destruction of the endothelial cells and the basement membrane through CD31.

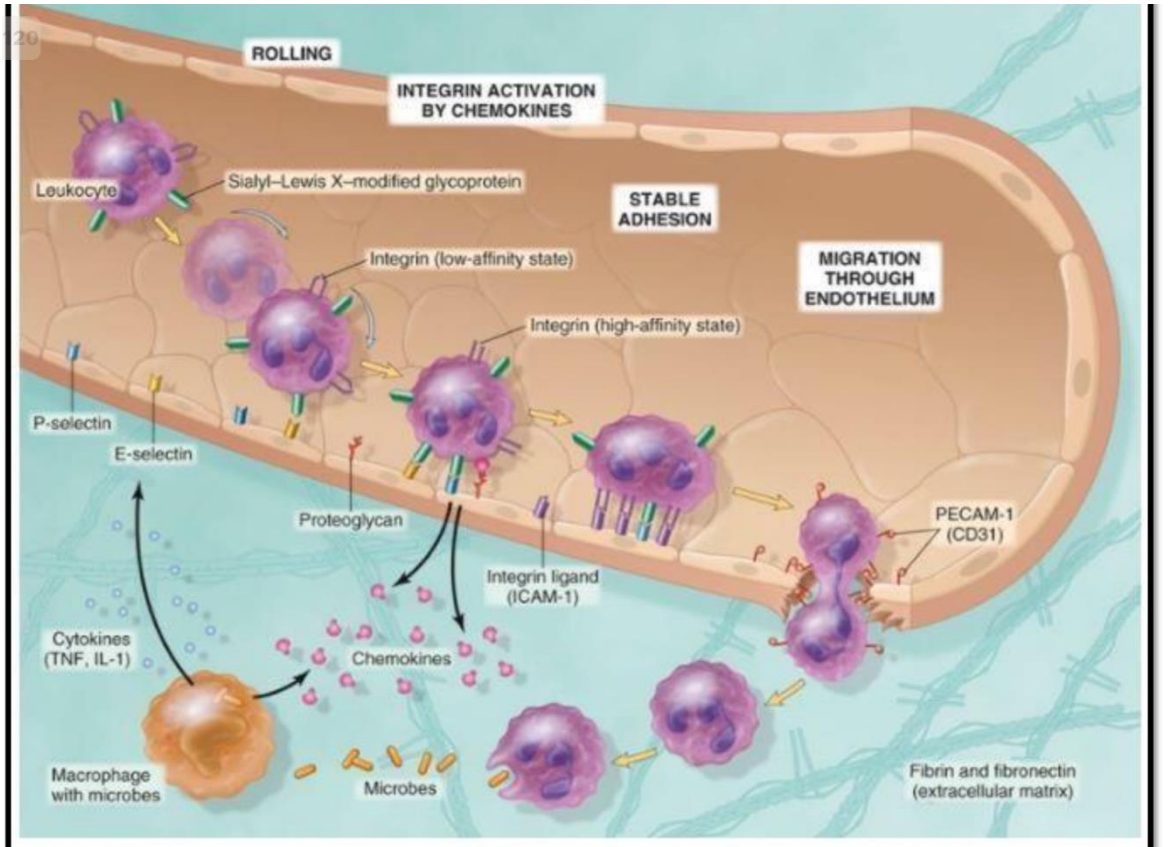


FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he…

Then we will go to interstitium, and they will start releasing chemical mediators of inflammation, and continue their phagocytosis and intracellular killing which are steps which come later which will explain more in details.

This table is explaining the different types of integrins and selectins, and the immunoglobulin CD31 which is also responsible for endothelial cell injury.

Let's repeat some points, the selectins are group of proteins which are present in the endothelial cells and they are responsible for the initial weak attachment with these white blood cells, for preparing them for the next group of proteins integrins, where stronger attachments are present and they will hold a neutrophil or WBC's close to the endothelial cells for preparing them for PECAM-1 or CD31 where the destruction of the basement membrane will happen and the cell will squeeze itself and sneak into the outside of the blood vessels.

This is summary of the previous slides.

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.

You don't have to memorize this table. Just remember what did we say.

CD31 (PECAM-1), platelet endothelial cell adhesion molecule which is expressed on leukocytes and endothelial cells.

WBCs (through transmigration process) will pierce through the wall by **collagenases** (enzyme) to destroy plasma membrane, because the major components of the basement membrane is collagen type 4 and laminin.

Collagenase will increase or reduced by the function of CD31, for making a hole and helping WBCs to move outside.

تم بحمد الله والله ولي التوفيق