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Pathology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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-**In the last lecture** we talked about the two kinds of inflammation:

1- Acute inflammation: it will declare itself (usually mild and self-limited).
2- Chronic inflammation: it is insidious (often severe and progressive).

Causes of inflammation:

1- Infection:

Bacteria, fungi, viruses, parasites **and** their toxins [like in food poisoning (acute bacterial poisoning), where the bacteria produces toxins] are among the most common causes of inflammation. (we called these toxins: exotoxins).

2- Necrosis:

Ischemia, trauma (accidental causes), physical and chemical injuries, burns(radiation), frostbite, irradiation (we use it nowadays to treat tumors and cancer).

3- Foreign bodies:

Splinters, dirt, uric acid crystals that are deposited in joints and causes acute arthritis (Gout), and cholesterol crystals in atherosclerosis.

4- Immune reactions:

- Acute allergic reactions (Hypersensitivity reactions). Severe acute allergic reaction is called acute Anaphylaxis. When there are too much acute responses, it causes systemic effects. It may cause death in some cases, because the stimuli for these inflammatory responses can't be eliminated or avoided.

-Autoimmune diseases

Causes of inflammation:	
INFECTIONS	Bacteria, fungi, viruses, parasites And their toxins
NECROSIS	Ischemia, trauma, physical and chemical injuries, burns, frostbite, irradiation
FOREIGN BODIES	Splinters, dirt, urate crystals (gout), Cholesterol crystals (atherosclerosis)
IMMUNE REACTIONS	Allergies and autoimmune diseases

The Five Rs of Inflammation:

The first R is **recognizing** the element. After recognizing the injury, foreign material, or viral material, we start **recruiting** WBCs and mediators (proteins). WBCs try to **remove** the enemy (make it inactive; for example(dormant)). The response is then **regulated** (the inflammation is controlled). Finally, the **repair** of tissue will return everything back to normal.

Recognition of microbes or damaged cells

- It is the first step in inflammatory Response.

→ Cellular receptors:

Toll-like Receptors (TLRs): found on membranes (especially inflammatory cells) and endosomes (inside the cell's structure). Recognizing certain sequences called Pathogen Associated Molecular Patterns (**PAMPs**)

-They recognize all foreign bodies that come from outside by recognition of their molecular patterns (PAMPs) ➔ TLRs are not specific receptors.

→ Sensors of cell damage:

Recognize Damage Associated Molecular Patterns (**DAMPs**) such as uric acid, ATP, K, & DNA (caused by ischemia, necrosis or radiation that are make some injuries). Consequently, multiple cytoplasmic proteins get activated (inflammasomes)

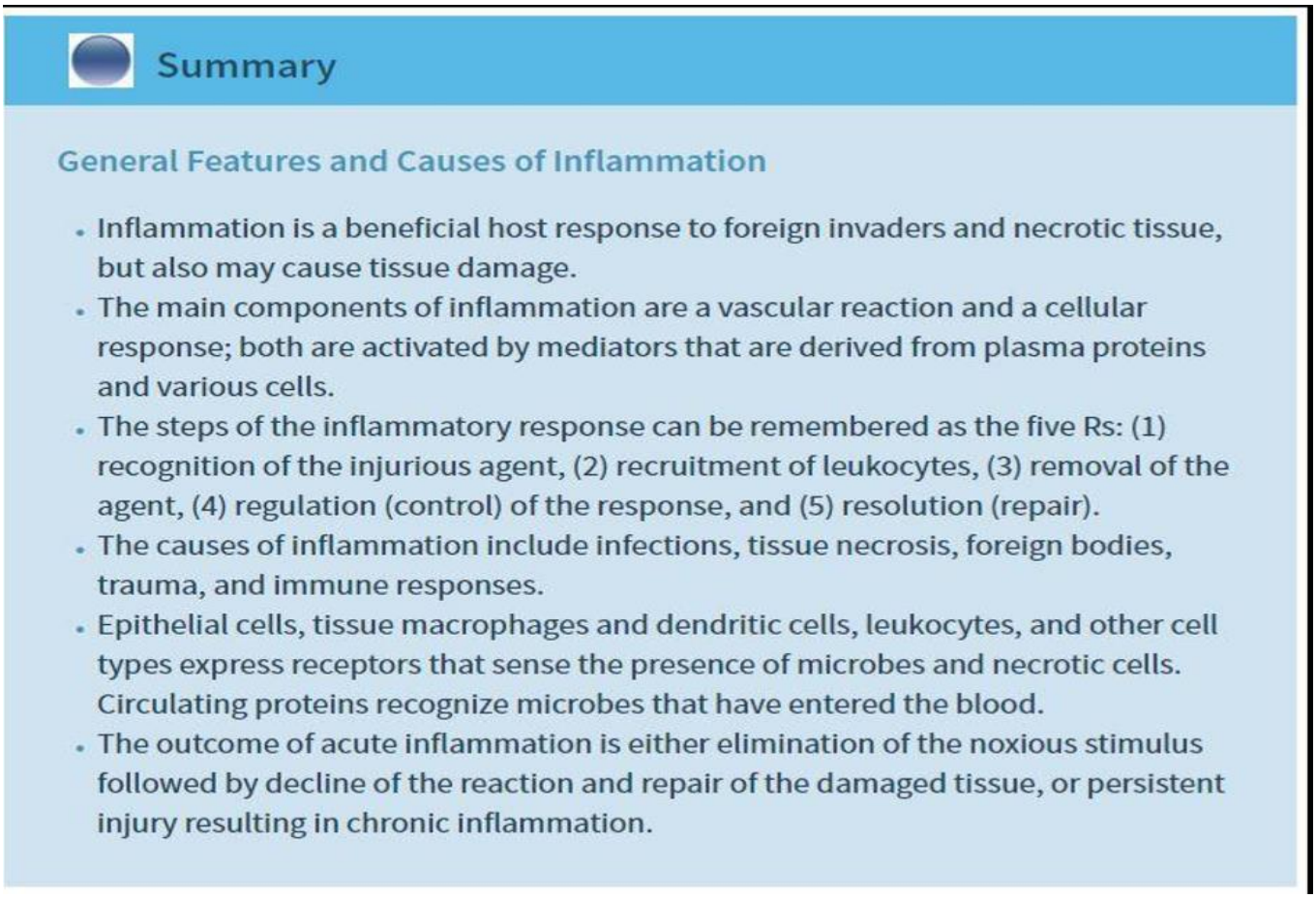
NOTE: cellular responses + sensors of cell damage have a **major** role in recognition.

→**Circulating proteins** (They circulate in plasma, and have a minor role in recognition): complement system, mannose binding lectins and collectins.

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.
- This phase composed of 3 major steps:
  1- blood vessels dilatation.
  2- Increased vessels permeability.
  3- Emigration of WBCs.

- Each step has its unique mediator(s) which enhance and stimulate it.
- Blood vessels dilation step is mediated by vasoactive amines (histamine),the most important modulator, which is responsible for vascular dilation (its major function).



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.

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

➔ Normal blood vessels contain vascular wall, plasma proteins, fluid, BRCs, WBCs, monocyte (remember that monocytes will become macrophages when exposed to the site of inflammation).
At normal conditions we have colloid osmotic pressure (depends on the amount of plasma proteins), and hydrostatic pressure (depends on the amount of the fluid inside the vessels), and they are always in equilibrium.

➔ In case of inflammation, equilibrium will be disrupted.

For better understanding:

-If hydrostatic pressure increases>>fluid will exit the vessels.

-If colloid osmotic pressure increases>>fluid will enter the vessels.

-If equilibrium is disrupted due to inflammation, the intravascular fluids, cells, and other molecules will move to extravascular compartment (interstitial compartment). This movement will cause swelling or congestion that we call **edema**.

- In general, we have two types of edema:

1- Exudate

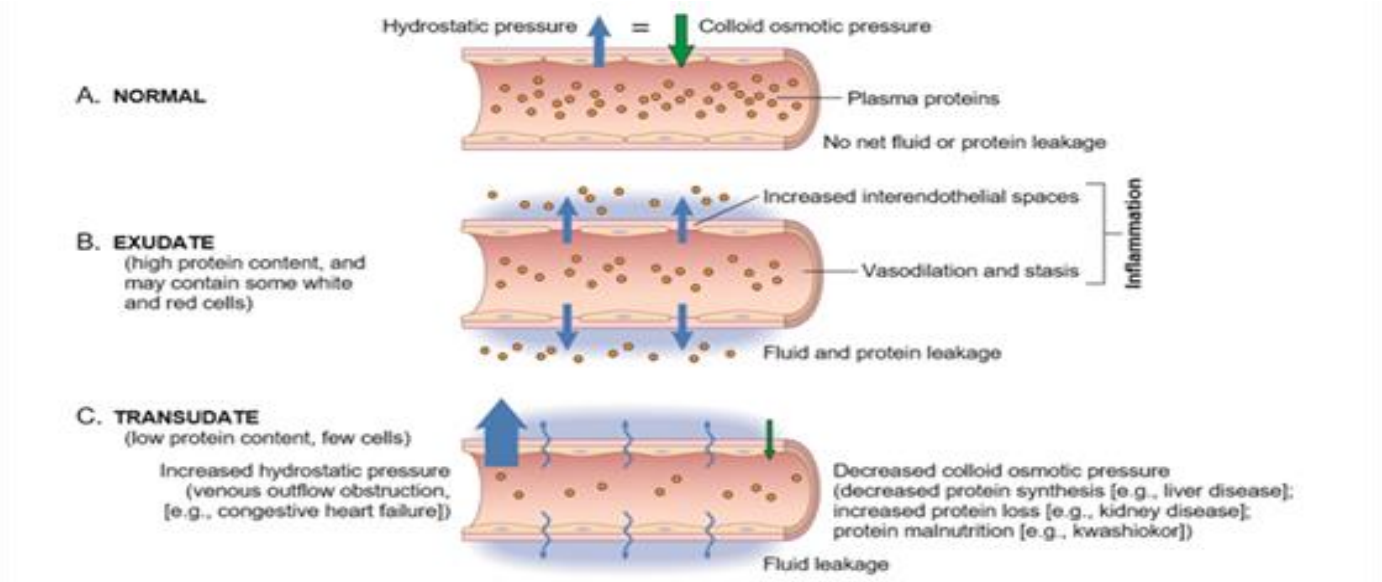
2- Transudate

- **Exudate**: interstitial fluid rich in proteins and is rich with cells (high levels of proteins and cells).
- **Transudate**: low proteins & low cellular content. (mainly fluid)

*** so, if we want to identify whether the fluid is transudate or exudate, we count the number of cells and the amount of proteins.

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

***** This table is very important.**



-**Exudate**: is formed during inflammation because vascular permeability increases as a result of the increase in interendothelial space. (damage in vascular epithelium cells→ vascular permeability increases due to severe inflammatory reactions)

-**Transudate**: is formed when fluid leaks out because of increased hydrostatic pressure or decreased osmotic pressure.

** In both cases the fluid leaks out of the vessels, but the reasons are different**

- In the case of liver failure (low protein synthesis) (hypoproteinemia)→low protein in the vessels→fluid exits the vessels to interstitial compartment due to low osmotic pressure (**Transudate**).
- In the case of congestive heart failure (Increased hydrostatic pressure)→ ascites (swelling of the abdomen) → (**Transudate**).

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Edema & Pus

***Edema: excess fluids in interstitium or serous cavities (either transudate or exudate).

-For example:

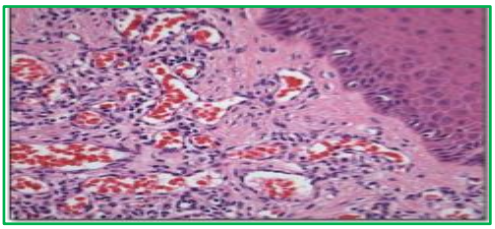
-Someone with heart failure has edema, which caused him to have a swollen leg. If you press on the swollen area, traces of pressing will be left, making it a **pitting edema**.

-**Edema** is fluid mainly due to transudate, caused by the hydrostatic & colloid osmotic pressure difference.

-Sometimes it occurs in the interstitial compartment and sometimes in the serous cavities, causing: plural effusion and ascites due to the congestive heart failure.

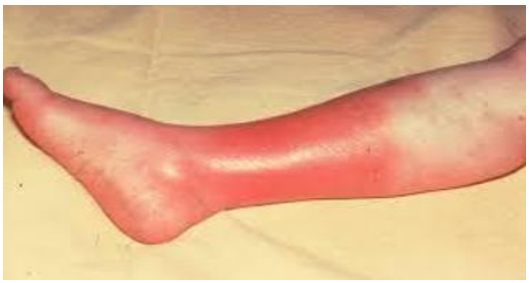
- In some cases, the edema starts as transudate, then becomes exudate. **EX**, you have ascites due to heart failure (Transudate), but if infected, it becomes Exudate.

*** **PUS**: purulent **exudate**; inflammatory exudate **rich** in WBCs, proteins, debris, and microbes, it's really severe inflammatory reaction.



**Some points about this picture:

The leg in this picture is suffering from **acute cellulitis.**



-Vasodilatation (Initial step): **histamine**; increased blood flow causing redness (erythema) and heat.

- Followed by increased permeability (exudate).

- In the area where the vasodilatation and permeability take place, the blood in that region stays for a long time ➔ this, what we refer to as **Stasis**.

-Stasis; congestion and erythema

** congestion means that per meter square, there are more structures, RBCs, and more inflammatory cells.

**Erythema: reddening of the skin.

- If the inflammation is contentious, PMNs (neutrophils) accumulate and adhere to endothelium, then migrate outside the vessel into the interstitium (**diapedesis**).

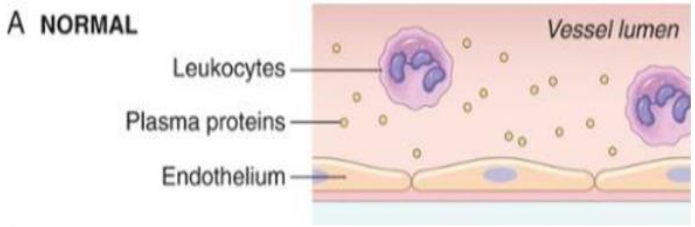
Diapedesis: The movement of WBC, especially neutrophils, during inflammation and stasis, **from inside to outside**. Diapedesis is highly regulated by specific steps and mediators.

The main driver of the initial phase of vascular events is **histamine,other amines, and mediators.

Vasodilation has 2 phases:

In picture A → Endothelial cells are

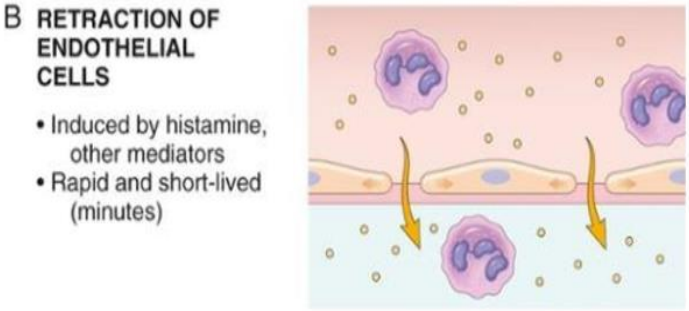
compacted, and are in equilibrium (no actions).



Initial phase:(quick & transient)

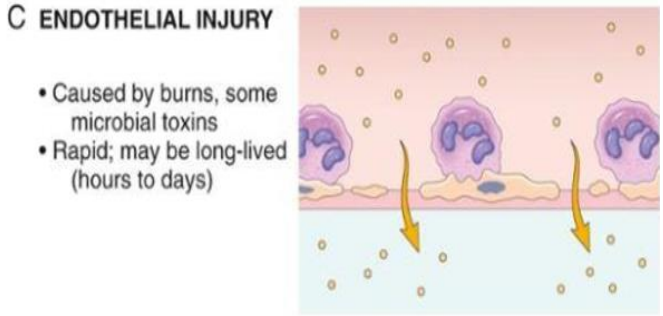
In picture B→HISTAMINE

Retraction of endothelial cells, which is induce by histamine and other modulators to allow proteins, fluids, and cells to enter. There is a contraction of cytoskeleton proteins by activation of certain enzymes to create spaces between cells➔ active



in phase 2: (severe)

Damage epithelial cells and basement membrane. More proteins and fluids will leave the vessel .



**The structure of basement membrane:

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

→Basement membrane couldn't be damaged without the help certain enzymes due to its strength.

→Usually this happens during **severe injuries** such as burning.

Mild inflammation + short and quick+ small amount of proteins get outside = phase 1

Sever inflammation+ active damage to epithelium+ more amount of fluids and proteins get out = phase 2

**Questions:

-If there is just simple retraction → **Transudate** (only small amount of fluids & proteins are leaked).

-If there is severe damage → **Exudate** (more fluid & more proteins are leaked).

Lymphatic vessels and lymph nodes

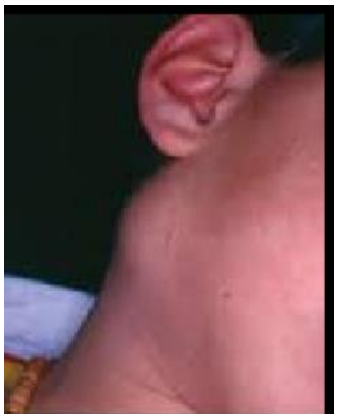
-**Lymphatic vessels** are vascular channels, specifically designed to drain and repair after inflammation.

- We have **lymph nodes** in many areas in our body, and each one of them drains from a different location.

- Sometimes lymphatic vessels get inflamed due to drainage of fluids or other elements, so we call them inflamed lymphatic vessels (**Lymphangitis**). (Transudate or exudate depending on the inflammation) ➔ Drainage to nearby lymph nodes, hence causing

lymphadenitis (reactive lymphadenitis or inflammatory lymphadenitis) (enlargement of lymph node).

➔ Posterior cervical lymph nodes (very common)
➔ The most common causes of lymphadenitis (enlargement of lymph node) are viral or bacterial infections.



➔ **The risk** when there is lymph node enlargement due to known initial infection →taking drug (antiviruses or antibacterial→ the problem is **not resolved**!
-Here we take a **biopsy** for example to know the reasons of swelling.

➔ Inflammatory (ACTIVE) lymphadenitis:

Example: If women has mastitis (inflammation of breast tissue) after two weeks from delivery, then this is a common scenario. She will have a fever and pain in the breast (**mastitis** from lactation), **OR** maybe an inflamed **axillary lymph nodes**.

> During emergencies, if a patient comes with pain, redness, tenderness in his lymph node>> it can be **good news** if there are bacterial and viral symptoms (inflammatory lymphadenitis). By taking antibiotics, he should heal, returning to his/her normal state. But if the **cause is cancer**, antibiotics will change nothing in his body and this is a case of **bad news.**

***This summary is very important.

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 pathologists have * to connect the 3D shape of the cell in the body with the 2D shape under the LM.

GOOD LUCK