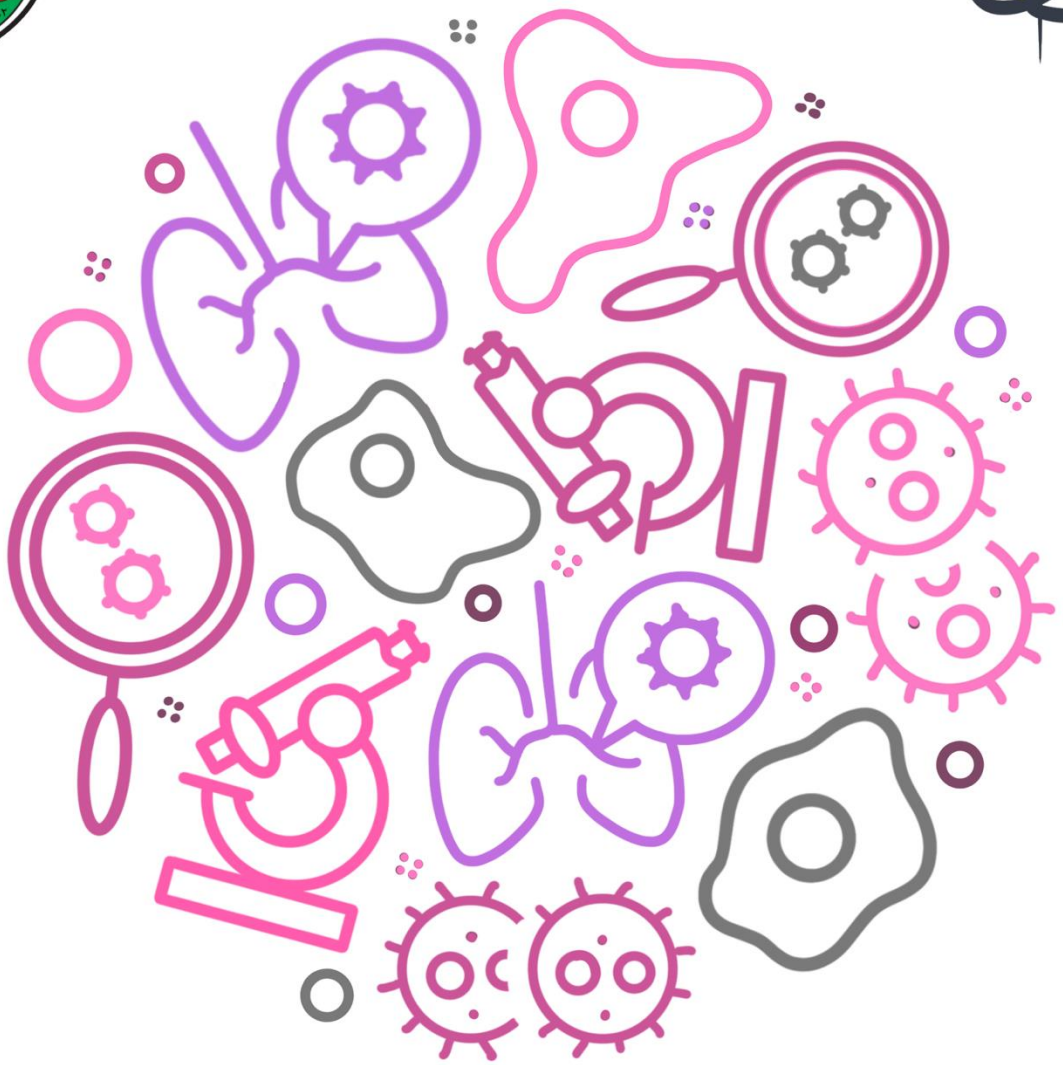
SHEET NO. 8



PATHOLOGY

DOCTOR 2019 | MEDICINE | JU

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In the last lecture we have talked about the main vascular reactions of acute inflammation which are vasodilation, then increased blood flow, then increase in vascular permeability, and ALL due to chemical mediator's release such as; Histamine. Then Recruitment take place: the movement of the inflammatory cells, mainly neutrophils and macrophages, from the intravascular compartment (blood) to the extravascular compartment, through a multi-step process: **Margination**, then **Rolling** (loose attachment mediated by selectins), then **Adhesion** (firm attachment mediated by integrins), then **Transmigration** due to the CD31 role utilizing collagenase, destroying the basement membrane, and helping cells to reach the site of injury.
Now let's continue the 2nd R: Recruitment

Chemotaxis

Chemotaxis: the movement of WBCs from blood to the site of injury. And it occurs **after** extravasating from the blood.

- if the site of injury is your tonsils/skin, then chemotaxis will occur toward the tonsils/skin by WBCs.
- It is considered as an active process, and is induced by certain group of mediators called, **Chemoattractants**.
  Chemoattractants: strong mediators that induce and stimulate the movement of leukocytes, and they can be either: exogenous (from outside the body) or endogenous (produced from inside the body), including the following:

Exogenous	**Bacterial products** -**Particularly** Peptides **of N-… termini**
Endogenous	**Cytokines:** a big family of chemical mediators produced mainly by lymphocytes and inflammatory cells like macrophages. -especially those of **Chemokine family**, which is the strongest family
	Complement system (part of plasma proteins) components -particularly **C5a**, which is the strongest (active.)
	Products of Lipoxygenase-pathway of arachidonic acid (AA) -particularly leukotriene B4 (**LTB4**), which is the strongest product of AA metabolites.

WBCs infiltrate in tissue

5:35

The type of emigrating leukocyte varies with the age of the inflammatory response and with the type of stimulus as shown in the table below:

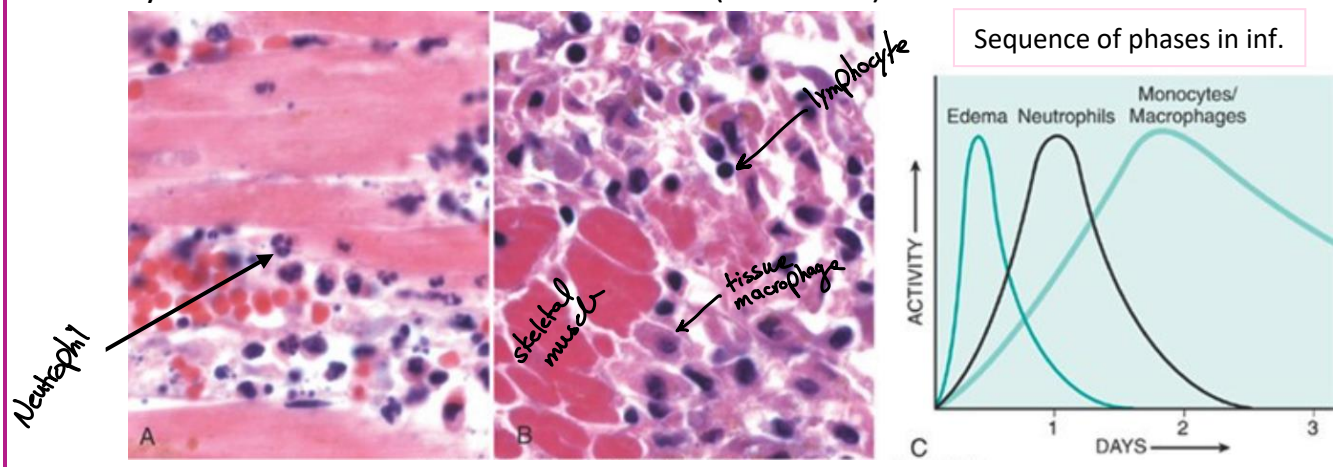
Neutrophils (PMNs)	6-24 hours **acute inf.**
Macrophages, Lymphocytes and Plasma cells	24-48 hours and may stay longer
Eosinophils	Allergic Reactions

<u>They are the HALLMARK of Acute inflammation</u>
If we see neutrophils, this indicates a **recent Acute inflammation**.
Neutrophils are short-lived that they don't stay more than 6-24 hours.

<u>They are chronic inflammatory cells</u>
They come later on, **<u>after</u>** neutrophils death by apoptosis, after 24-48 hours of infection, and they could stay for couple of days or weeks. And in specific conditions -like viral infections- Macrophages, Lymphocytes and plasma cells may be the first cells to arrive instead of neutrophils.

Eosinophils are seen in specific conditions, which are considered as allergic/hypersensitivity reactions and parasitic infections

Lets have a small discussion about the Nature of leukocytes infiltrating in Inflammatory Reactions, through those histological photomicrographs of an inflammatory reaction in the myocardium after an ischemic necrosis (infarction):



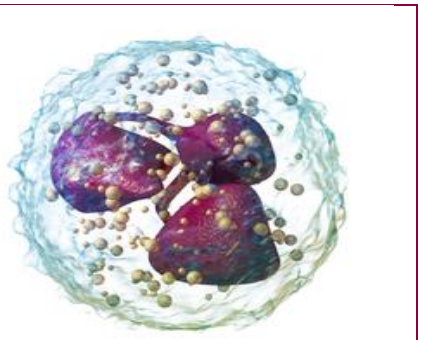
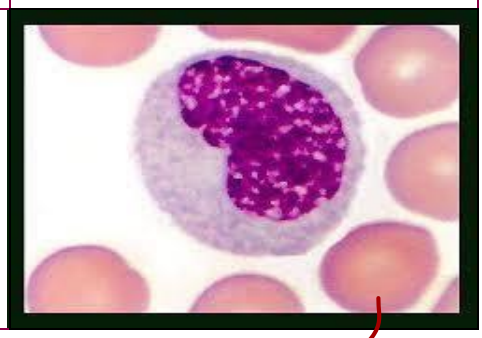
A. a lot of neutrophils, so this is an acute inflammatory process which indicates that those morphologic changes took place within the last 24 hours.

B. Mononuclear cells infiltration is shown, which indicates that this is the chronic phase of the inflammation.

C. -Edema: the first phase, the vascular phase, were edema ensues
-Neutrophils: the second phase, were neutrophils infiltrate the tissue then die
-Monocytes/Macrophages: chronic inflammatory cells peak at day 2 and <u>may</u> remain in the tissue and take longer time to disappear.

Leukocyte Activation

Once leukocytes have been recruited to the site of infection or tissue necrosis, they must be activated to perform their functions.
The two major cells that contribute in the initial phase of inflammation are:

Neutrophils	PMN(polymorphonuclear leukocyte) "mickymouse" with 3 nuclei. They have granules containing enzymes → when ruptured → enzymes are released and they digest the internal material (foreign bodies).	
Monocytes	The resident monocyte in the tissue is a macrophage. The monocyte circulating in the blood is not differentiated yet -have a phagocytic effect with a bean or kidney shaped nucleus. And it has less granules than neutrophils.	

So, Leukocyte activation mainly results in:

- **Phagocytosis.**
- **Intracellular killing/destruction of phagocytosed microbes and dead cells by substances produced in phagosomes:** NO, ROS.
- **Liberation of substances that destroy extracellular microbes and dead tissue such as:** NETs.

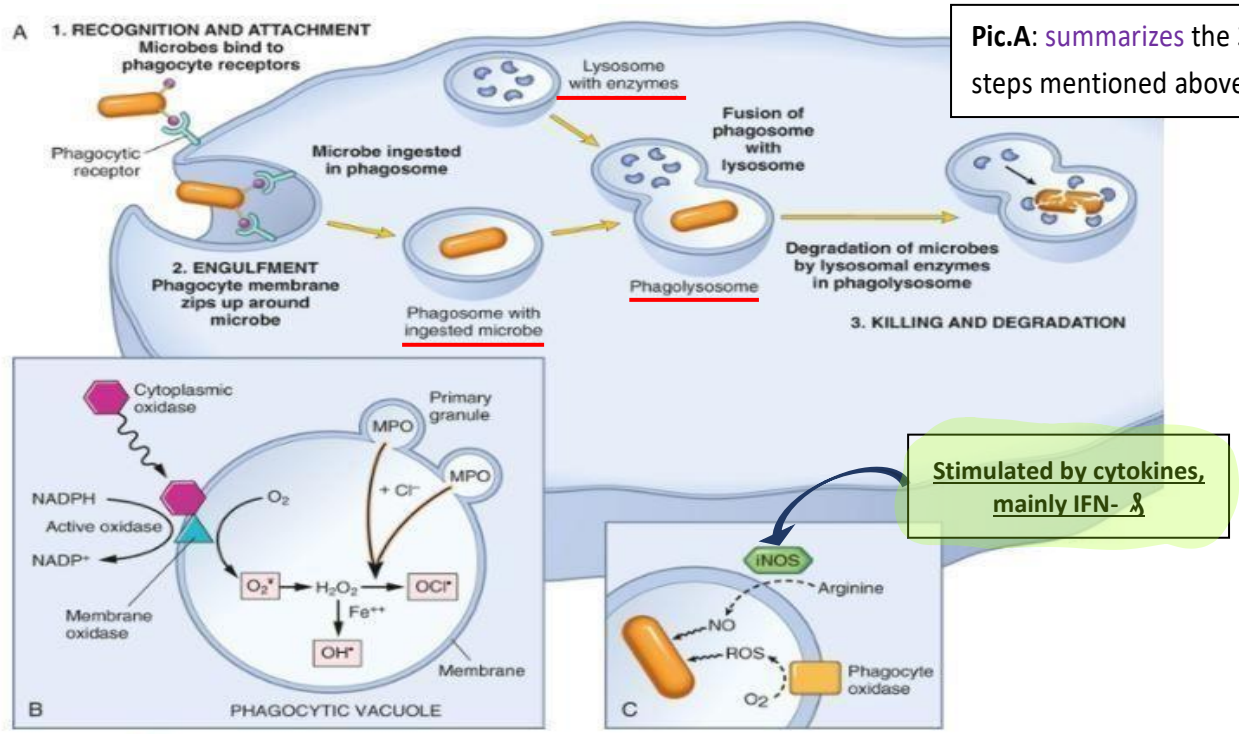
The process of Phagocytosis and Intracellular killing:

a Multi-step process:

1) Recognizing the invading/foreign agent, it is induced by specific receptors on the ingesting Phagocyte.
   Receptors on the phagocytes that recognize the offending agent:
   - Mannose receptor
   - Opsonins; (by opsonization*) including immunoglobulin IgG, and C3b
2) Engulfment of the foreign material and forming a phagocytic vacuole (phagosome) where the bacteria exists.

* Opsonization is an immune process which uses opsonins to tag foreign pathogens for elimination by phagocytes.

3) Killing and degradation: by an active process, induced by substances produced in Phagosomes, including ROS and Nitrogen Oxide (NO) and **MPO-halide, which is the most potent bactericidal system of neutrophils**.



Pic.A: summarizes the 3 steps mentioned above.

FIG. 3.7 Phagocytosis and intracellular destruction of microbes. (A) Phagocytosis of a p…

Nitric Oxide

a soluble gas produced from Arginine (amino acid), by the enzyme: NO synthase (NOS), and function in killing microbes in the phagosome.

Arginine → iNOS → Nitric Oxide

Types of NOS:

1- eNOS. (endothelial)
2- nNOS. (neuronal)
3- **iNOS, the one which is responsible for the intracellular killing, stimulated by cytokines, mainly IFN-γ (**interferon gamma**)**

All these types of NOS produce NO, but only iNOS is capable of killing microbes (other enzyme types have different function such as neurotransmitter)

Usually, this reaction happens, forming **much more potent ROS**

Nitric Oxide + Superoxide (O2-*) = Peroxynitrate (ONOO*)

Granule Enzymes

PMNs and Monocytes both have granules. However, Granules are more abundant in Neutrophils.

Types of granules in Neutrophils are:

- **Primary G** (large azurophilic granules)
- **Secondary G** (small granules).

Azurophil: due to the color of the dye reaction.

Granule types	Size	Components and secretions	Notes
Primary G / Azurophil	Large	Myelo Peroxidase (MPO), other enzymes which are needed in the intracellular killing	
Secondary G	Small	Lysozymes, other enzymes	Utilized after the production Phagolysosome in the later stages of phagocytosis

Those granules are always beneficial in case of injury, **unless they are uncontrolled**, and that's why checking and balancing them, always takes place in our body.

Thus, how is neutrophils' function controlled?

The released neutrophil proteases are normally regulated by a system of anti-proteases such as: ά-1 antitrypsin, which inhibits elastases.

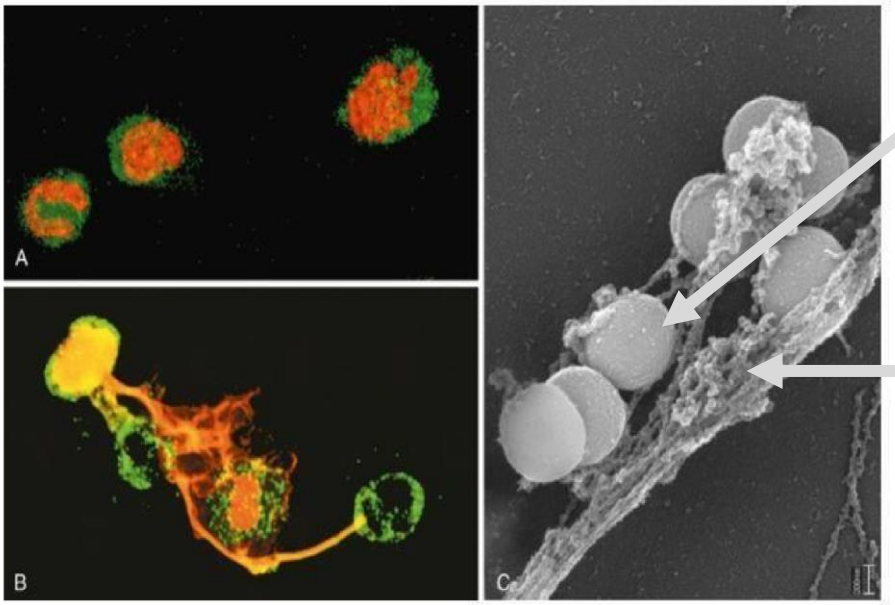
***In case of deficiency in those anti-proteases, especially in GI tract, there will be no inhibition of those lysozymes/different enzymes released by neutrophils and macrophages**, thus collateral damage in the site of injury will occur, leading to chronic diseases.

Neutrophil Extracellular Traps (NETs)

- A very thick viscous mesh work material which is composed of nuclear chromatin bound to it granule proteins, such as antimicrobial peptides and enzymes.
- Found after the death of neutrophils.
- Helps in trapping invaders at the site of injury in its fibrils, and killing them through the products released after Neutrophils death (NETosis).
- They play a major role in the pathogenesis of sepsis.
- Involved in SLE (**Systemic lupus erythematosus**), which is an autoimmune disease that mostly affect females causing widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels. And it results in rash, red cheeks, and joint pain.

Sepsis is a potentially life-threatening condition caused by the body's response to an infection. The body normally releases chemicals into the bloodstream to fight an infection. Sepsis occurs when the body's response to these chemicals is out of balance, triggering changes that can damage multiple organ systems.

A scanning picture explaining those thick viscous material:



Bacterial cocci

Pathogens stick to materials in the NET, allowing other inflammatory cells to come and kill those bacterial particles

NETs

FIG. 3.8 Neutrophil extracellular traps (NETs). (A) Healthy neutrophils with nuclei stain…

Leukocyte-Induced Tissue Injury

Although we have just mentioned that leukocytes are really needed for defense mechanism to get rid of pathogens, it would sometimes be harmful and disease-causing in certain scenarios:

A. **Prolonged inflammation,** consistently producing local leukocytes
for example if there was a prolonged inflammation, which occurs if the pathogen was very strong, such as:
   - Mycobacterium Tuber Culosis, a very strong bacteria that the host response contributes more to the pathologic process than does the microbe itself.
   - Hepatitis (Mainly type C, the most common in ME region), which can cause a chronic liver disease in the case of prolonged inflammation.

B. **Inappropriate inflammatory response,** the basic mechanism of Auto-Immune diseases. Your inflammatory response is inappropriate that they induce normal tissue damage, such as:
   - SLE
   - Rheumatoid arthritis
   - Mixed connective tissue disease

   Auto-Immune disorder which occurred due to inappropriate inflammatory response against a pathogen

C. **Exaggerated response,** the basic mechanism of asthma and allergic reactions. where the simplest immune reactions, like: flu, cold, stress, is going to induce an exaggerated inflammatory response causing allergic reactions

Additional functions of WBCs

We always need those white blood cells recruited to the tissue of injury. Now there are certain additional functions committed by WBCs:

1) Amplify -or- Limit the reaction

   Cytokines induce this function:

   Amplification: in the 2nd and 3rd phase of inflammation, we need amplification of all inflammatory soldiers, so WBCs will produce more cytokines to enhance and amplify the reaction.

   Limitation: if we reach to the point that most of the pathogens are dead, and phagocytosed, then we don't need any more armies, so WBCs will produce specific type of cytokines to limit, contain and terminate the inflammatory reaction.

2) Growth factors secretion

   extremely important in the latent phase of inflammation, which is repair. So, WBCs start secreting growth factors that help initiating the repair process.

3) T-lymphocytes

IMP

   There is a certain type of T-cells that function specifically in Acute inflammation, which are **T-Helper-17**. Those cells produce cytokines called, IL-17. Deficiency in this cytokine causes low immunity.

Summary (from the book)

• Leukocytes can eliminate microbes and dead cells by phagocytosis, followed by their destruction in phagolysosomes.
• Destruction is caused by free radicals (ROS, NO) generated in activated leukocytes and by granule enzymes.
• Neutrophils can extrude their nuclear contents to form extracellular nets that trap and destroy microbes.
• Granule enzymes may be released into the extracellular environment.
• The mechanisms that function to eliminate microbes and dead cells (the physiologic role of inflammation) also are capable of damaging normal tissues (the pathologic consequences of inflammation).
• Anti-inflammatory mediators terminate the acute inflammatory reaction when it is no longer needed.