PATHOLOGY

بسم الله الرحمن الرحيم

MID – Lecture #10

Inflammation 5

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

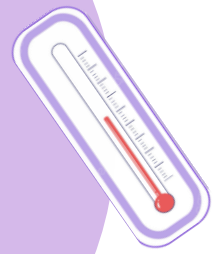
اللهم استعملنا ولا تستبدلنا

Written by:

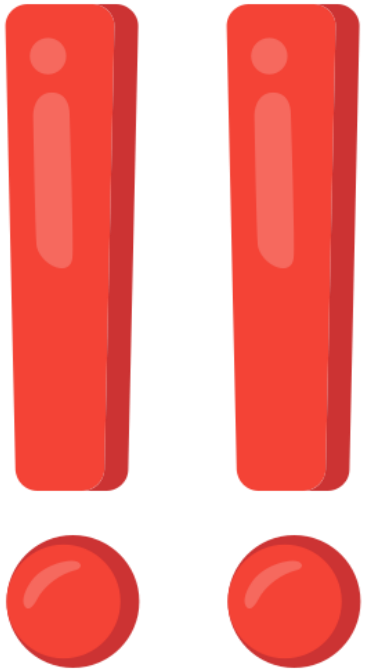
- Layan Al-Amir
- Raneem AH

Reviewed by:

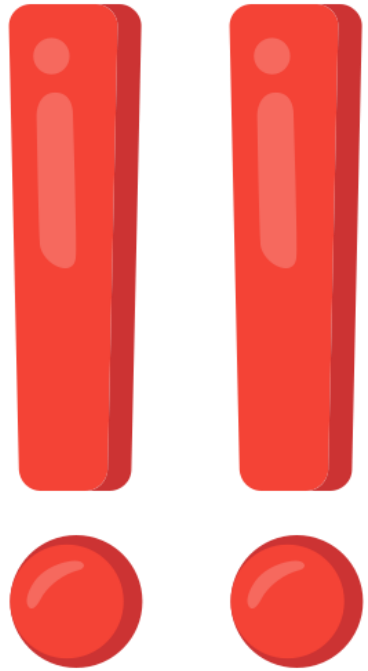
- Hala Alkaabneh



Previous Lecture Quiz



Quiz Link



Lecture 5

اللهم إني أسألك فَهم النبيين، وحفظ المرسلين، وإلهام الملائكة المقربين. اللهم اجعل دراستي هذه طريقًا للعلم والنور، وافتح لي أبواب الفهم والحكمة، وبارك لي في وقتي وجهدي، واجعل التوفيق حليفي في كل خطوة.

اللهم اجعلني من الناجحين، وارزقني الصبر والإصرار، ووفقني لتحقيق أهدافي وأحلامي. يا رب اجعل دراستي سببًا لرضاك عني، وسعادة لي ولأهلي، وارزقني التوفيق في كل ما أسعى إليه. آمين.

So far, We've highlighted the most important inflammation mediators in the previous lecture , but the list keeps growing with new discoveries.

OTHER MEDIATORS:

- **Platelet activating factor (PAF): platelet aggregation and other functions**
- **Protease activating receptors (PARs): platelet aggregation**
  - Since those two are important in platelet aggregation, they are incriminated in the pathogenesis of atherosclerosis and thromboembolic diseases, in addition to Prostaglandin I2 (PGI2) and thromboxane A2 (TXA2)
- **Kinins: vasoactive peptide, Bradykinin the active; VD, increase permeability, smooth muscle contraction, and pain.**

(vascular dilation)

(makes them play a role in active labor after the end of the pregnancy)

  - Kinins also have a therapeutic effect (discussed later in pharmacology)
  - The most important prototype is bradykinin
- **Neuropeptides: Substance P and neurokinin A**

**important table, memorize;)

TABLE 3.8 Role of Mediators in Different Reactions of Inflammation

function

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine
	Prostaglandins
Increased vascular permeability	Histamine
	C3a and C5a (by liberating vasoactive amines from mast cells, other cells)
	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Cytokines
	Chemokines
	C3a, C5a Complement
	Leukotriene B_4
Fever	IL-1, TNF
	Prostaglandins
Pain	Prostaglandins
	Bradykinin
Tissue damage a by stander of inflammatory response	Lysosomal enzymes of leukocytes
	Reactive oxygen species

- **leukotriene B4** is a very potent chemotactic agent.
- **Fever** is a manifestation of acute inflammation.
- **IL-1, TNF, and Prostaglandins** are targeted by certain medications to decrease the impact of fever on human tissue.
- Not all of the pathophysiology of pain production is known to us.
- **Prostaglandins and Bradykinin** also targeted in treatment.

Summary

Actions of the Principal Mediators of Inflammation

- Vasoactive amines, mainly histamine: vasodilation and increased vascular permeability
- Arachidonic acid metabolites (prostaglandins and leukotrienes): several forms exist and are involved in vascular reactions, leukocyte chemotaxis, and other reactions of inflammation; antagonized by lipoxins
- Cytokines: proteins produced by many cell types; usually act at short range; mediate multiple effects, mainly in leukocyte recruitment and migration; principal ones in acute inflammation are TNF, IL-1, and chemokines
- Complement proteins: Activation of the complement system by microbes or antibodies leads to the generation of multiple breakdown products, which are responsible for leukocyte chemotaxis, opsonization and phagocytosis of microbes and other particles, and cell killing
- Kinins: produced by proteolytic cleavage of precursors; mediate vascular reaction, pain

How the tissue will look like in the presence of acute inflammation

MORPHOLOGY OF ACUTE INFLAMMATION

- **The critical issue is blood vessel dilatation** (initial vascular phase) **and accumulation of WBCs and fluids in the extravascular tissue.**
- Some morphological patterns can be observed with the naked eye, under a light microscope, or even through an electron microscope (e.g., neutrophil traps).

Edema	Fluid and proteins in interstitium
Redness	rubor
Warmth	calor
Swelling	tumor
Loss of function	Functio laesa
Pain	dolor

MORPHOLOGY OF ACUTE INFLAMMATION

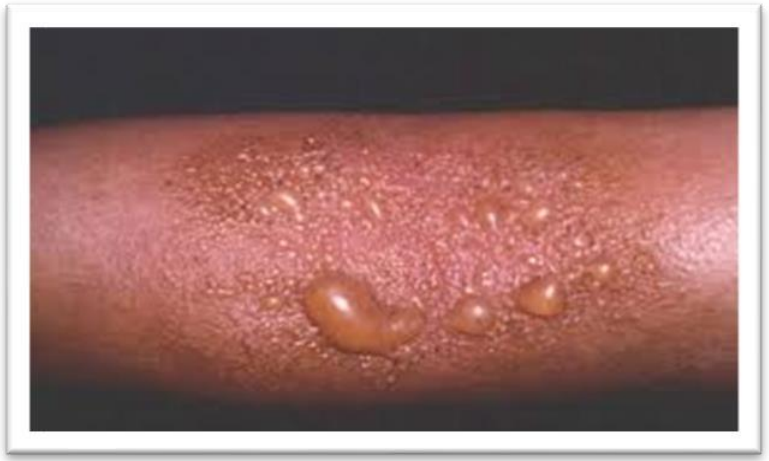
- **The critical issue is blood vessel dilatation** (initial vascular phase) **and accumulation of WBCs and fluids in the extravascular tissue.**

Edema	**Fluid and proteins in interstitium**
Redness	**rubor**
Warmth	**calor**
Swelling	**tumor**
Loss of function	**Functio laesa**
Pain	**dolor**

1. **Edema:** Excess much fluids and proteins in the interstitium after the initial vascular phase (VD) and increased vascular permeability. >> The organ involved is edematous, enlarged
2. **Redness:** Explained by an increased number of blood vessels in the affected area.
3. **Warmth:** Active angiogenesis and vascular changes produce heat in the affected organ.
4. **Swelling:** Due to edema.
5. **Loss of Function:** Pain and edema reduce functionality in the affected organ.
6. **Pain:** Pain arises from specific mediators that promote its production (as mentioned previously). While pain can be bad, it has a positive aspect as well, it prompts you to go to the doctor, helping you get treated sooner.

What are the gross and microscopic characteristics of the different types of morphological changes in acute inflammation? each of the following is a morphologic feature/change in AI, and we'll discuss their characteristics

SEROUS INFLAMMATION:



- Prominent feature:
- **Cell poor fluid (transudate)**
- Transudative nature of the inflammatory response >> too much fluid, very little cell debris .
- Common examples:
  - **Serous effusions**
  - **Skin blisters**
  - **Seromas**
    - They are common

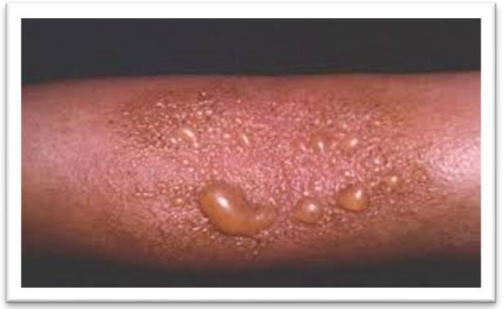
SEROUS INFLAMMATION:

1. Serous Effusions

(the accumulation of a clear, pale yellow, protein-poor fluid in body cavities)

A patient with bilateral pleural effusion due to heart failure or Hyponatremia from liver failure/liver disease,
leading to decreased oncotic pressure, which causes fluid to leak into interstitium/body cavities, or in the inter-abdominal acidic fluid area. This fluid, often yellow, is collected by tapping (aspiration) to examine for malignancy, culture the fluid, or check protein levels. Under the microscope, it appears with low cellularity(cellular content).

2. Skin Blisters



Seen in first-degree burns, What is present in those areas is serous transudate, cell-poor fluid from the acute injury.

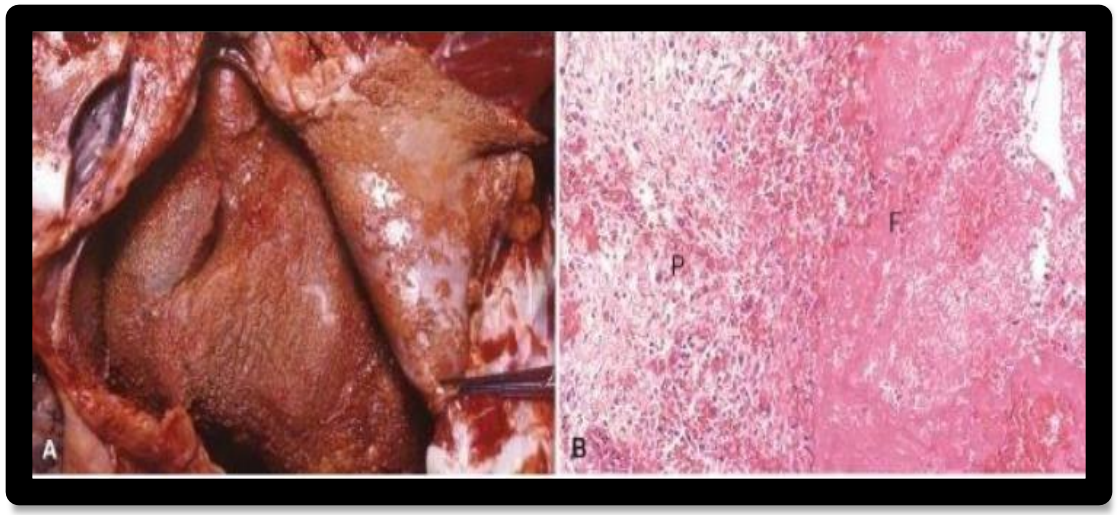
3. Seromas

a collection of clear, straw-colored fluid that builds up in tissues after surgery or injury.

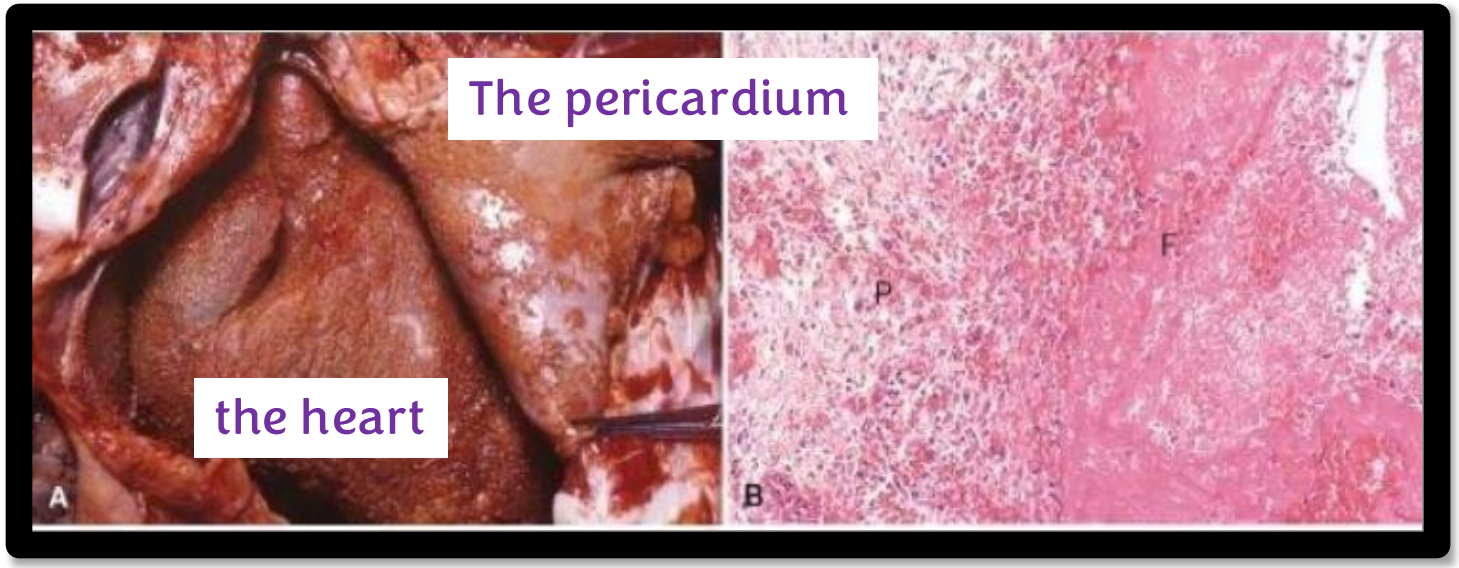
It is a sac or collection of serum which is transudate inflammatory fluid. Those are common after surgery. Certain surgeries will induce the production of seromas, like **hernia repair** and **breast surgery**. Sometimes, 1-3 weeks after surgery, patients return with a swollen area. When you aspirate them, they look clear/yellow. You may need to tap (aspirate) them two or three times until they disappear.

FIBRINOUS INFLAMMATION:

- similar to serous inflammation (also transudate), however here :
- **Large vascular leakage +** a lot of **coagulation** in the fluid pouring out into the area.
- characteristically seen in certain **Body cavities: pericardium** (fibrinous pericarditis) and **the pleura** (fibrinous pleuritis)



FIBRINOUS INFLAMMATION:



Histologically, it appears as an inflammatory response characterized by coagulation, platelets and abundant fibrin deposits (the pinkish material).

- If a patient comes with **fibrinous pericarditis,** it must be treated quickly. Otherwise, the pericardium can thicken due to fibrinous inflammation with large vascular leakage and a lot of coagulum, proteins, and platelets. This can sometimes cause fatal consequences unless treated quickly.
- Treatment: open the chest> make a pericardial window> drain the fluid> goes for examination with a piece of the pericardium to determine inflammation

PURULENT (SUPPURATIVE) INFLAMMATION, ABSCESS:

- **Pus: exudate rich in PMNs** (neutrophils) **mainly**+ **debris + edema**
  PMNs indicate that there is severe acute inflammation to the point that the body can't cope with this IR, these components will form small pockets of suppurative/purulent inflammation/ pus.
- **Bacteria (staph.)**
  Staphylococcus aureus bacteria cause necrotizing suppurative inf wherever they infect.
- **Abscess: localized collection of pus**

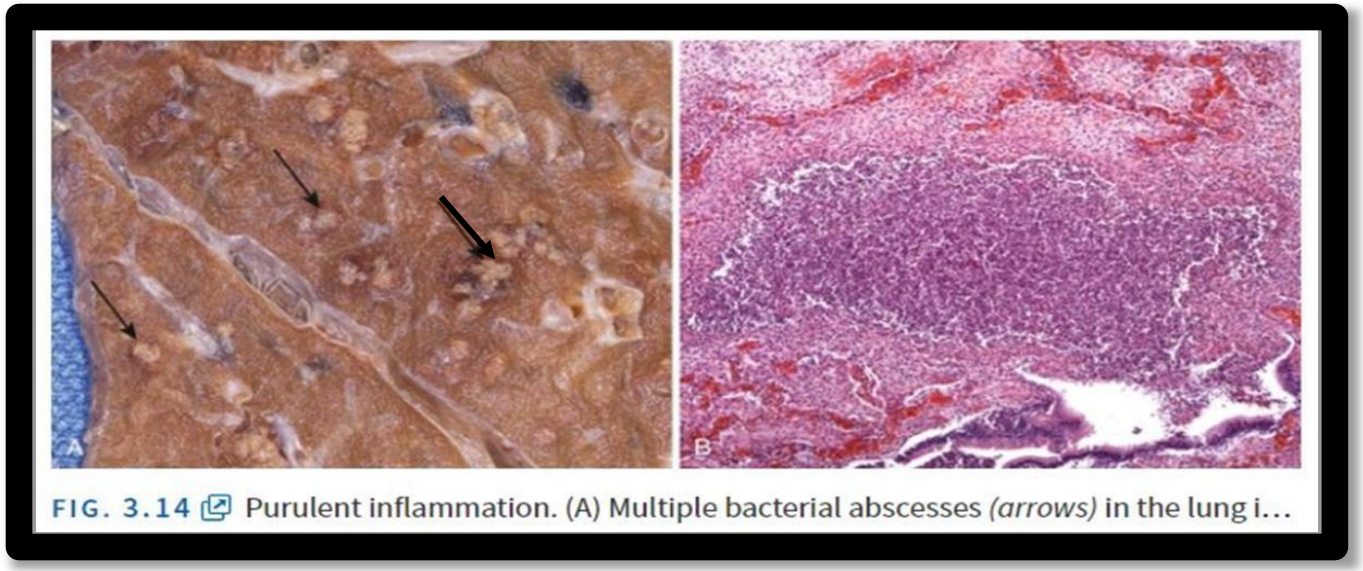


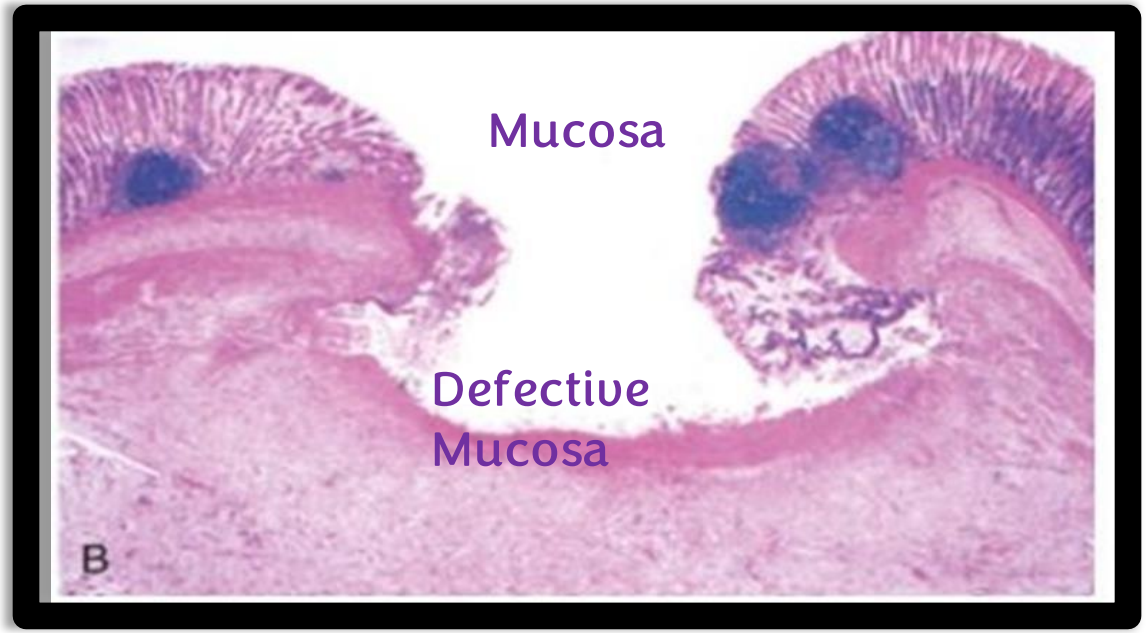
FIG. 3.14 Purulent inflammation. (A) Multiple bacterial abscesses *(arrows)* in the lung i…

A lung section from a patient who died from severe pneumonia >> gross appearance shows micro-abscesses (pointed out by arrows)

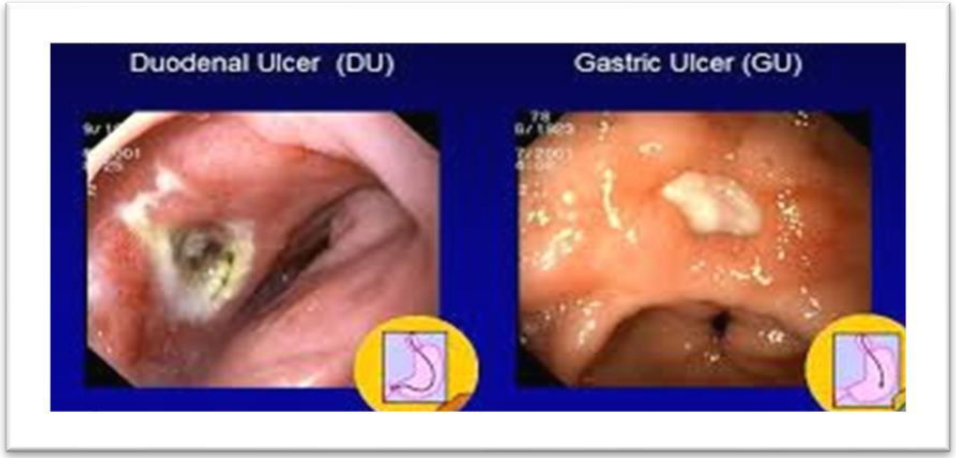
Microscopically, this lesion is a neutrophil collection forming an abscess, surrounded by reactive lung tissue. Inside the abscess are acute inflammatory cells, including neutrophils, bacteria, & other inf cells. This is the bronchial epithelium, and because the process begins in the bronchial region, it is called bronchopneumonia.

ULCERS: (Ulcerative inflammation)

- **Defect on a surface**
- **Common in mucosal surfaces and skin**
  Discontinuity of a mucosal surface
- **Mostly acute and chronic inflammation**



- Microscopic view of a stomach that shows discontinuity of its mucosa >> an ulcer
- Those blue collections are lymphoid follicles, which are typically associated with chronic inflammation. They are found adjacent to areas of acute and chronic inflammation.



- A bronchoscopic appearance image (when the gastroenterologist introduces the bronchoscope to look at those ulcers)
- If a section was taken to examine, a definite, big deep ulcer/ defect will be seen

OUTCOMES OF ACUTE INFLAMMATION:

سبحان الله وبحمده سبحان الله العظيم

- **Each one of us will have an acute inflammatory response at a certain time in oue life.**
- **Most of us 95% will go back to normal.**
- **However, there are different types of outcomes of acute inflammation:**

Chronic inflammation

- **When we can't get rid of the acute inflammation due to certain reasons , and this acute inflammation will transform to chronic inflammation .**
- **Sometimes the chronic inflammation will be so severe and prolonged and progressive with damaging that order(tissue),there is a tissue damage at the end .**

Complete resolution

- **the most common outcome and most desirable one .**
- **The acute inflammation comes, it goes through 5 stages which we have mentioned in previous lectures(5Rs) and then tissue repair will start and most of the time 98-99% the tissue goes back completely to the preacute episode phase.**

Healing by fibrosis

- **some affected tissues will go and heal, healing process consists of fibrosis and scar formation. which will have sometimes a negative impacts on the cosmetic appearence of that organ or its function .**
- **If you have an attack of acute inflammation with small scar it may not look good but it doesn't affect the function, however the process could be severe enough to the point that the fibrous scar is so huge might affect on the function especially in certain anatomical area .** (we will talk about it in repair lectures)

*****To summarize the outcomes of acute inflammation this diagram is drawn to explain the initial injury, the vascular phases and the presence of acute inflammation with its outcomes:**

1. At the end of the acute inflammation, there will be a complete resolution and the tissue will go back to pre-inflammatory stage, so this is the first outcome which we would like to have most of the time.
2. The second outcome in the presence of too much tissue destruction or severe acute inflammation and there is a healing process needing tissue repair forming fibrosis scar in that area. The tissue characters here isn't exactly the same as the pre-inflammatory stage.
3. However, there is a scar tissue here and depending on this scar tissue or fibrosis tissue, the impact on the function will ensure. If the acute inflammation was progressive due to a virulent injurious agent or bad immunity there will be chronic inflammation with new vascularization , too much changes in the tissue, and sometimes severe fibrosis and scar formation leading to loss of function.

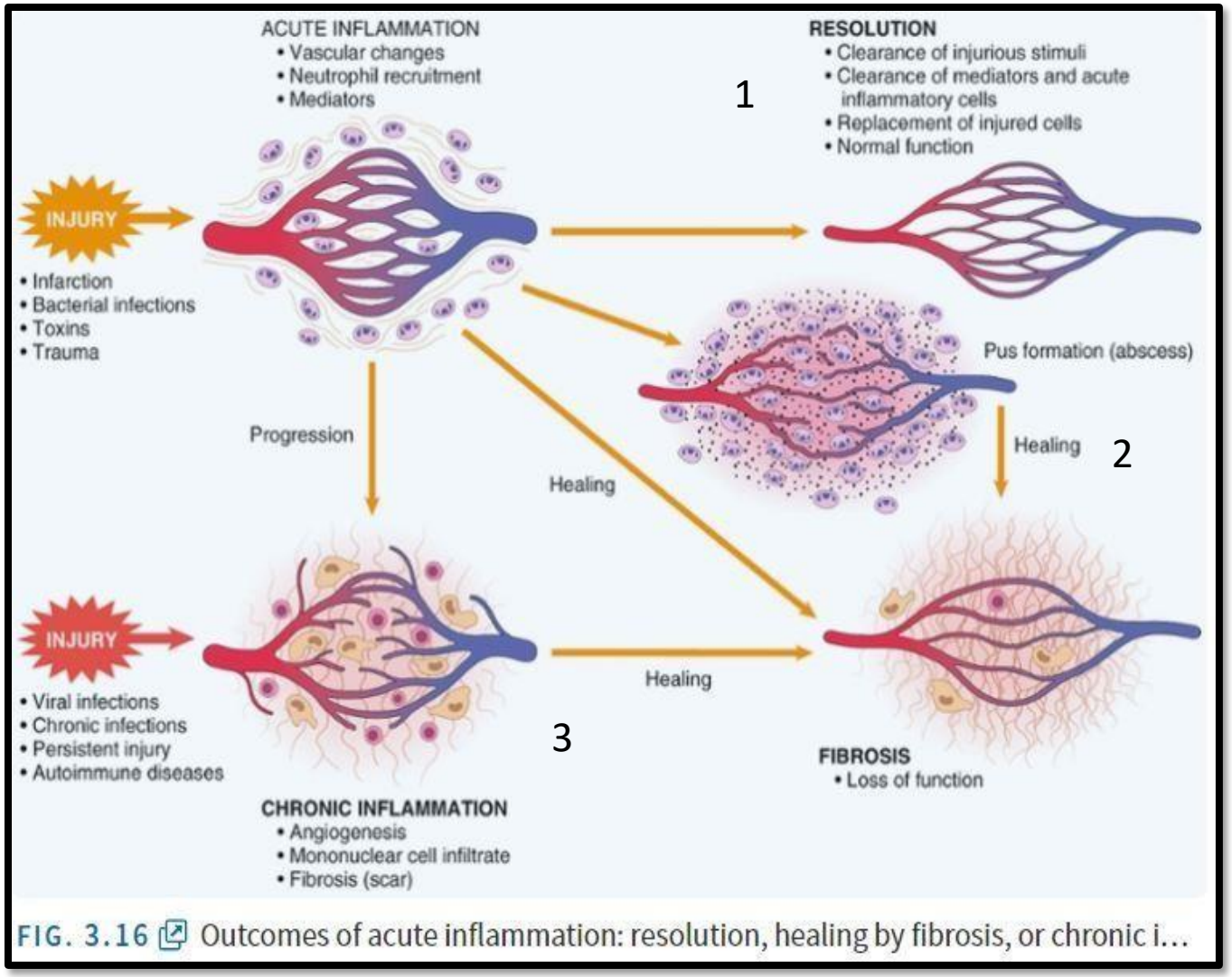


FIG. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic i…

CHRONIC INFLAMMATION:

Defined by: The exact time is not really clear

- **Prolonged inflammation (weeks-months-years): inflammation, tissue injury and attempts at repair coexist at the same time with varying degree.**
- **May follow acute inflammation but may be insidious or smoldering**

➢ Most of the time chronic inflammation follow acute inflammation, but in certain circumstances that's not the case; sometimes the acute inflammation phase is so subclinical it does not bother you anymore so the chronic inflammation continues ,insidious or smoldering it will not present itself clinically ,those slightly dangerous because sometimes when the clinical is presented sometimes it's too late .

➢ Prolonged chronic inflammatory response is associated with tissue injury, with each tissue injury your body is attempting or attempted to repair it at the same time with various degrees of (repair-injury – repair – injury)

➢ If the chronic inflammation did not stop and continues there will be severe scar and fibrosis imparking on the function of that organ.

➢ Ex : If you have a chronic active hepatitis for 10 years , at the end cirrhosis and fibrosis of the liver leading to liver failure in the liver .

CAUSES OF CHRONIC INFLAMMATION:

- **Prolonged exposure** : Silica : A disease called silicosis due to the silica , the patient occupation will expose them daily on parts of silica inhaled into lung tissue ,then this will induce fibrosis and silicosis.
  Atherosclerosis: Due to the cholesterol clusters which are actually produced Endogenously.

Persistent infections	**Mycobacteria (TB), viruses, fungi, parasites. Delayed hypersensitivity reaction. Granulomatous inflammation.** viruses: Hepatitis C Virus.
Hypersensitivity diseases	**RA, asthma, MS. May end in fibrosis of end organs**
Prolonged exposure to toxic agents (exogenous or endogenous)	**Silica (silicosis) Atherosclerosis (cholesterol)**
Other associated diseases	**Alzheimer's, Metabolic syndrome of DM**(diabetes mellitus)

we understand pathology of some and we understand part of it in others, so it take time to understand why in these diseases

- **persistent**: especially with certain tough virulent bad organisms causes specific type of inflammation which we called it granulomatous inflammation which is specific type of chronic inflammation .

- **Hypersensitivity**: They are big group of auto immune disease .

-RA: rheumatoid arthritis
-MS: multiple sclerosis

MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION:

- **Infiltration by chronic inflammatory cells (macrophages, lymphocytes and plasma cells)**
- **Tissue destruction**
- **Attempts at healing by angiogenesis and fibrosis**

This is how the pathologist can tell if the biopsy or tissue sent to him has acute inflammation or chronic inflammation under the microscope

see next slide and صلّ على رسول الله

MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION:

1. If we have a tissue with chronic inflammation, What are the microscopic features of the chronic inflammation response?

In the acute inflammatory response, the cell infiltrate is predominantly by neutrophils. In chronic inflammation, the inflammatory cells which are present and can be seen under the microscope (macrophage, lymphocytes, plasma cells) whenever we see those in large numbers then it is chronic inflammation. So the first critical feature of chronic inflammation is the infiltration of the tissue by chronic inflammatory cells (macrophage, lymphocytes, plasma cells).

2. In addition to infiltration , you can see that there is tissue damage or tissue destruction, usually the chronic inflammatory response will be associated with tissue destruction in varying degrees , if there is severe tissue destruction you will see severe changes like replacement of the normal liver parenchyma by thick bands of fibrosis and serotic patients.

3. The body is not standing still , it always attempting to induce repair and healing by production of new blood vessels a process which we called **Angiogenesis** and then replacement of lost tissue by scar tissue or fibrosis rich in collagen and those can be seen under the microscope .

These are the major morphological features of chronic inflammation .

Chronic pneumonia

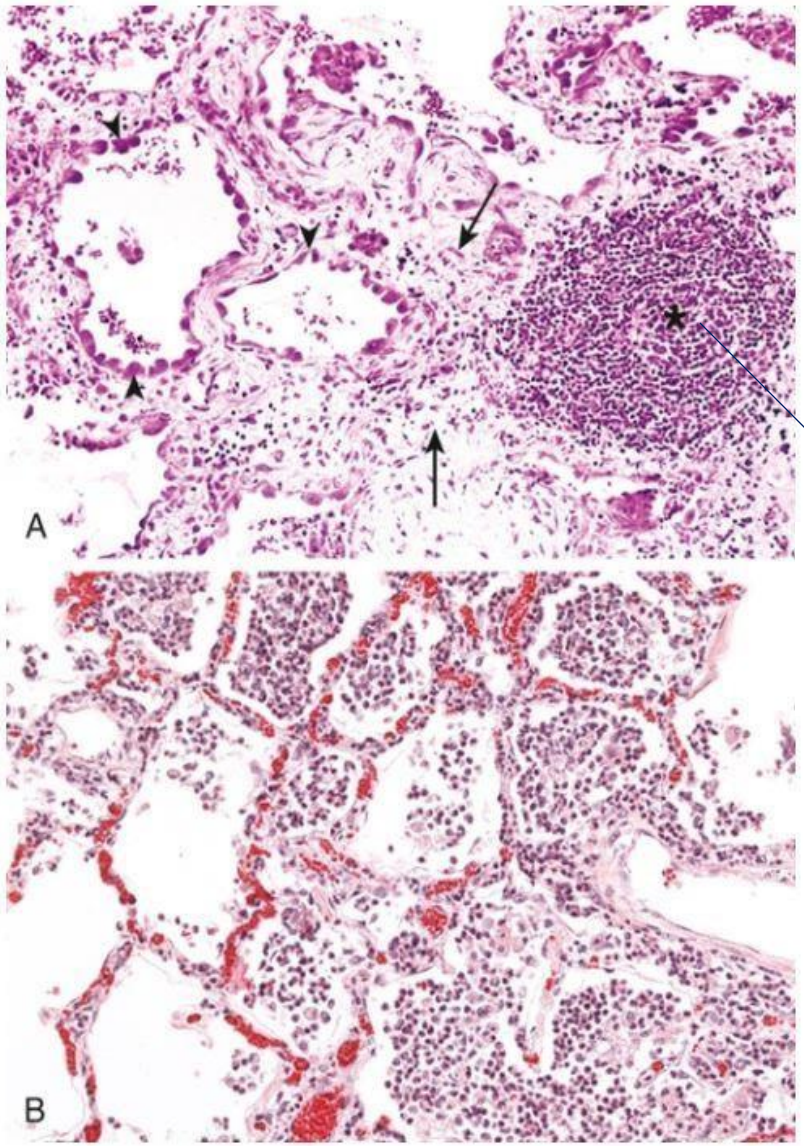


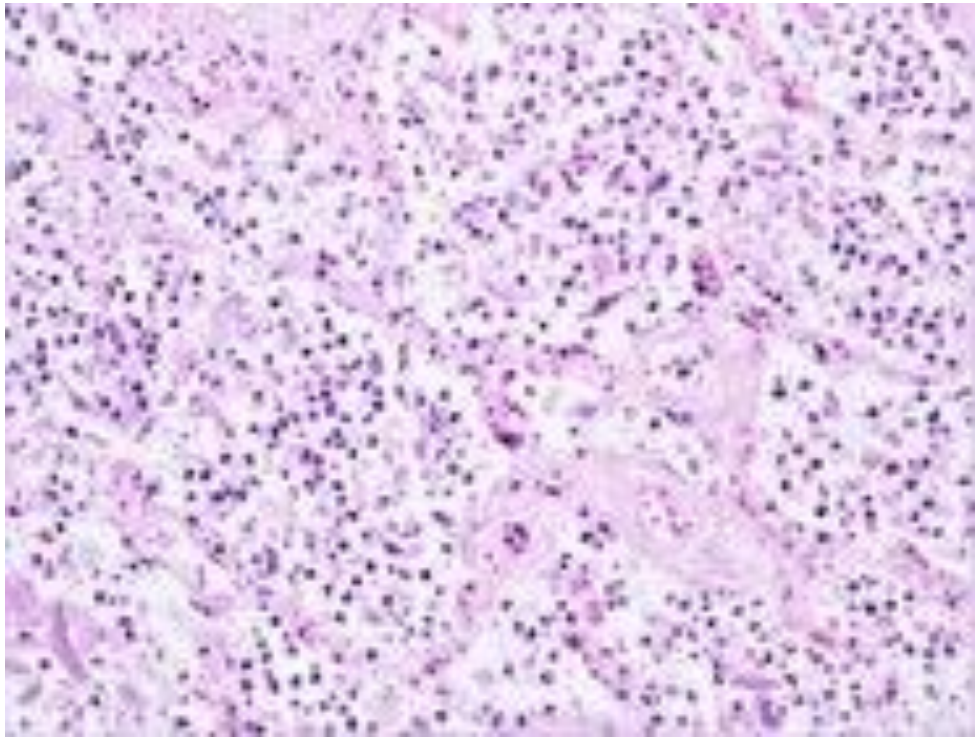
FIG. 3.17 (A) Chronic inflammation in the lung, showing all three characteristic histolo…

These two sections are from the lung(H&E STAINED)

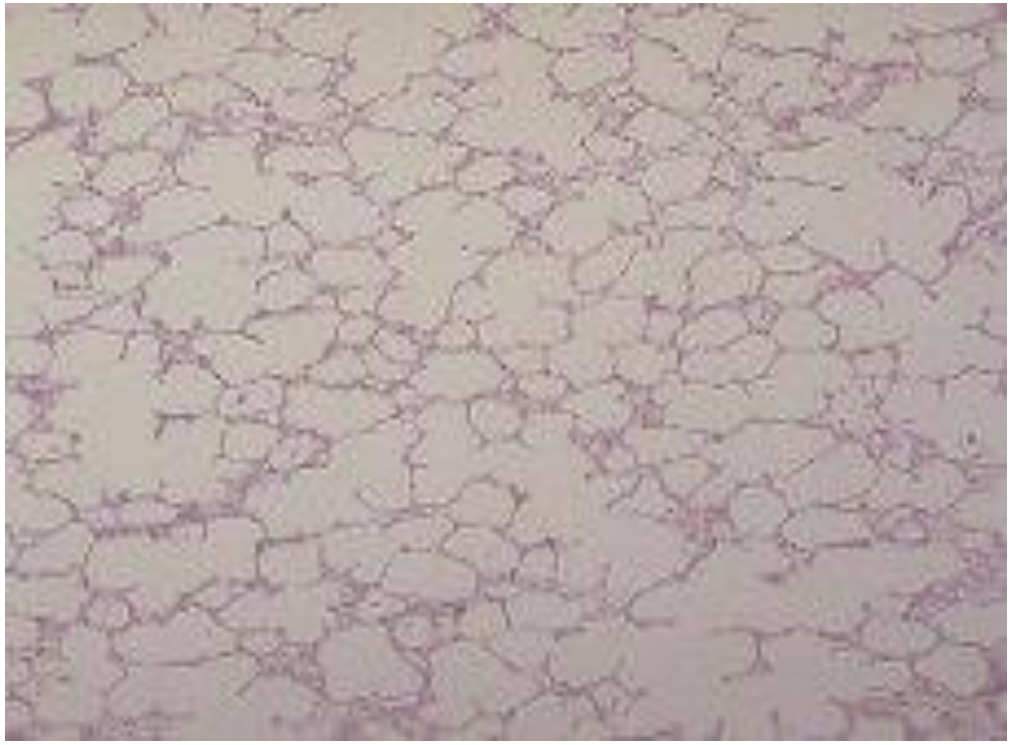
-The one above(A) is another lung where alveoli has been replaced by fibrous tissue, there is also a chronic inflammatory follicle , if we look at higher power of microscope in the follicle we will see macrophages , lymphocytes and plasma cells. Its chronic inflammation of the lung with fibrosis .

-The one at bottom(B), alveoli parenchymal and the architecture is still well preserved, however the alveoli are full of neutrophils and this is severe acute lobar pneumonia(inflammation in one lobe of lung)

Acute pneumonia



NORMAL



CELLS AND MEDIATORS OF CHRONIC INFLAMMATION:

- **Macrophages**
- **Lymphocytes**

- **Eosinophils**
- **Mast cells**

The mediators which we have talked about they are not only involved in acute inflammation , chronic inflammation also requires a meditators of chronic inflammation.
All these cells play a role in producing many of these chemical mediators similar to acute inflammatory response, so as well as acute inflammation response requires a mediators , chronic inflammatory response needs too .

MACROPHAGES

- **Secretion of mediators (TNF,IL-1,CHEMOKINES)**
  Increase or decrease of the inflammatory response
- **Feedback loop with T-cells.**
- **Phagocytosis (the function of macrophages and neutrophils)**
- **Circulating monocytes(one day half day)**
- **Tissue macs: kupfer cells (in the liver) , sinus histiocytes (in lymph nodes) , alveolar macrophages (in the lungs) , microglia (in the brain) (non-nuclear phagocytic system), half-life month. (all originate from circulating monocytes)**
- **Activation of macs:M1 classic pathway , M2 alternative pathway**

learnt recently

MACROPHAGES

- When they are circulating they are actually monocytes , they secrete cytokines, TNF, IL-1,chemokines, in addition, they have strong connection with T-cell there is always a communication between T-cell and macrophages, T-cells also give the macrophages feedback about increasing and decreasing of inflammatory response.

- When they circulating in the blood before they get recruited and activated into the tissue to transform to tissue macrophages or tissue monocytes to or tissue histiocytes. The half life of monocytes is one day ,but when they get to the tissue the half life extended weeks and months.

- The macrophages are produced by bone morrow ,in adults ‘HEMATOPOIETIC STEM CELLS’ , then they matured to their monocyte shape in blood.
- The first picture is the classic appearance of those circulating monocytes (Abundant in cytoplasm and less granules) it has coffee bean shaped or kidney shaped nucleus.
- when they get released to tissue they are activated macrophages in the tissue. they become bigger ,have more lysosomes, more organelles, more granulated, more cytoplasmic process, more active mitochondria , the nuclear cytoplasmic ratio is less and they are called tissue macrophages Depending on the origin .
- sometimes in fetal life they are Produced from yolk sacs as a progenitor cells and mature in the tissue.

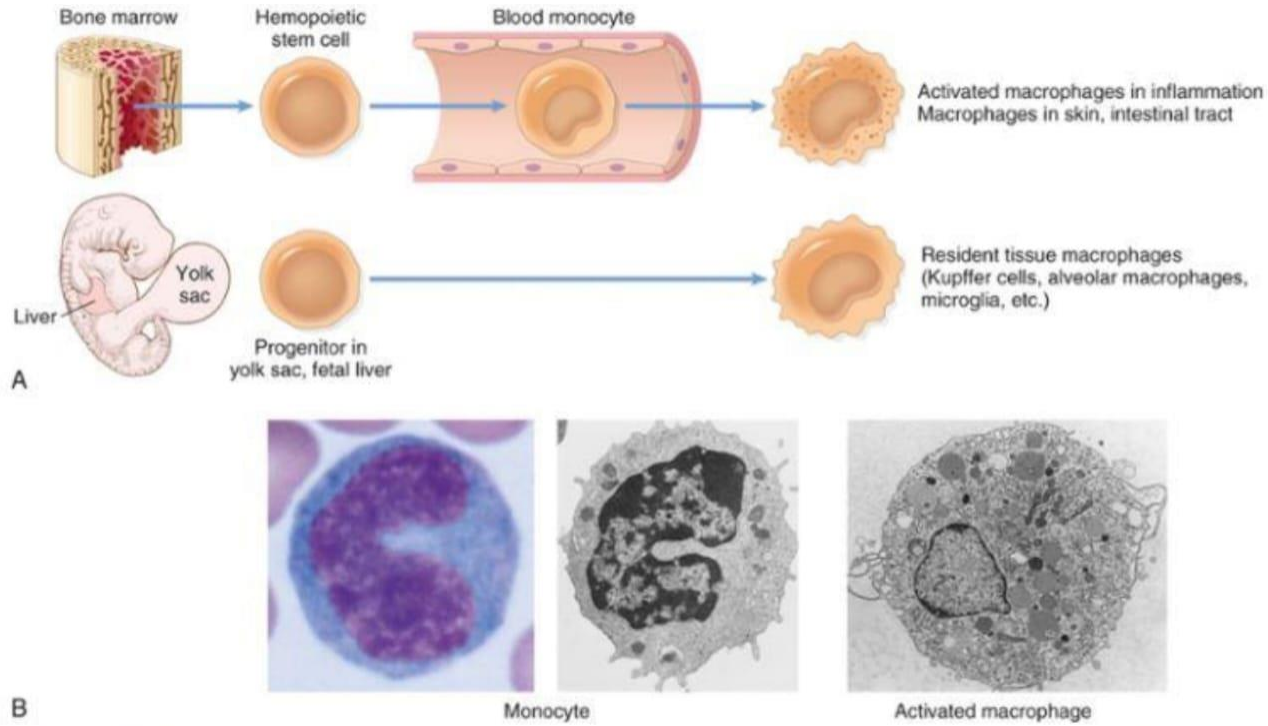


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

M1

- Let's talk about the classic pathway(M1) in activating macrophages.
- Macrophages activated by M1 ensure in controlling and producing many of the chemical mediators and involved in the process of killing and getting red of the organisms and ultimately resolution of the inflammation.
- So, it's actually pro-inflammatory pathway induces excess inflammatory mediators and they are active in trying to fight invading organisms and leading to secretion of IL-1, TNF and different chemokines.
- The main driver of recruitment of monocytes in M1 pathway are different stimuli (like: microbial drugs, TLRs, interferon gamma).
- The action of this pathway is ending up in augmenting the inflammatory response.

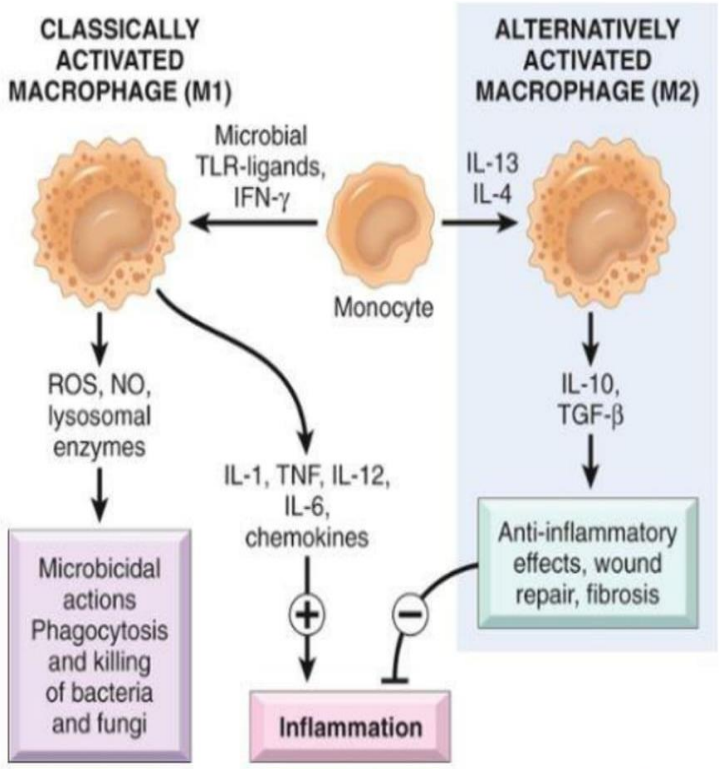


FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate

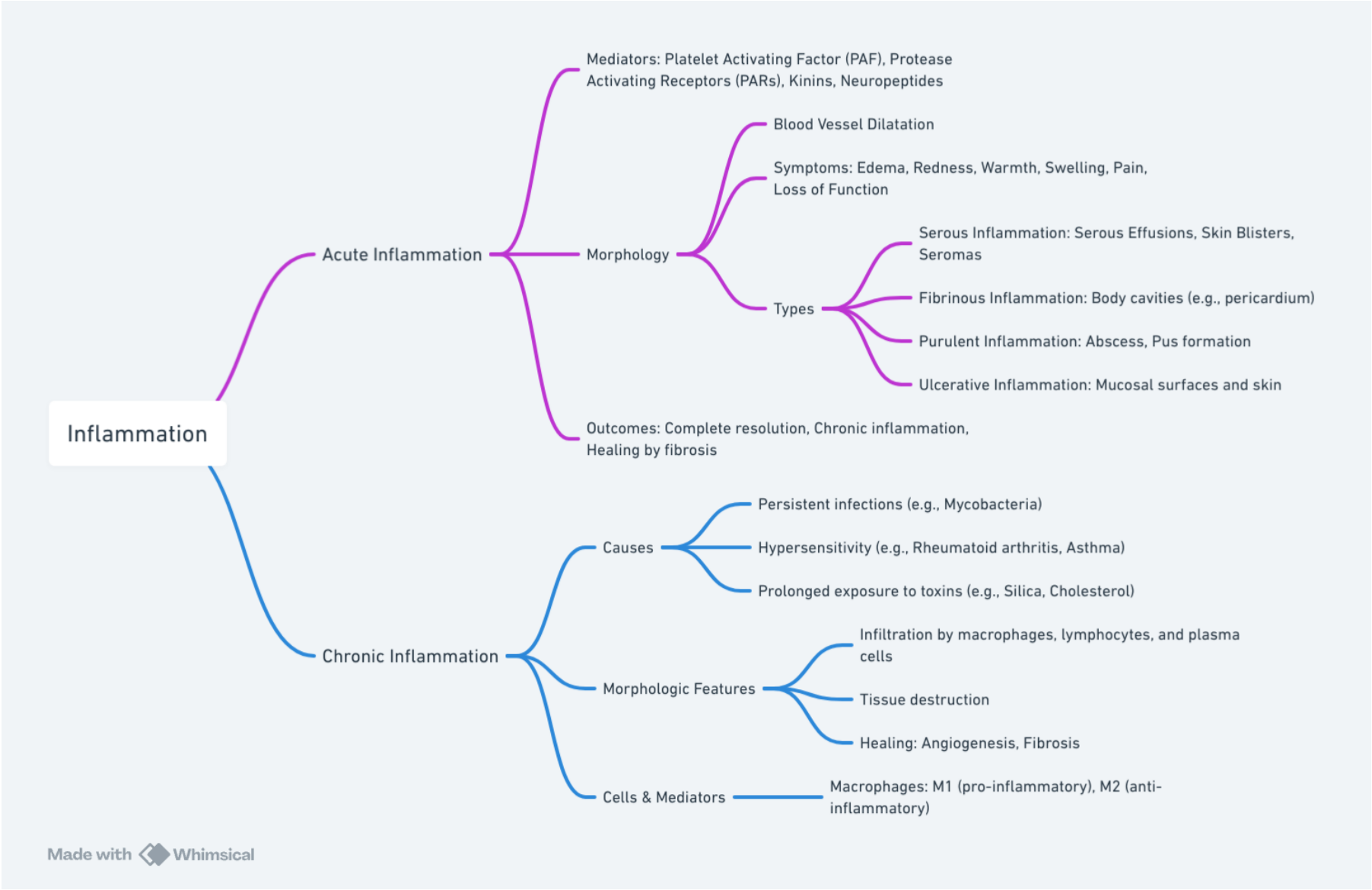
M2

- The another pathway is the alternative activated pathway(M2).

- Has certain cytokines(IL-13, IL-4); they will push the monocytes to go in this pathway activating macrophages to secrete IL-10,TGF-beta(transforming growth factor); those will have anti inflammatory effects trying to inhibit inflammaroru response so the reparative process will start.

  - **M1 pathway is pro-inflammatory(indue inflammatory rxn).**
  - **M2 pathway is an inhibitory (inhibites inflammatory rxn).**

الحمد لله رب العالمين


Inflammation
Acute Inflammation
Mediators: Platelet Activating Factor (PAF), Protease Activating Receptors (PARs), Kinins, Neuropeptides
Morphology
Blood Vessel Dilatation
Symptoms: Edema, Redness, Warmth, Swelling, Pain, Loss of Function
Types
Serous Inflammation: Serous Effusions, Skin Blisters, Seromas
Fibrinous Inflammation: Body cavities (e.g., pericardium)
Purulent Inflammation: Abscess, Pus formation
Ulcerative Inflammation: Mucosal surfaces and skin
Outcomes: Complete resolution, Chronic inflammation, Healing by fibrosis
Chronic Inflammation
Causes
Persistent infections (e.g., Mycobacteria)
Hypersensitivity (e.g., Rheumatoid arthritis, Asthma)
Prolonged exposure to toxins (e.g., Silica, Cholesterol)
Morphologic Features
Infiltration by macrophages, lymphocytes, and plasma cells
Tissue destruction
Healing: Angiogenesis, Fibrosis
Cells & Mediators
Macrophages: M1 (pro-inflammatory), M2 (anti-inflammatory)
Made with Whimsical

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

Corrections from previous versions:

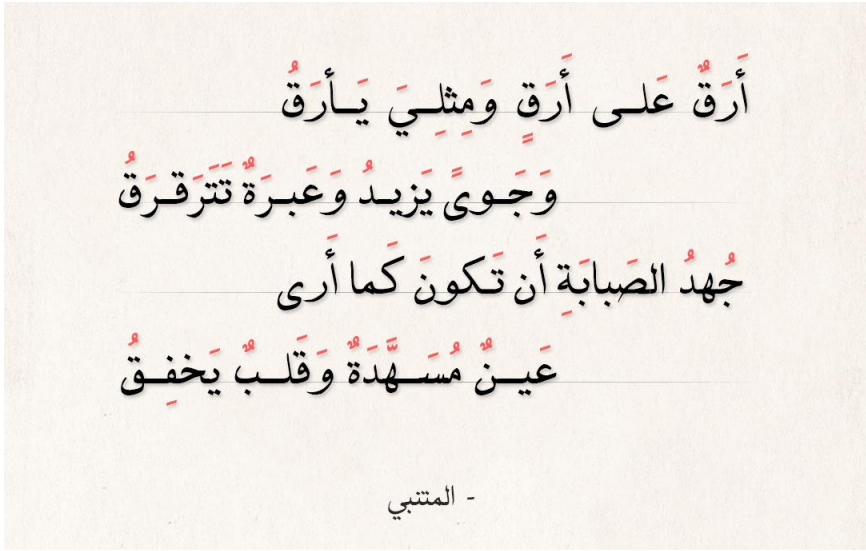
Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

- والعلم لن يعطيكَ بَعْضَه إلا إذا أعْطيته كُلَّك.

- اللهم احفظ اخواننا في غزّة والسّودان ولبنان وارفق بحالهم وارحمهم وصبّرهم، اللهم استعملنا ولا تستبدلنا.
- سبحان الله وبحمده، سبحان الله العظيم



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

1. Robbin's Basic Pathology 10th ed.
   - Mediators Pgs 70-78
   - Morphologic Patterns Pgs 78-79
   - Outcomes Pgs 79-81
   - Chronic Pgs 81-86

External Resources for the reader:

1. Mediators of Inflammation YT Video
2. Acute Inflammation Morphology & Outcomes YT.V
3. Chronic Inflammation YT.V
4. USMLE STEP1 Book Pages 209-212 (NOT everything is included*****)