بسم الله الرحمـٰن الرحيم

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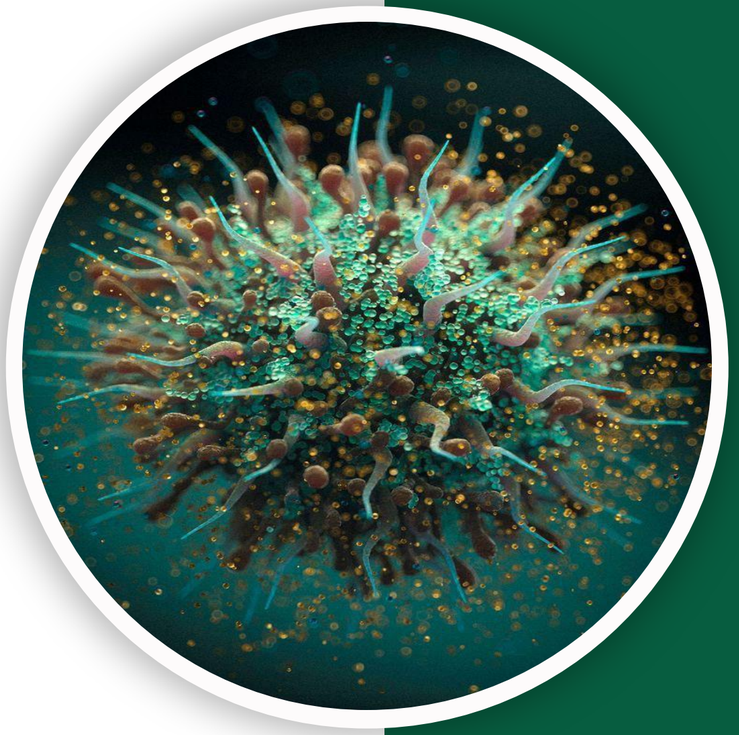
Pathology | Lecture 10

Inflammation Pt.5



Written by : NST member
Rawan Okour

Reviewed by : NST

Lecture 5

OTHER MEDIATORS:

- **Platelet activating factor (PAF): platelet aggregation and other functions**
- **Protease activating receptors (PARs): platelet aggregation**

PAF & PARs since they 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:** specific group of **vasoactive peptide, Bradykinin the active; VD, increase permeability, smooth muscle contraction** of which make **them play a role in active labor at the end of pregnancy and therapeutic implications which will be taken in pharmacology and pain.**
- **Neuropeptides: Substance P and neurokinin A**

TABLE 3.8 Role of Mediators in Different Reactions of Inflammation

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	Lysosomal enzymes of leukocytes
	Reactive oxygen species

- **Leukotriene B4** is a very potent **chemotactic agent**.
- **Fever** is one of the major **manifestations of acute inflammation**.
- **Interleukin-1 (IL-1)**, **Tumor Necrosis Factor (TNF)**, and **Prostaglandins** are targeted by certain medications to **reduce the effects of fever** on body tissues.
- The complete **pathophysiology of pain production** is **not yet fully understood**. However, **Prostaglandins** and **Bradykinin** are known to play important roles and are therefore **targeted in treatment**.

Another table!!!!!!!!!!!

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

MORPHOLOGY OF ACUTE INFLAMMATION

- **The critical issue is blood vessel dilatation** (intial vasscular 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*

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.

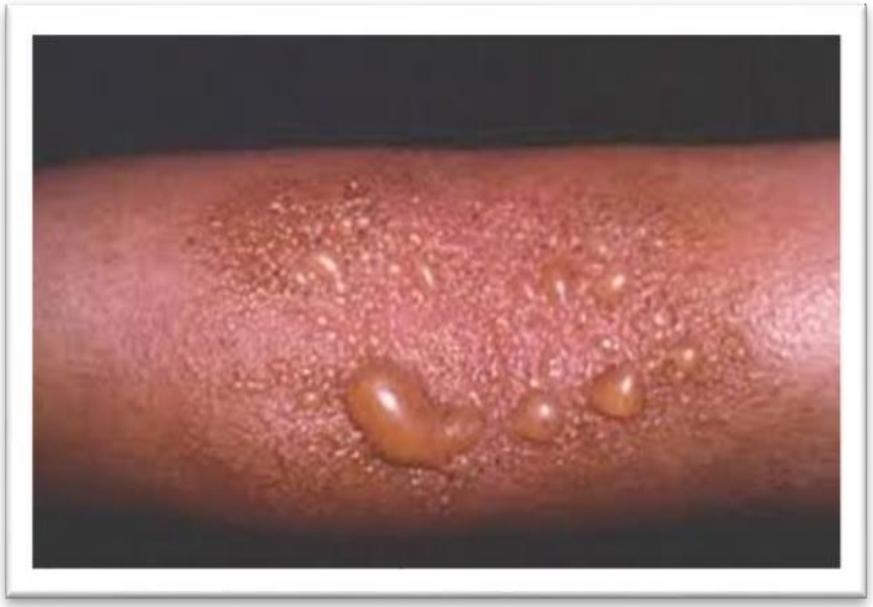
4. Swelling: Due to edema.

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.

SEROUS INFLAMMATION:

An acute inflammatory response which is transudative in nature



- 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**

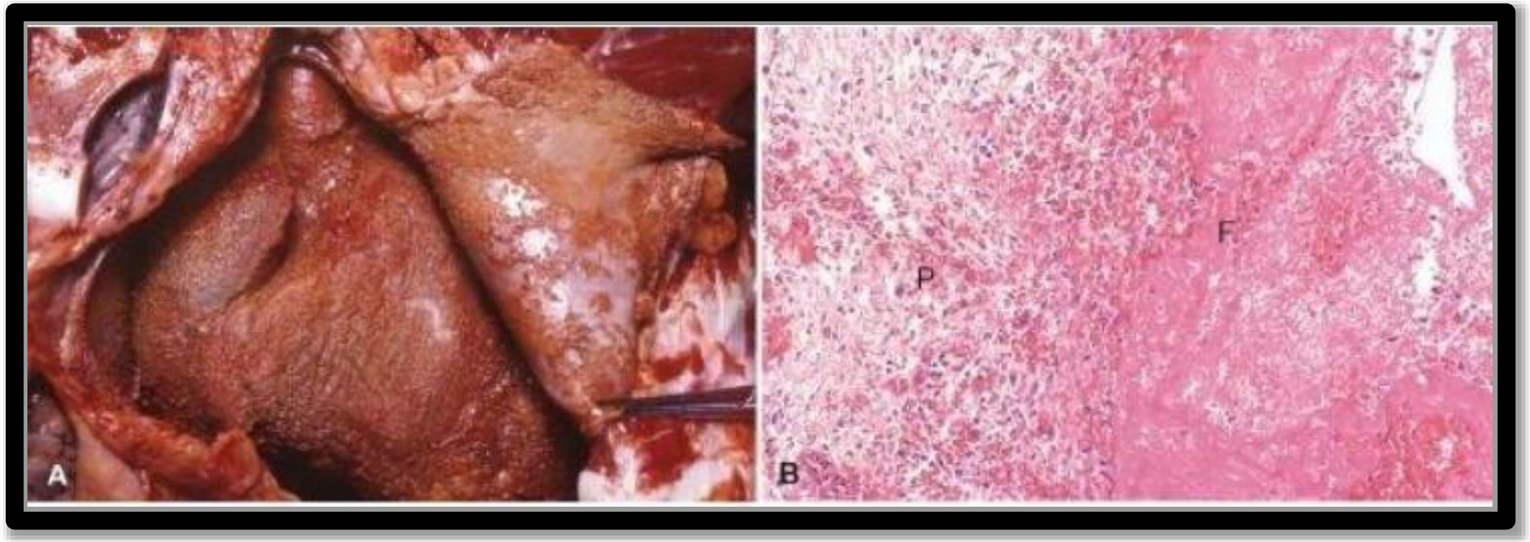
➢ **Seromas**

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.

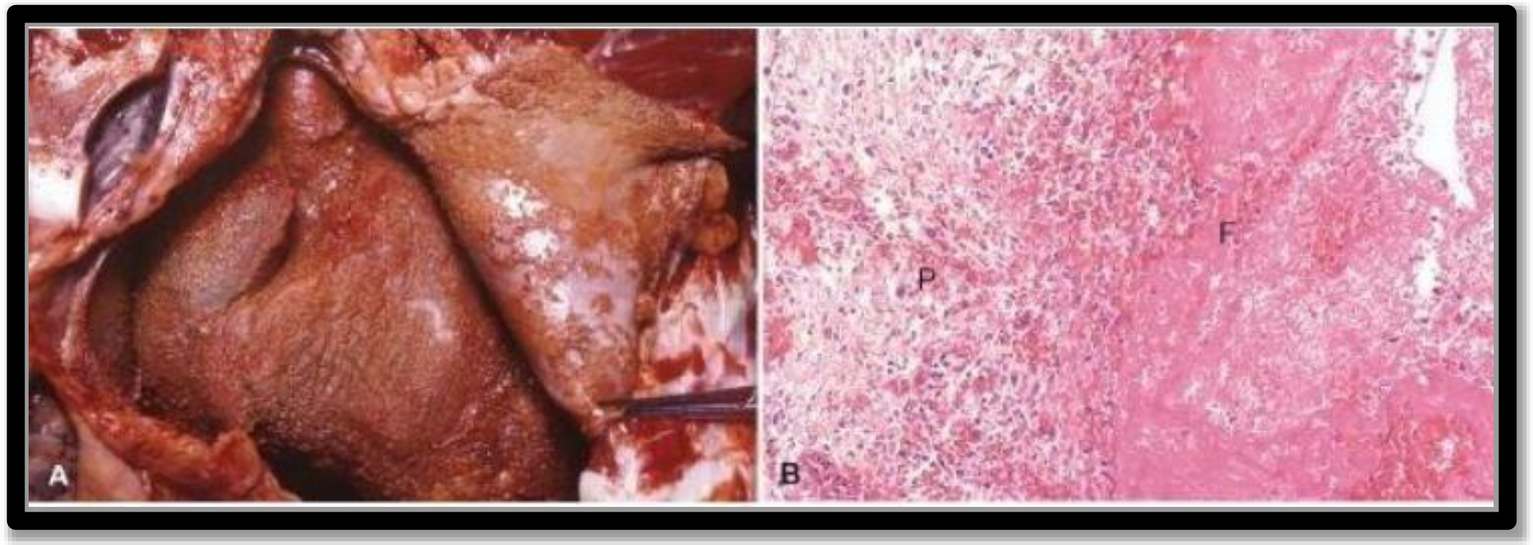
FIBRINOUS INFLAMMATION:

- **Large vascular leakage + coagulation**
- **Body cavities: pericardium**



Fibrinous inflammation could be transudate or exudate based on the severity of the inflammation

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**

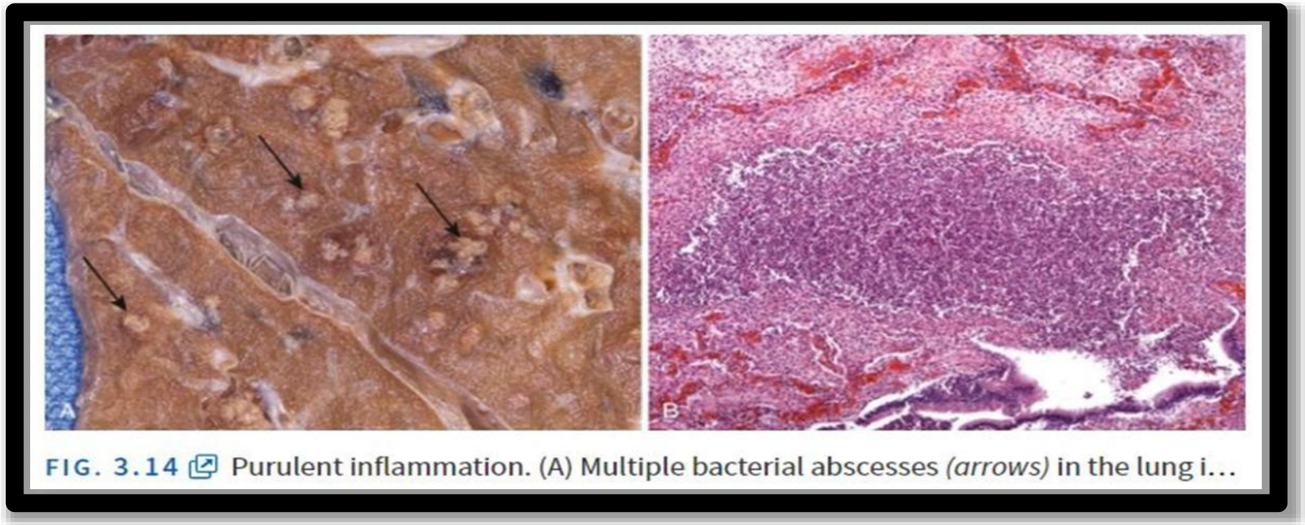


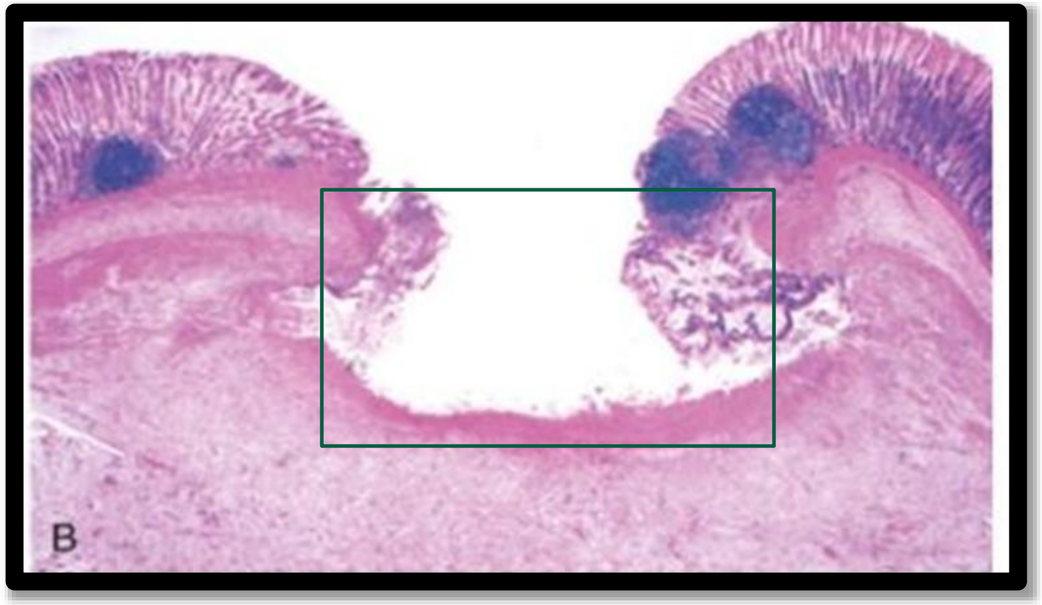
FIG. 3.14 Purulent inflammation. (A) Multiple bacterial abscesses *(arrows)* in the lung i…

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:

- **Defect on a surface**
- **Common in mucosal surfaces and skin**
- **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:

➢Each one of us will have an acute inflammatory response at a certain time in our life.

➢ Most of us 95% will go back to normal.

➢However, there are different types of outcomes of acute inflammation:

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.

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 .

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 .

This simplified diagram is intended to highlight these three principal outcomes of acute inflammation.

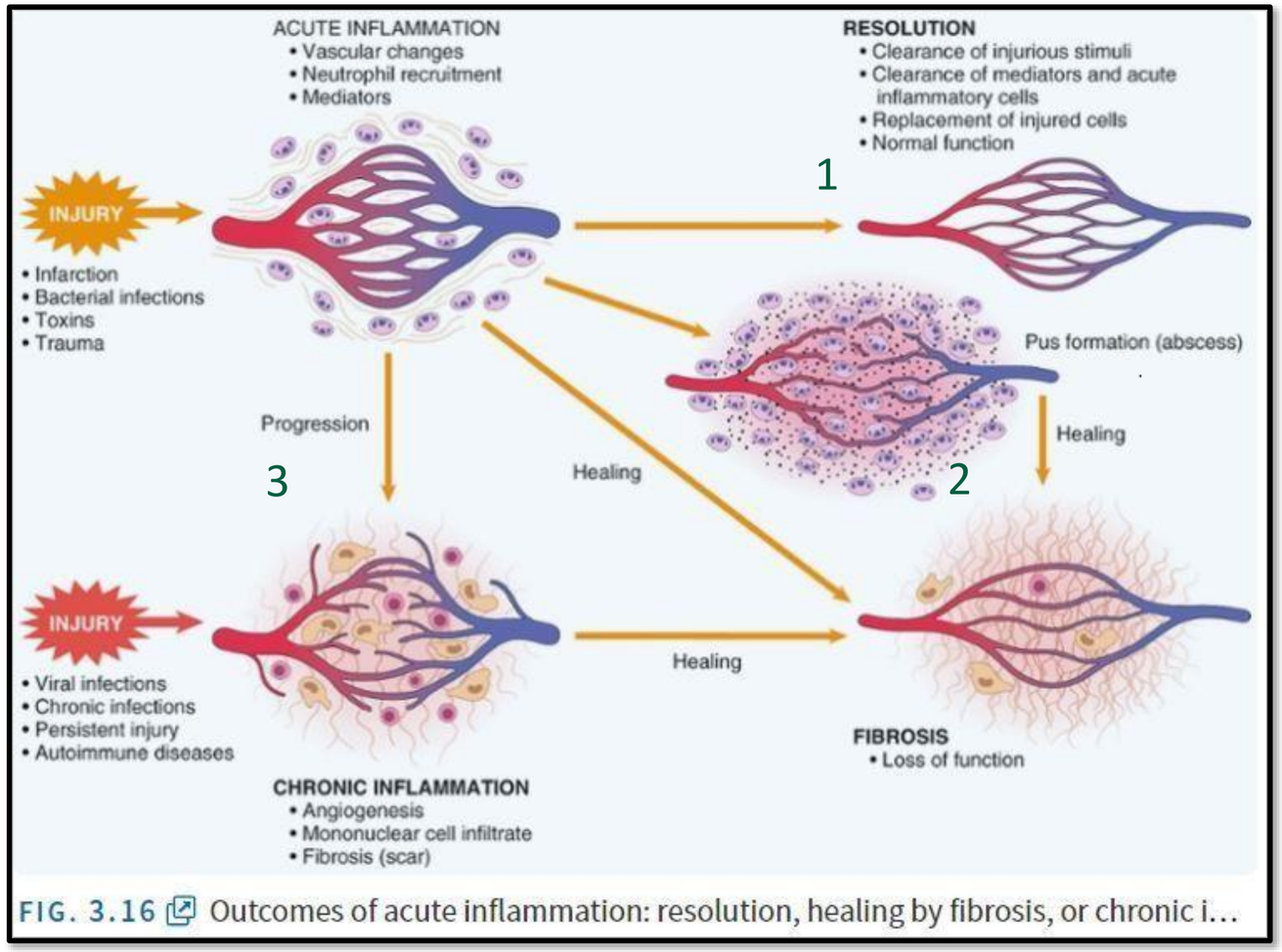


FIG. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic i…

To summarize the possible outcomes of **acute inflammation**, this diagram illustrates the sequence beginning with **tissue injury**, followed by the **vascular and cellular phases** characteristic of acute inflammation.
At the end of this process, one of several outcomes can occur:

1. **Complete Resolution:**
   This is the ideal and most desirable outcome. The tissue returns entirely to its **pre-inflammatory state** with restoration of normal structure and function. Resolution occurs when the injury is limited or short-lived and when the tissue has a high regenerative capacity, such as the liver or epithelium.
2. **Healing by Fibrosis (Scar Formation):**
   When there is **substantial tissue destruction**, or the inflammatory process is severe, or the tissue cannot regenerate, healing occurs by replacement with **fibrous connective tissue**.
   The resulting **scar tissue** differs from the original tissue in both structure and function. The degree of functional loss depends on the extent and location of the fibrosis.
3. **Progression to Chronic Inflammation:**
   If the acute inflammatory response **fails to eliminate the injurious agent**, whether due to **persistent infection**, **prolonged irritation**, or **impaired host immunity**, the process transitions into **chronic inflammation**.
   This stage is characterized by **angiogenesis (new blood vessel formation)**, **fibrosis**, and **tissue remodeling**, often leading to **loss of normal tissue architecture and function**.

CHRONIC INFLAMMATION:

The exact date and 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**

It is important to note that **chronic inflammation often follows acute inflammation**, but not always. In some cases, the **acute phase is minimal or subclinical**, and the disease progresses **insidiously** as chronic inflammation without obvious symptoms.
These cases are particularly dangerous because **by the time clinical signs appear**, significant **irreversible tissue damage** may have already occurred.

If the inflammatory process fails to resolve and instead **persists**, it can lead to **progressive scarring (fibrosis)**, which severely interferes with the function of the affected organ.
A classic example is **chronic active hepatitis**:
When inflammation of the liver continues for **10 to 15 years**, it leads to **fibrosis and cirrhosis**, ultimately resulting in **liver failure** due to loss of normal hepatic parenchyma.

Causes of chronic inflammations

1. Persistent Infections

🦠 Definition:

Some microorganisms are *difficult to eliminate* from the body because they are very strong, resist destruction, or hide inside cells.
So, the immune system keeps trying to attack them — leading to long-term (chronic) inflammation.

🔍 Examples:

- **Mycobacteria** (e.g., *Mycobacterium tuberculosis* → causes **Tuberculosis**)
- **Viruses** (e.g., *Hepatitis C virus* → chronic inflammation in the liver)
- **Fungi**
- **Parasites**

💡 Special form:

These infections often cause a *specific* type of chronic inflammation called **Granulomatous inflammation**, where immune cells form clusters (granulomas) to "wall off" the infection.

🧠 Extra notes:

- Persistent infections trigger continuous immune activation.
- Diseases like **asthma** and **multiple sclerosis (MS)** may show chronic inflammation leading to fibrosis and organ damage.

2. Hypersensitivity Diseases (Autoimmune and Allergic)

🧬 Definition:

The immune system **overreacts** or mistakenly attacks the body's own tissues (autoimmunity), or reacts repeatedly to harmless substances (allergy).
This constant immune activity causes chronic inflammation.

🔍 Examples:

- **Rheumatoid arthritis (RA):** immune system attacks joints → chronic joint inflammation
- **Asthma:** repeated inflammation of airways
- **Multiple sclerosis (MS):** immune system attacks nervous tissue → brain/spinal cord damage

💡 Result:

These conditions may end with **fibrosis** (scarring) and **end-organ failure** (loss of function).

3. Prolonged Exposure to Toxic Agents

☣️ **Definition:**

Continuous exposure to harmful substances – from outside the body (*exogenous*) or produced inside (*endogenous*) – can maintain inflammation for years.

🔍 **Examples:**

- **Silica (silicosis):**
  - People who inhale fine silica particles (e.g., construction workers, miners) develop inflammation and **fibrosis** in the lungs.
- **Atherosclerosis (cholesterol):**
  - Excess **cholesterol** (produced in the body) accumulates in blood vessel walls, causing a chronic inflammatory reaction and hardening of arteries.

4. Other Associated Diseases

🧩 **Definition:**

Some chronic diseases involve inflammation as part of their development – even if infection or toxins aren't the main cause.

🔍 **Examples:**

- **Alzheimer's disease** 🧠 → chronic inflammation contributes to neuron damage.
- **Metabolic syndrome / Diabetes Mellitus (DM)** → chronic low-grade inflammation damages blood vessels and tissues.

CAUSES OF CHRONIC INFLAMMATION:

Persistent infections	**Mycobacteria (TB), viruses, fungi, parasites. Delayed hypersensitivity reaction. Granulomatous inflammation.**
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**

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

In summary, **chronic inflammation** may develop:

- When an infection or injury persists,
- When the immune system is dysregulated, or
- When the tissue is exposed to long-term harmful stimuli.

Over time, these processes lead to **fibrosis, scarring, and organ failure**. The underlying mechanisms vary, and in some diseases, we still only understand part of the complex interactions between the **immune system**, **cells**, and **tissue response**.

MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION:

If you have tissue with chronic inflammation what are the microscopic or morphologic features of the chronic inflammatory response?

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

Thus, the **three cardinal morphologic features** of chronic inflammation are:

- Infiltration with mononuclear cells (macrophages, lymphocytes, plasma cells).
- Tissue destruction.
- Attempts at repair via angiogenesis and fibrosis.

When examining a **biopsy**, a pathologist identifies chronic inflammation by observing these specific histologic features under the microscope.

In **acute inflammation**, the predominant cellular infiltrate consists of **neutrophils**.
However, in **chronic inflammation**, the characteristic cells are **macrophages, lymphocytes, and plasma cells**.
Therefore, the **first key feature** of chronic inflammation is:

1. **Infiltration by chronic inflammatory cells** – primarily macrophages, lymphocytes, and plasma cells.

In addition to this infiltrate, two more morphologic features are typically present:

2. **Tissue Destruction:**
   Chronic inflammatory responses are frequently accompanied by **ongoing tissue injury**, caused by both the **persistent offending agent** and the **activated inflammatory cells** themselves.
   When tissue destruction is extensive, normal structures may be replaced by **fibrous tissue**.
   For instance, in **chronic liver inflammation**, normal hepatic lobules can be replaced by **fibrous septa**, leading to **cirrhosis**.
3. **Attempts at Healing and Repair:**
   The body simultaneously tries to heal the damaged tissue through:

- **Angiogenesis:** Formation of new blood vessels.
- **Fibrosis:** Deposition of collagen and extracellular matrix to replace lost parenchyma.

Both images are from the lung

Chronic pneumonia

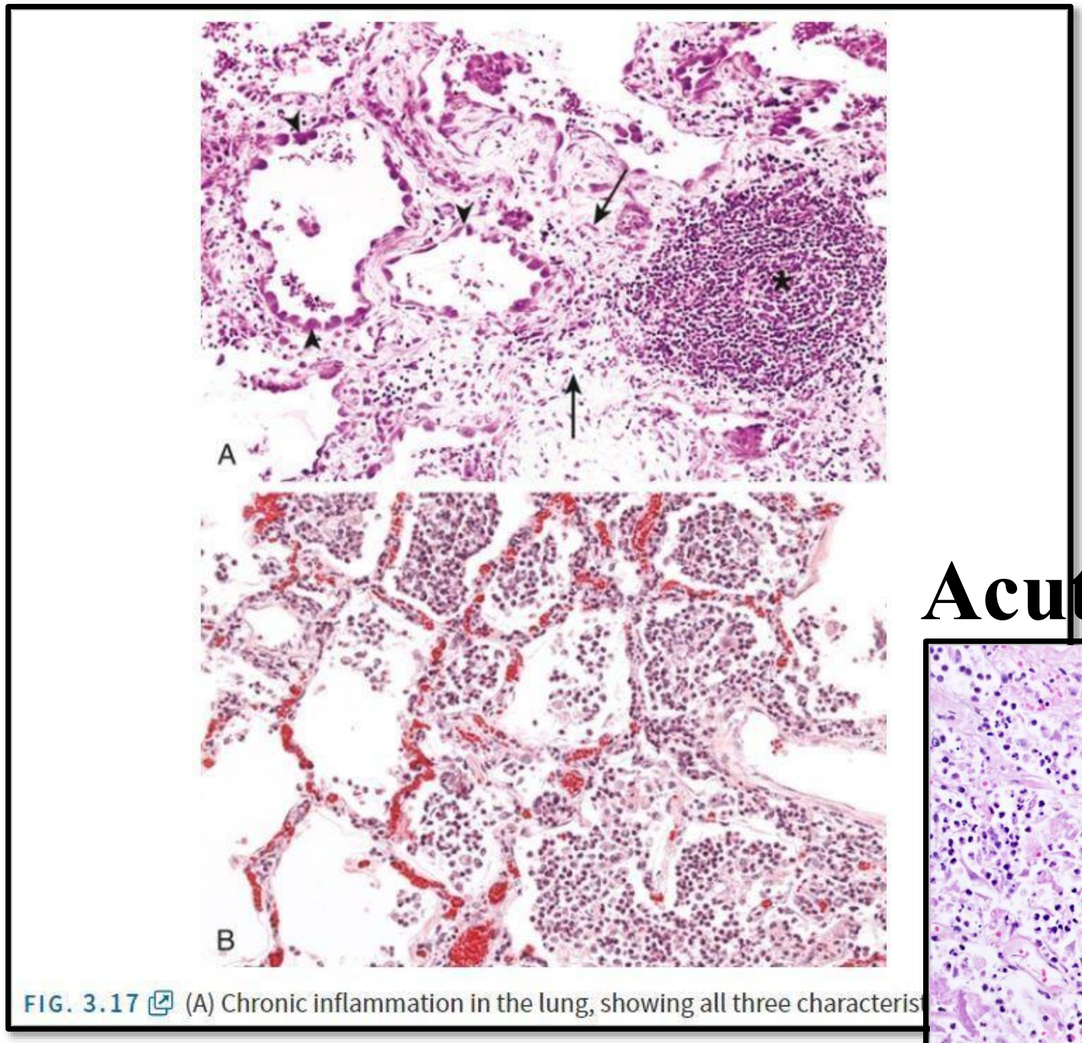
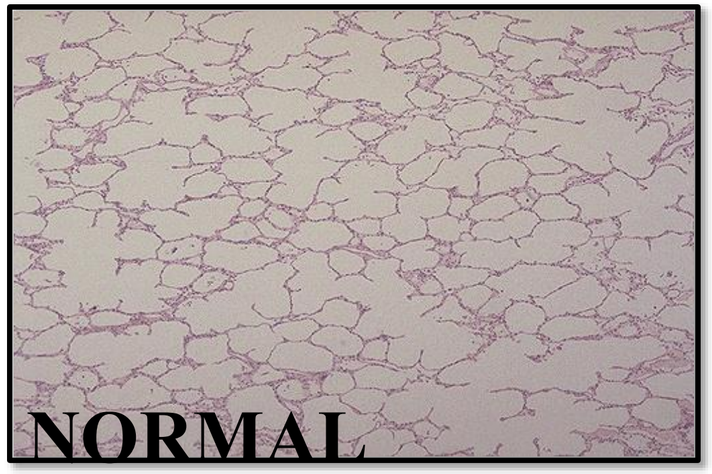
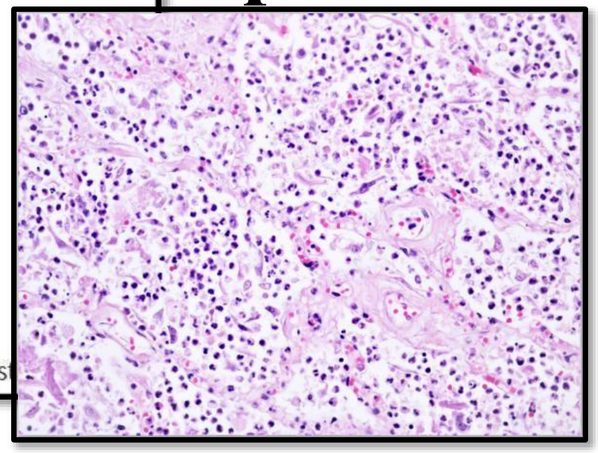


FIG. 3.17 (A) Chronic inflammation in the lung, showing all three characteris



Acute pneumonia



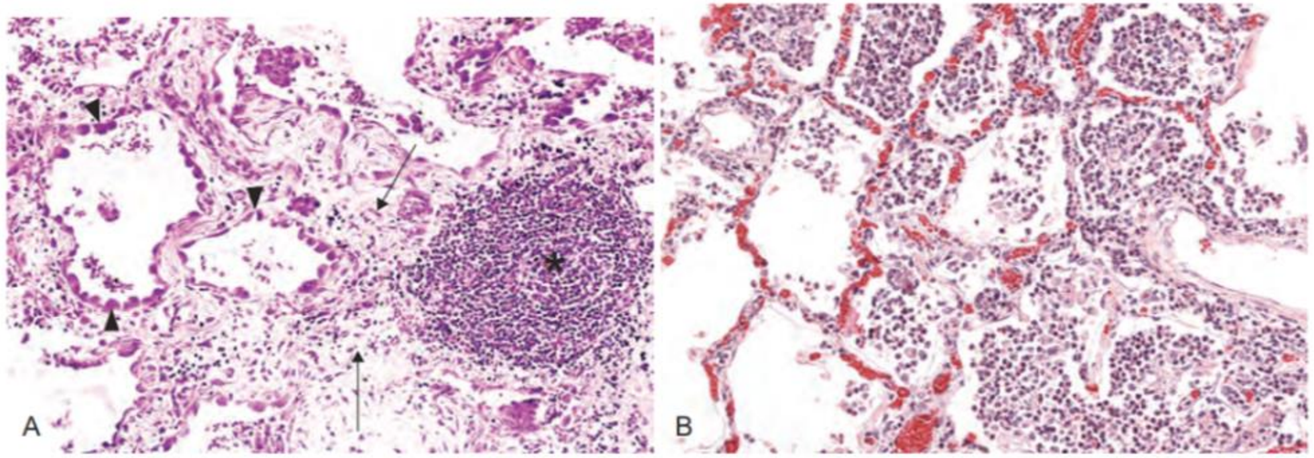


Figure 3.18 (A) Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells *(asterisk)*, (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium) *(arrowheads)*, and (3) replacement by connective tissue (fibrosis) *(arrows)*. (B) In contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces, and blood vessels are congested.

Summary:

- **Image (A):** Chronic pneumonia – fibrosis, granulomatous inflammation, macrophages, lymphocytes, plasma cells.
- **Image (B):** Acute lobar pneumonia – preserved structure, alveoli filled with neutrophils.

In this slide, we are observing two **histologic sections of lung tissue** stained with **Hematoxylin and Eosin (H&E)**, illustrating the difference between **chronic** and **acute** inflammatory processes in the lung.

(A) Chronic Pneumonia

In the **right section (A)**, we can see that the **normal alveolar architecture** has been **partially or completely replaced by fibrous connective tissue**.

- The fibrosis is particularly evident **within the interstitial spaces** surrounding the **inflammatory follicle (granuloma)** and extending **around the alveolar walls**.
- Within the granulomatous focus, **chronic inflammatory cells** are clearly identifiable under higher magnification – mainly **macrophages**, **lymphocytes**, and **plasma cells**.

This represents **chronic inflammation of the lung** associated with **fibrosis and granuloma formation** – a typical feature of **chronic pneumonia** or **granulomatous inflammation**, where persistent infection or irritation leads to tissue remodeling and scarring.

(B) Acute Lobar Pneumonia

In contrast, the **left section (B)** demonstrates a **different inflammatory pattern**.

Here, the **alveolar architecture** is still **well preserved**, meaning that the alveolar walls remain intact.

However, the **alveolar spaces** are **densely filled with neutrophils**, indicating **severe acute inflammation**.

This histologic appearance is characteristic of **acute lobar pneumonia**, where inflammation involves an **entire lobe of the lung**.

The dominant cell type – **neutrophils** – reflects the **acute** phase of inflammation, in contrast to the **macrophage- and lymphocyte-dominated** infiltrate seen in chronic pneumonia.

CELLS AND MEDIATORS OF CHRONIC INFLAMMATION:

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

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

Just as **acute inflammation** depends on chemical mediators, **chronic inflammation** also involves a complex network of **cytokines, chemokines, and growth factors** that sustain the inflammatory response and promote tissue changes.

Cells that participate in the production and regulation of these mediators include:

- **Macrophages**
- **Lymphocytes**
- **Eosinophils**
- **Mast cells**

These cells release numerous **chemical mediators**—some are similar to those seen in acute inflammation (like TNF, IL-1, prostaglandins), while others are specific to the **chronic phase**, promoting **fibrosis, angiogenesis, and prolonged immune activation**.

Lecture 6

MACROPHAGES

- **Secretion of mediators (TNF, IL-1, Chemokines..)**
- **Feedback loop with T cells**
- **Phagocytosis**
- **Circulating monocytes (1 day half life)**
- **Tissue Macs: Kupfer cells, sinus histiocytes, alveolar macrophages & microglia (mononuclear phagocytic system), half life months**
- **Activation of Macs: M1 classic pathway, M alternative pathway**

Let's now focus on the macrophages – the central players in chronic inflammation.
When circulating in the blood, these cells are known as **monocytes**.
Monocytes perform several important functions:

1. **Cytokine Secretion:** They produce **cytokines** such as *Tumor Necrosis Factor (TNF)*, *Interleukin-1 (IL-1)*, and **chemokines**, which regulate leukocyte recruitment and inflammation.
2. **Interaction with T Lymphocytes:** There is **bidirectional communication** between macrophages and T cells.
   - T cells secrete cytokines that **activate macrophages**.
   - Activated macrophages, in turn, present antigens and secrete cytokines that **stimulate T cells**, creating a **feedback loop** that maintains chronic inflammation.
3. **Phagocytosis:** Like neutrophils, macrophages engulf and destroy pathogens and debris.
   They can persist in tissues for **weeks to months**, unlike neutrophils, which die within hours

When monocytes migrate from the bloodstream into tissues, they differentiate into **tissue macrophages (histiocytes)**, which may be long-lived.
Examples include:

- **Kupffer cells** in the liver.
- **Sinus histiocytes** in lymph nodes.
- **Alveolar macrophages** in the lungs.
- **Microglia** in the brain.

These are all part of the **mononuclear phagocyte system**.
Macrophage activation is crucial for effective inflammation and can occur through **two main pathways**:

- The **classical (M1) pathway**
- The **alternative (M2) pathway**

This division has been clearly recognized in the last decade or two and explains the dual roles of macrophages in both **inflammation** and **repair**.

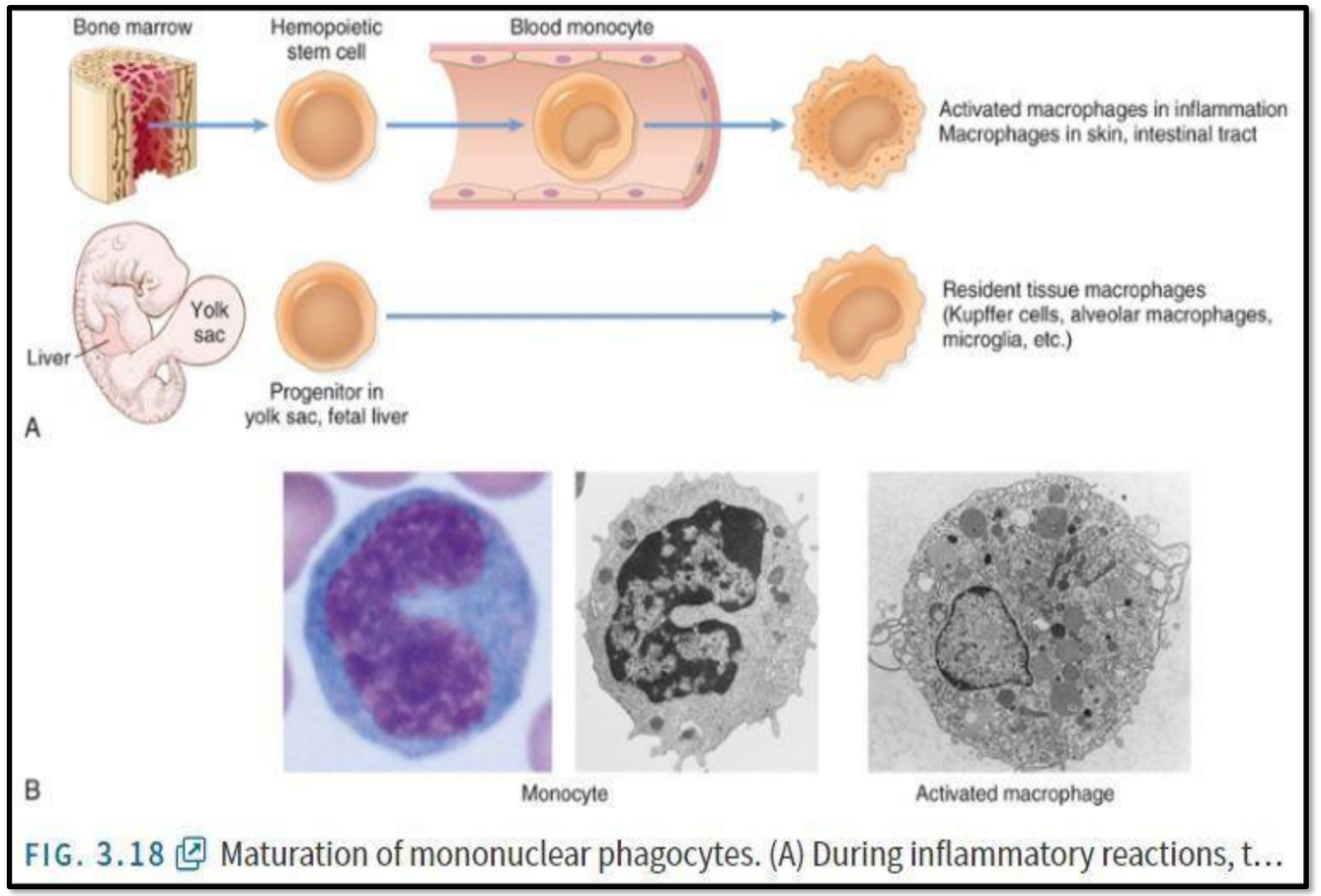


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

In adults, macrophages originate from **hematopoietic stem cells in the bone marrow**. They mature into **monocytes**, which circulate in the blood for about **one day** before entering tissues, where they differentiate into **tissue macrophages**.

Morphologically, circulating monocytes have:

- **Abundant cytoplasm** with few granules.
- A **kidney-shaped or coffee bean-shaped nucleus**.

Upon entering tissues and becoming activated, macrophages:

- Enlarge and develop **more cytoplasmic granules and lysosomes**.
- Show a **lower nuclear-to-cytoplasmic ratio**.
- Acquire greater metabolic activity.

In fetal life, some tissue macrophages derive from **yolk sac progenitor cells**, which later mature into specialized resident macrophages that persist throughout life.

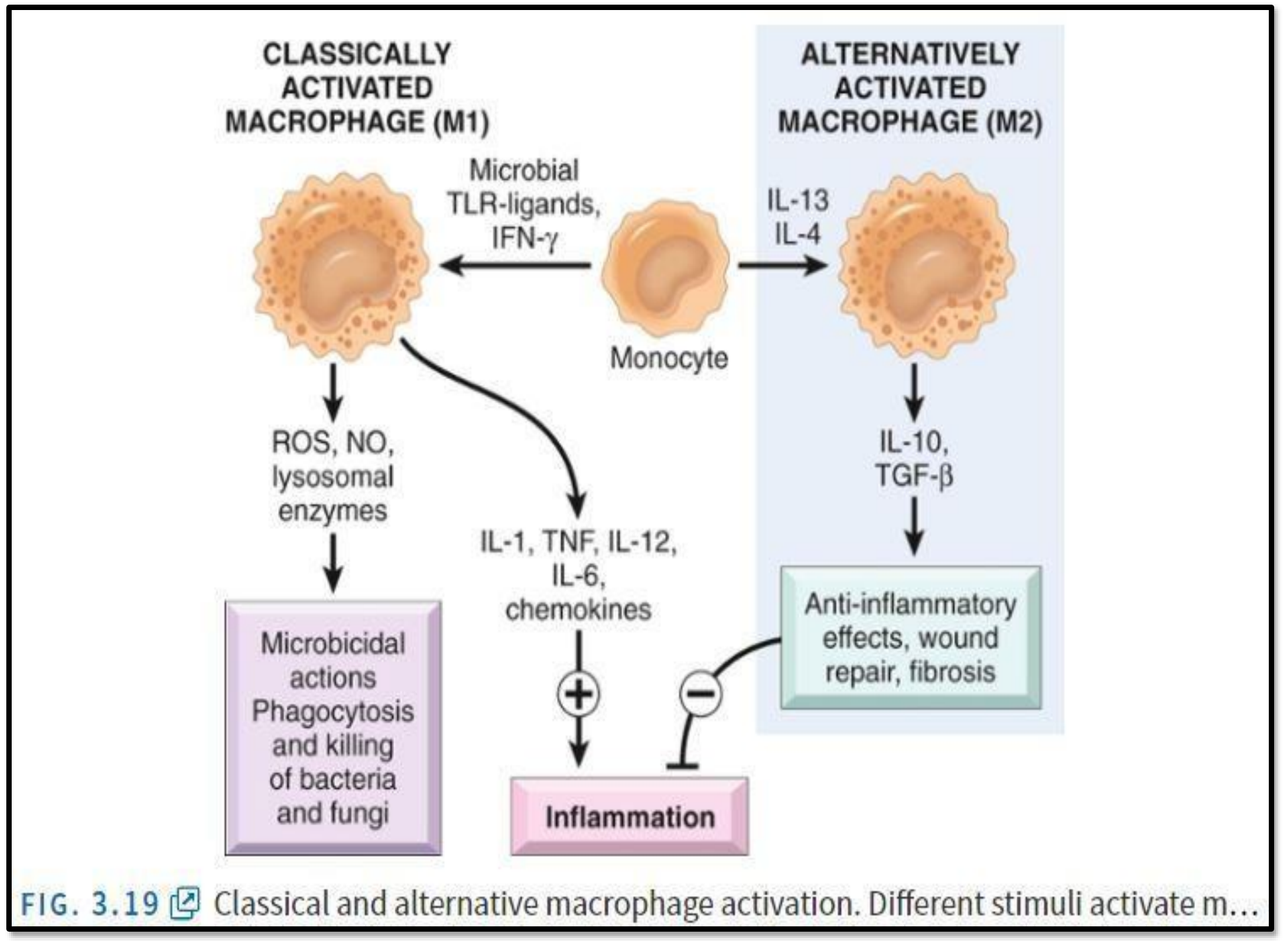


FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate m…

There are two distinct activation pathways for macrophages:

1. Classically Activated (M1) Macrophages:

- Induced by **microbial products**, **Toll-like receptor (TLR) ligands**, and **Interferon-gamma (IFN-γ)** from activated T cells.
- M1 macrophages are **pro-inflammatory** and play a central role in **host defense** and **pathogen killing**.
- They secrete **IL-1**, **TNF**, **chemokines**, and **reactive oxygen and nitrogen species** to destroy microbes and amplify inflammation.
- Therefore, the M1 pathway enhances the **inflammatory response** and contributes to tissue injury during prolonged inflammation.

2. Alternatively Activated (M2) Macrophages:

- Induced by cytokines **IL-4** and **IL-13**.
- These macrophages are **anti-inflammatory** and promote **tissue repair**.
- They secrete **IL-10** and **Transforming Growth Factor-beta (TGF-β)**, which suppress inflammation and stimulate **fibrosis** and **wound healing**.
- **TGF-β** is particularly important as it promotes **scar formation** and deposition of collagen.

Thus, M1 macrophages **promote inflammation and microbial killing**, whereas M2 macrophages **suppress inflammation and facilitate repair**.

A balanced interaction between these two pathways determines the overall outcome of chronic inflammation.

Morphology:

- **Circulating monocytes** show a kidney-shaped nucleus and relatively clear cytoplasm.
- **Activated macrophages**, in contrast, have abundant granular cytoplasm packed with lysosomes and mitochondria, and a reduced nuclear-to-cytoplasmic ratio—features that reflect their heightened metabolic and secretory activity.

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

1. DST MODIFIED
2. Robbins & Cotran Pathologic Basis of Disease 10th edition

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			