MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

Eman Krieshan, M.D.

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- The morphologic hallmarks of acute inflammatory reactions are:

- Dilation of small blood vessels.:
- Clinically :
- It presented as edema, redness , warmth and swelling .

- Accumulation of leukocytes and fluid in the extravascular tissue.
- Clinically :
- It presented as tissue damage and loss of function .

1.Serous Inflammation

- Marked by the exudation of cell poor fluid into spaces created by injury to surface epithelial or into body cavities such as peritoneal, pleural, or pericardial cavities.

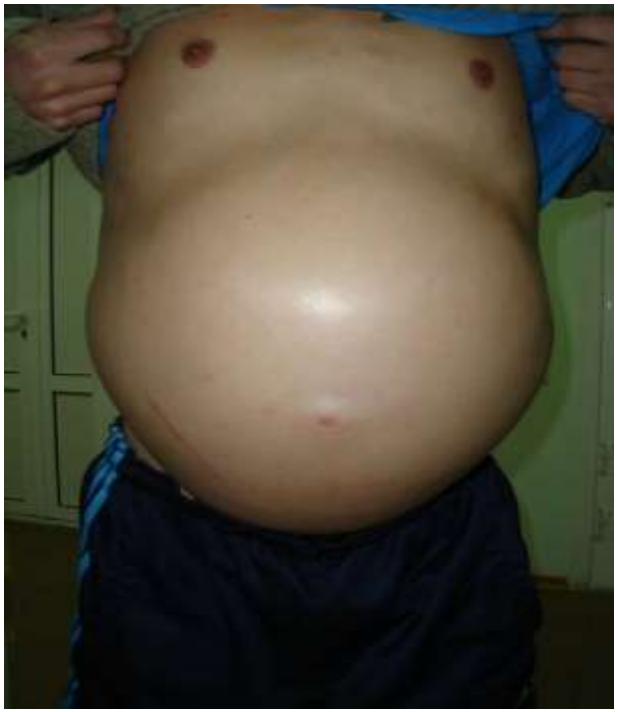
- The fluid in serous inflammation is not infected by destructive organisms and does not contain large numbers of leukocytes

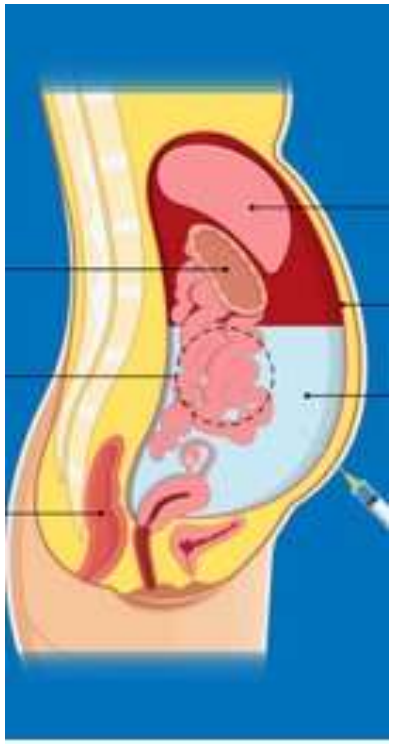
- Accumulation of fluid in these cavities is called an effusion.

❖Peritoneal effusion

➢In body cavities the fluid may be derived from :

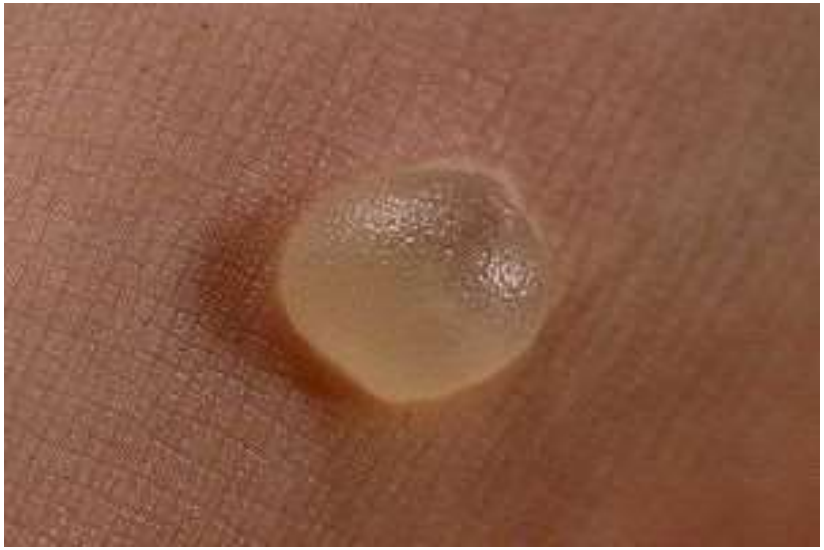
•The plasma (as a result of increased vascular permeability).
• From the secretions of mesothelial cells (as a result of local irritation).

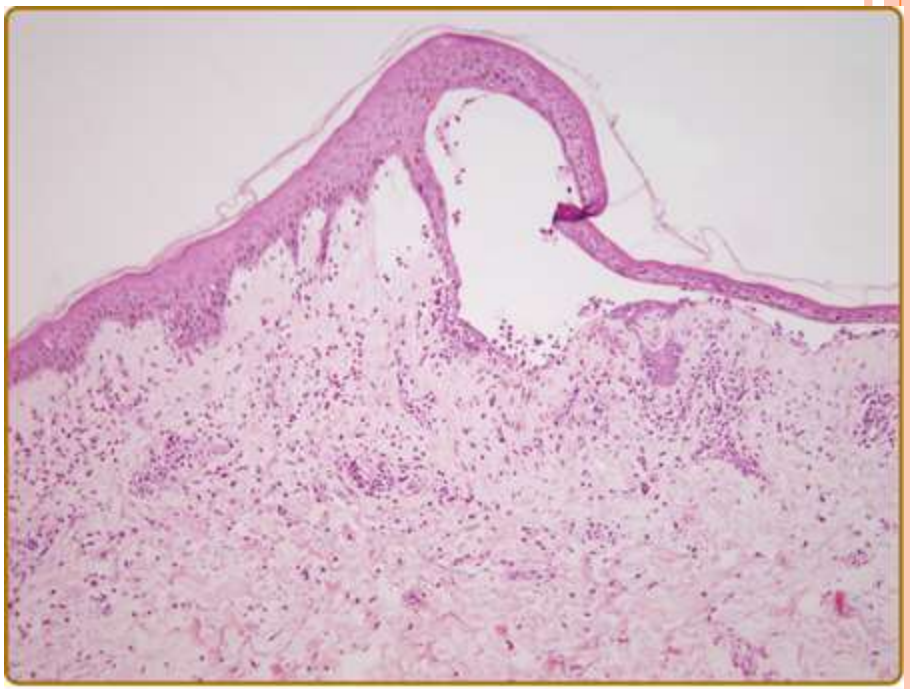




❖SKIN BLISTER

- Resulting from a burn or viral infection.
- Represents accumulation of serous fluid within or immediately beneath the damaged epidermis of the skin





2. Fibrinous Inflammation

- A fibrinous exudate develops when the vascular leaks are large or there is a local procoagulant stimulus.

- A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura.

Mechanism of formation

- Large increase in vascular permeability.

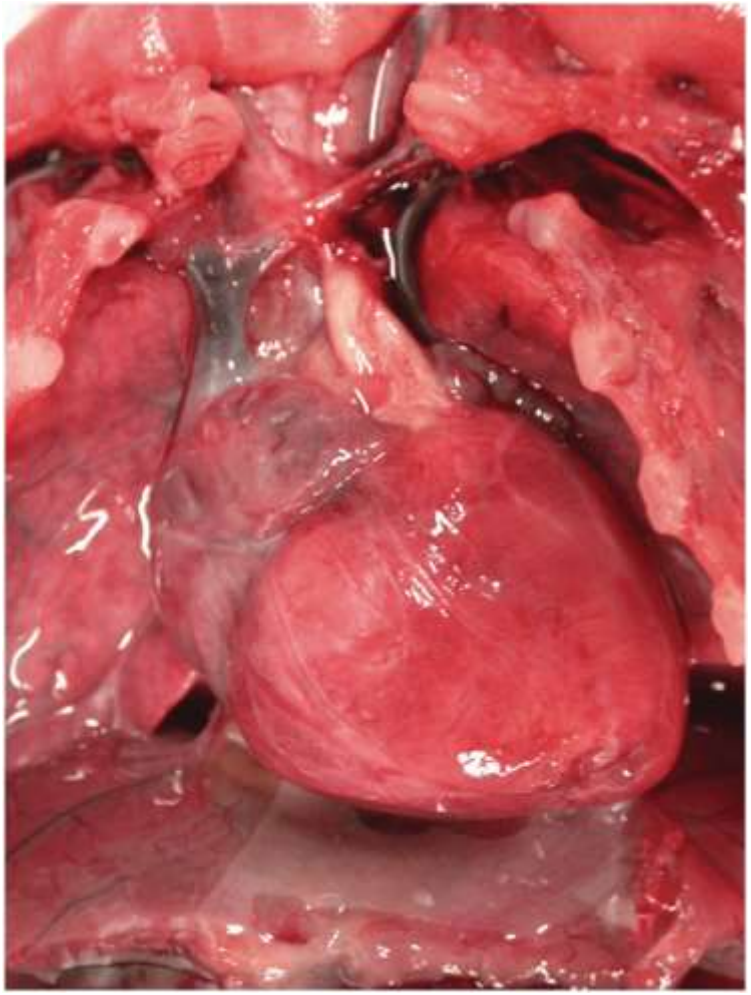
↓

- higher-molecular weight proteins such as fibrinogen pass out of the blood.

↓

- fibrin is formed and deposited in the extracellular space

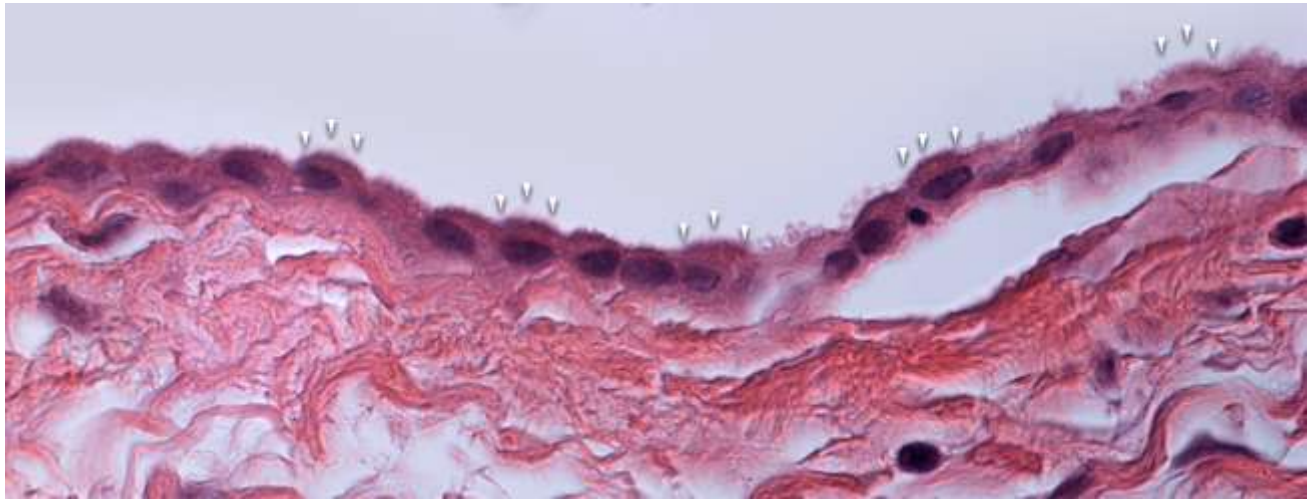
❖GROSSLY



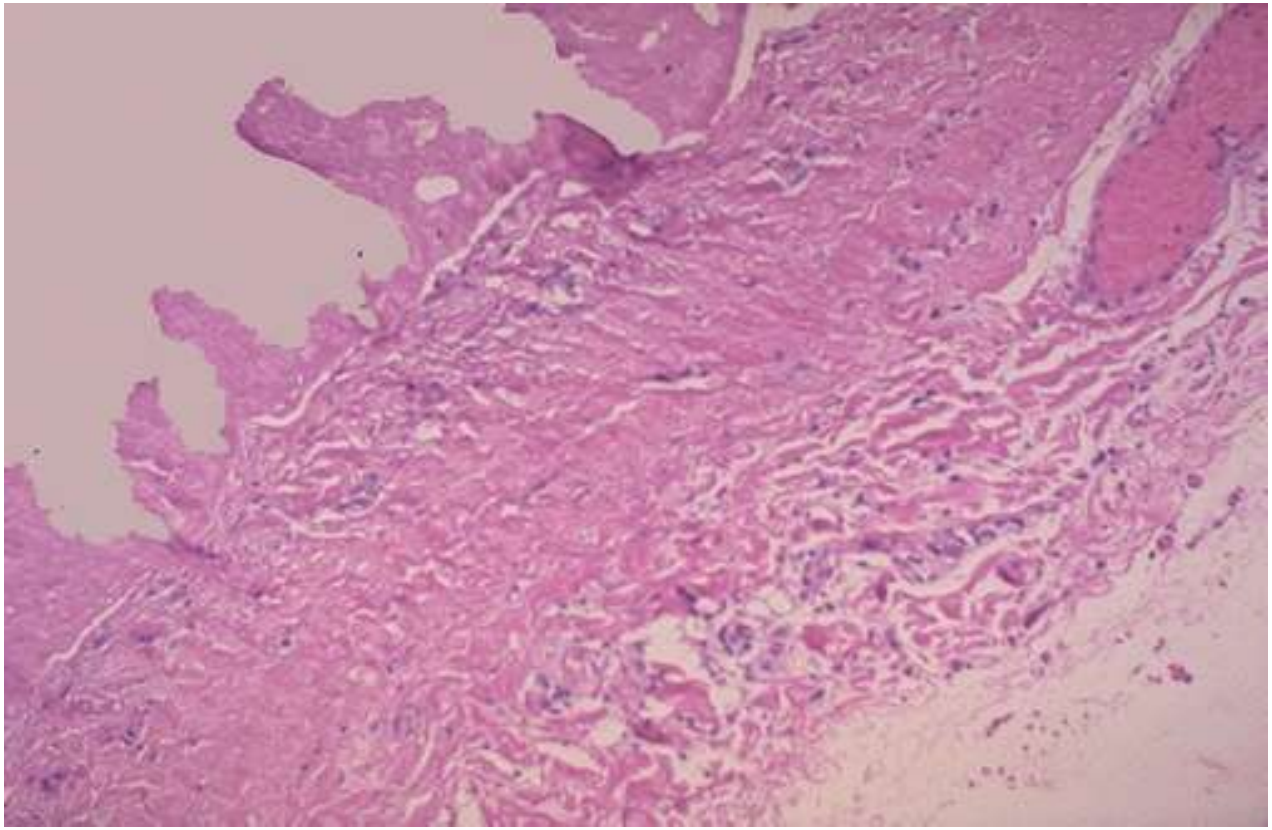
The **pericardial surface** is **dry** with a **coarse granular appearance** caused by **fibrinous exudate**

Normally, the visceral **pericardium** is **translucent**

Histology

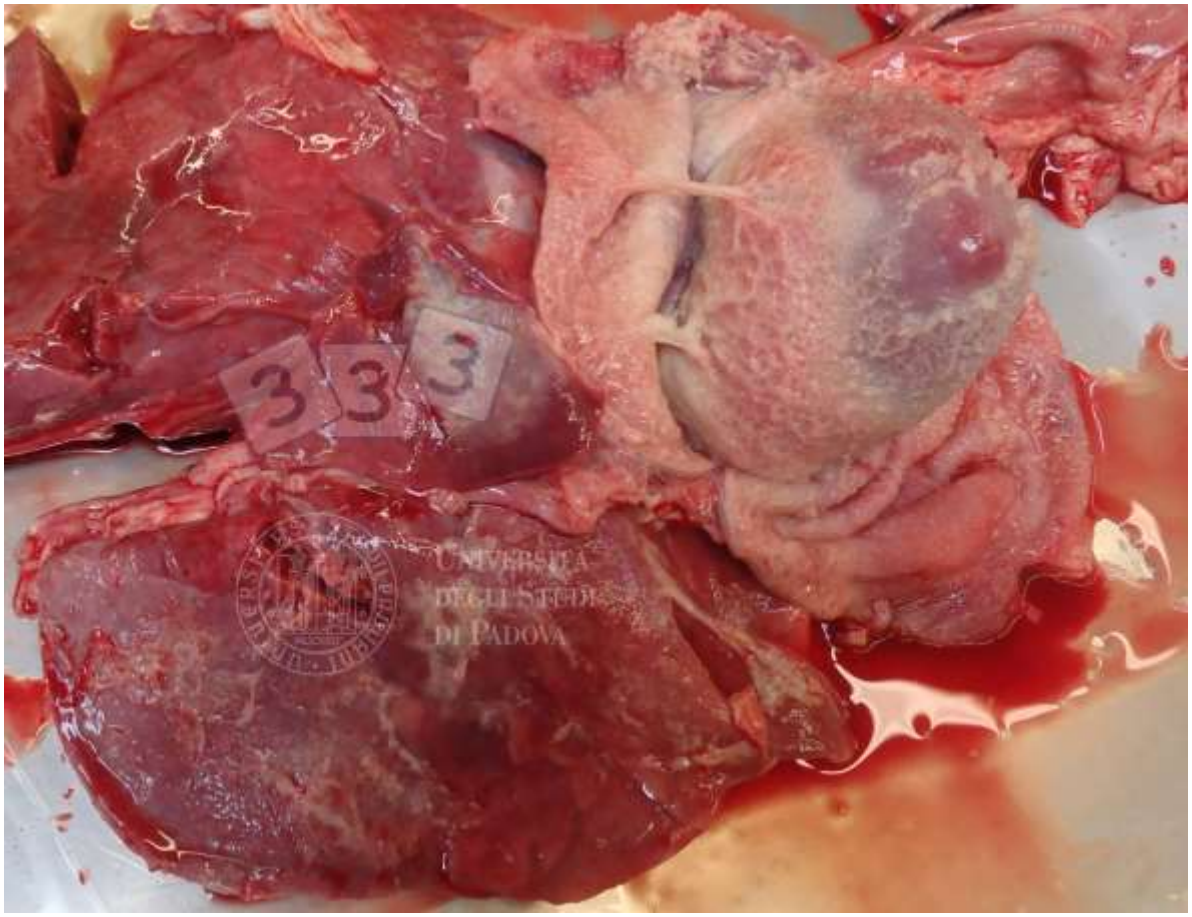


Norml pericrdium composed of thin fibrous wall
Covered by single layer of mesothelial cells



the pericardial surface here shows strands of pink fibrin extending outward. There is underlying inflammation.
fibrin appears as an eosinophilic meshwork of threads

- Conversion of the fibrinous exudate to scar tissue (organization) within the pericardial sac
- if the fibrosis is extensive, obliteration of the pericardial space will occure.

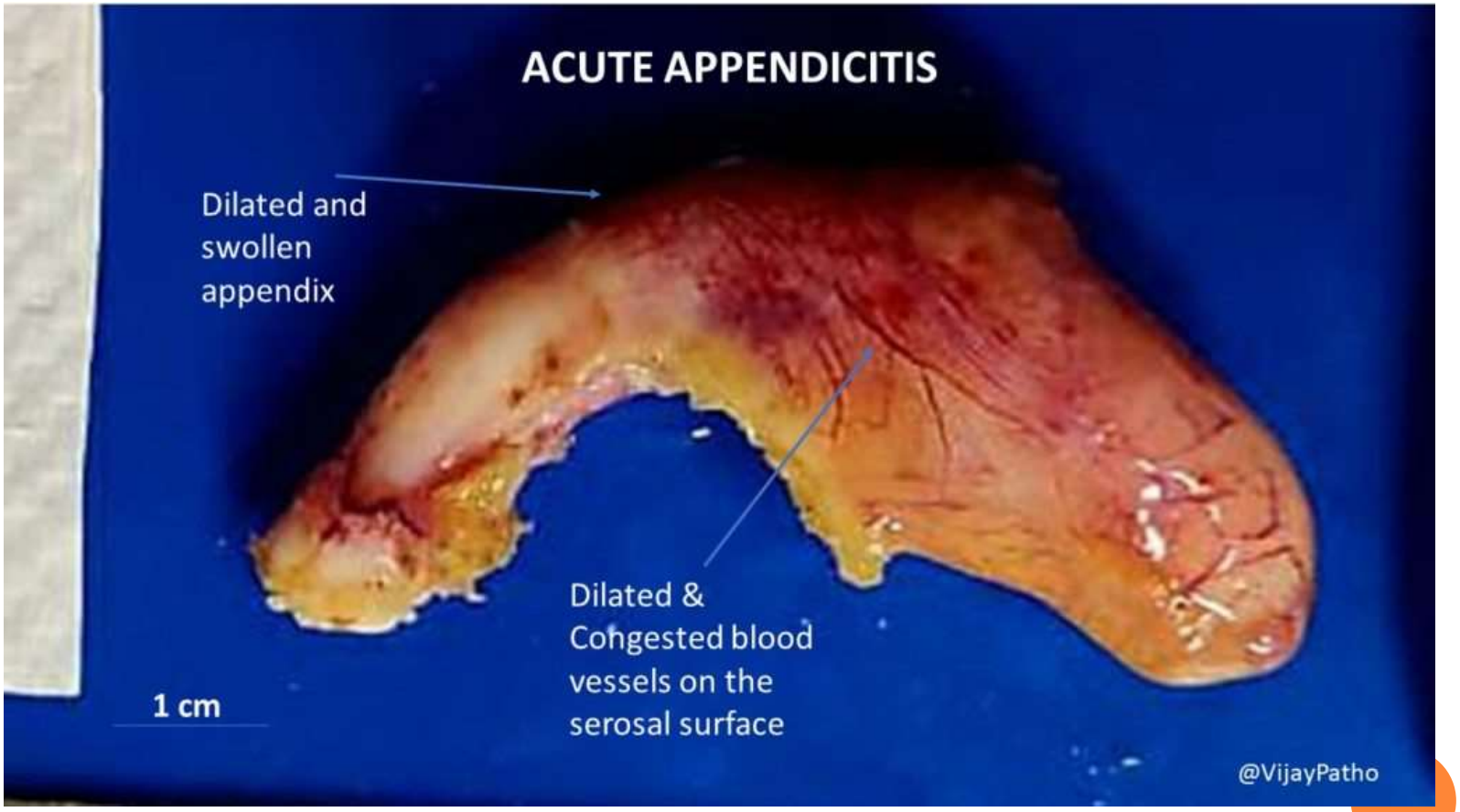


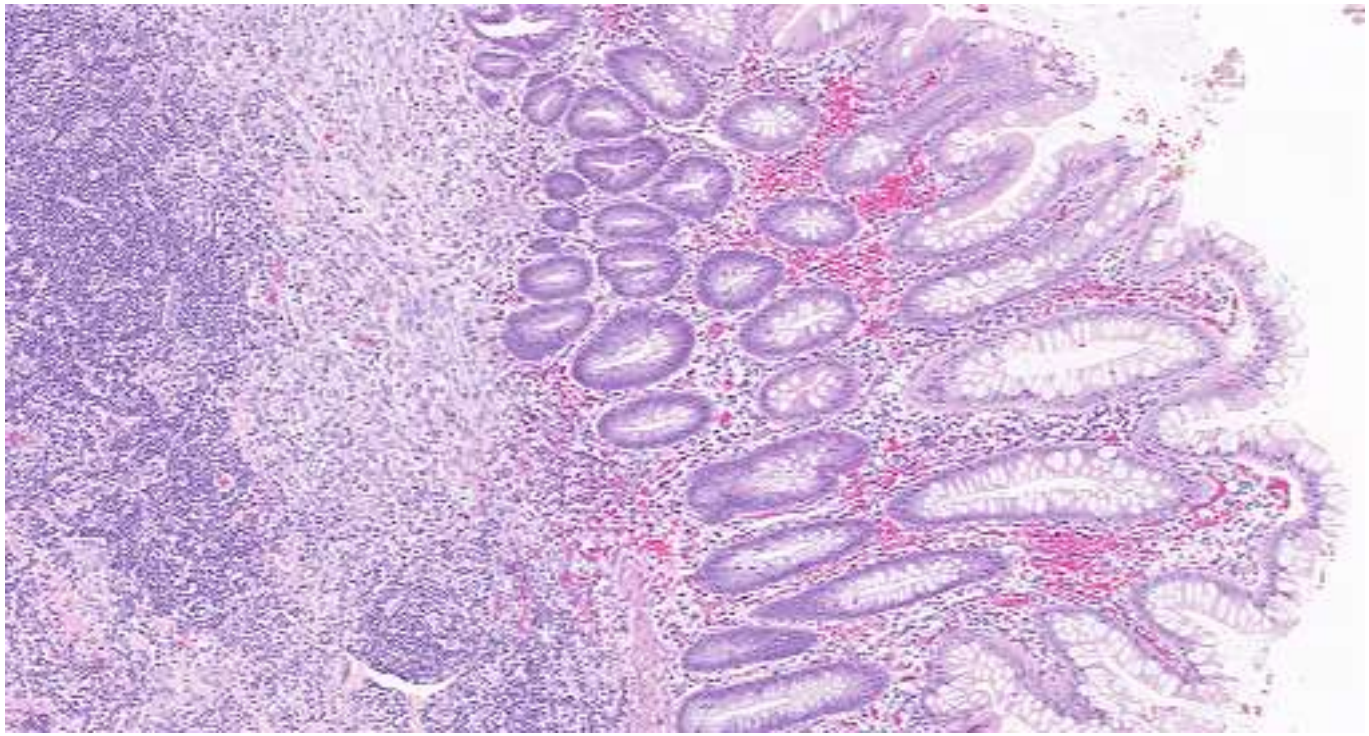
3. Purulent (Suppurative) Inflammation, Abscess

- Purulent inflammation is characterized by the production of pus, an exudate consisting of neutrophils, the liquefied debris of necrotic cells, and edema fluid.

- The most frequent cause:
  - Infection with bacteria that cause liquefactive tissue necrosis, such as staphylococci.
  - These pathogens are referred to as pyogenic (pus-producing) bacteria.

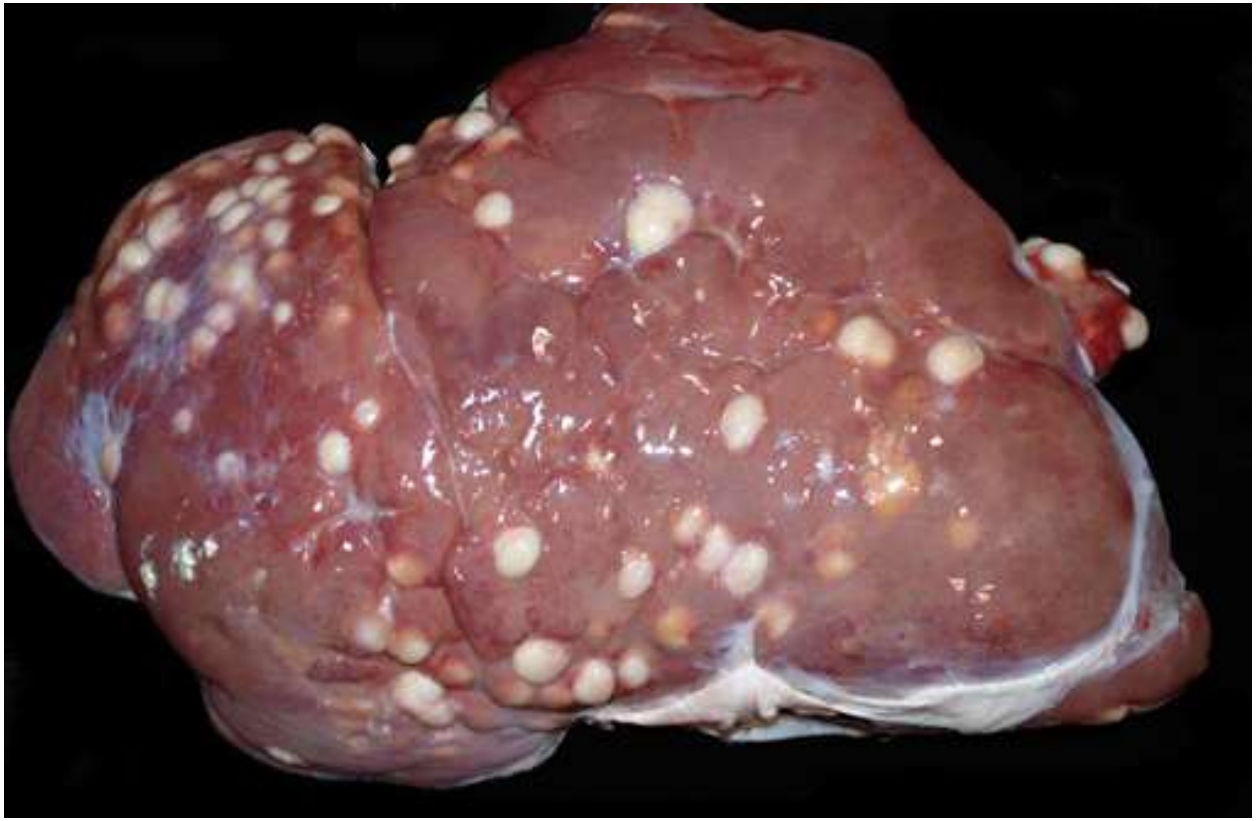
A COMMON EXAMPLE OF AN ACUTE SUPPURATIVE INFLAMMATION IS ACUTE APPENDICITIS





Variable acute inflammation with predominance of neutrophils; involves some or all layers of the appendiceal wall.

- Abscesses:
- are localized collections of pus caused by suppuration buried in a tissue, an organ, or a confined space.
- They are produced by seeding of pyogenic bacteria into a tissue . In time the abscess may become walled off and ultimately replaced by connective tissue

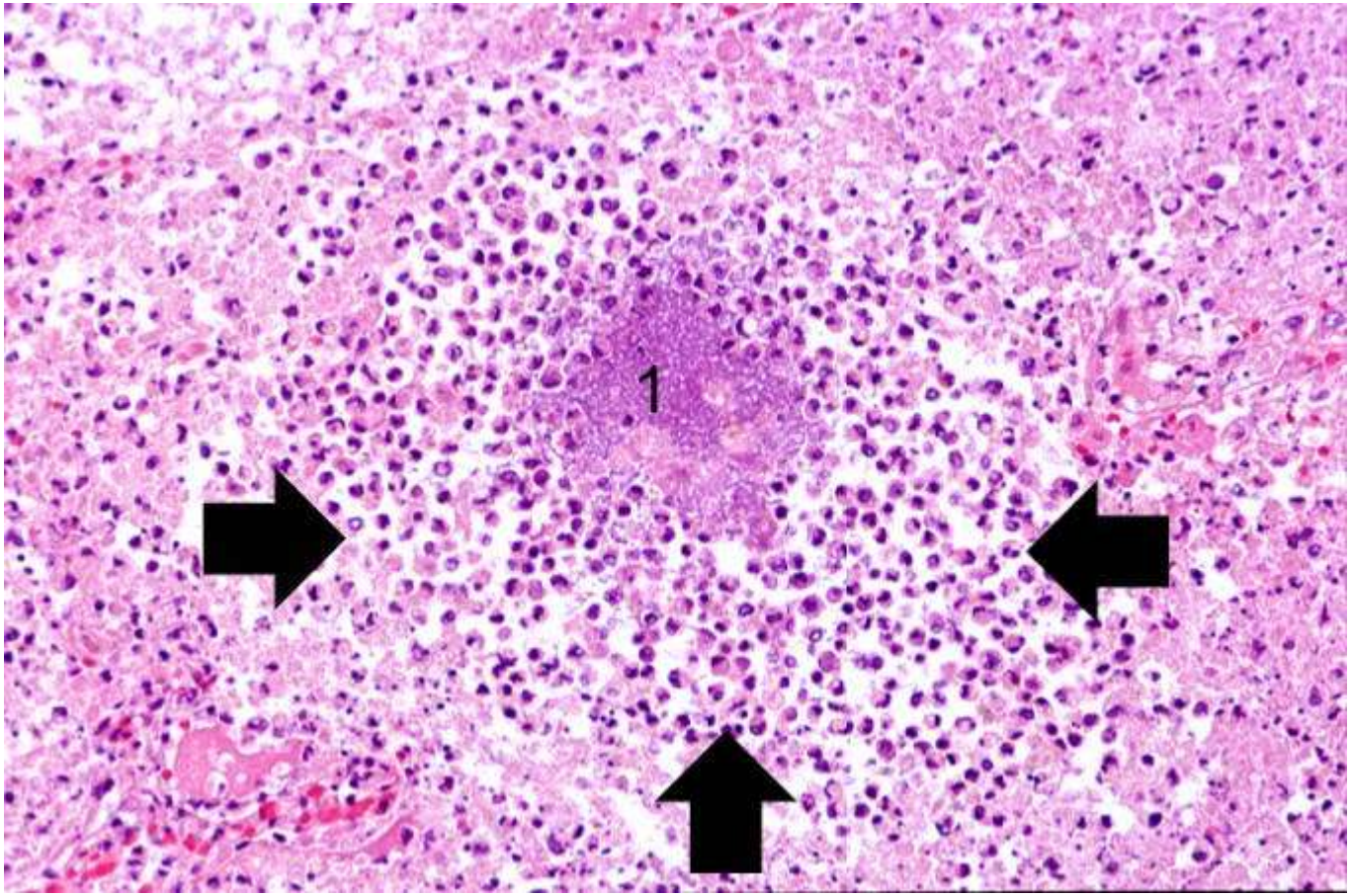


Variably sized abscesses are distributed randomly throughout all lobes of the liver.

Abscesses have a central region that appears as a mass of necrotic leukocytes and tissue cells.

There is usually a zone of preserved neutrophils around this necrotic focus.

outside this region there may be vascular dilation and parenchymal and fibroblastic proliferation, indicating chronic inflammation and repair.

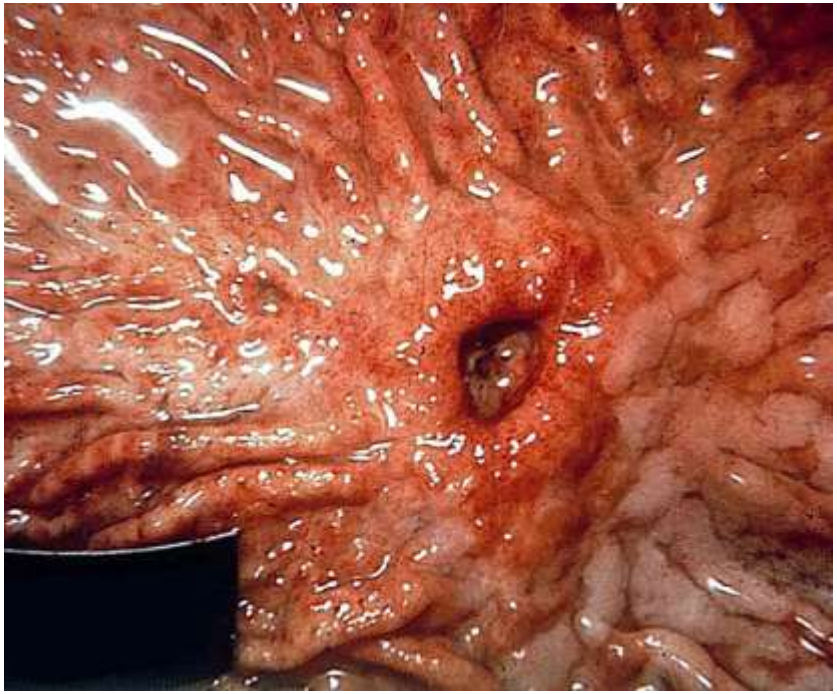


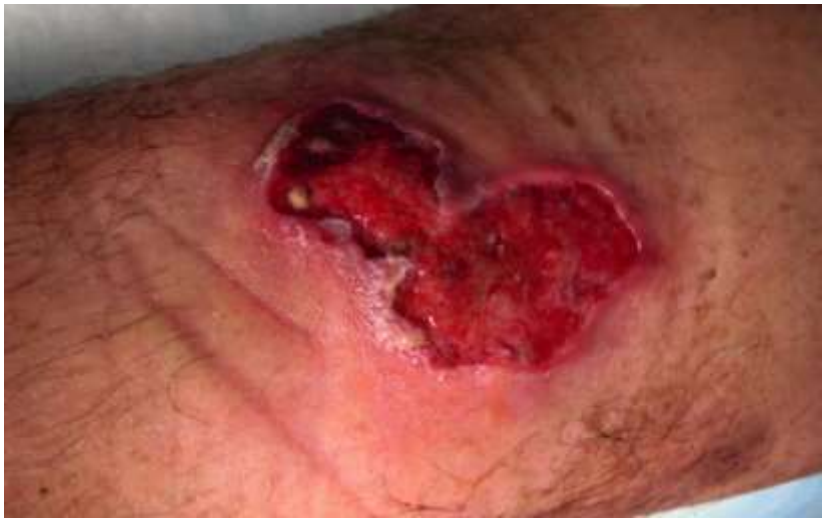
4. Ulcers

- An ulcer is a local defect, or excavation, of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflamed necrotic tissue.

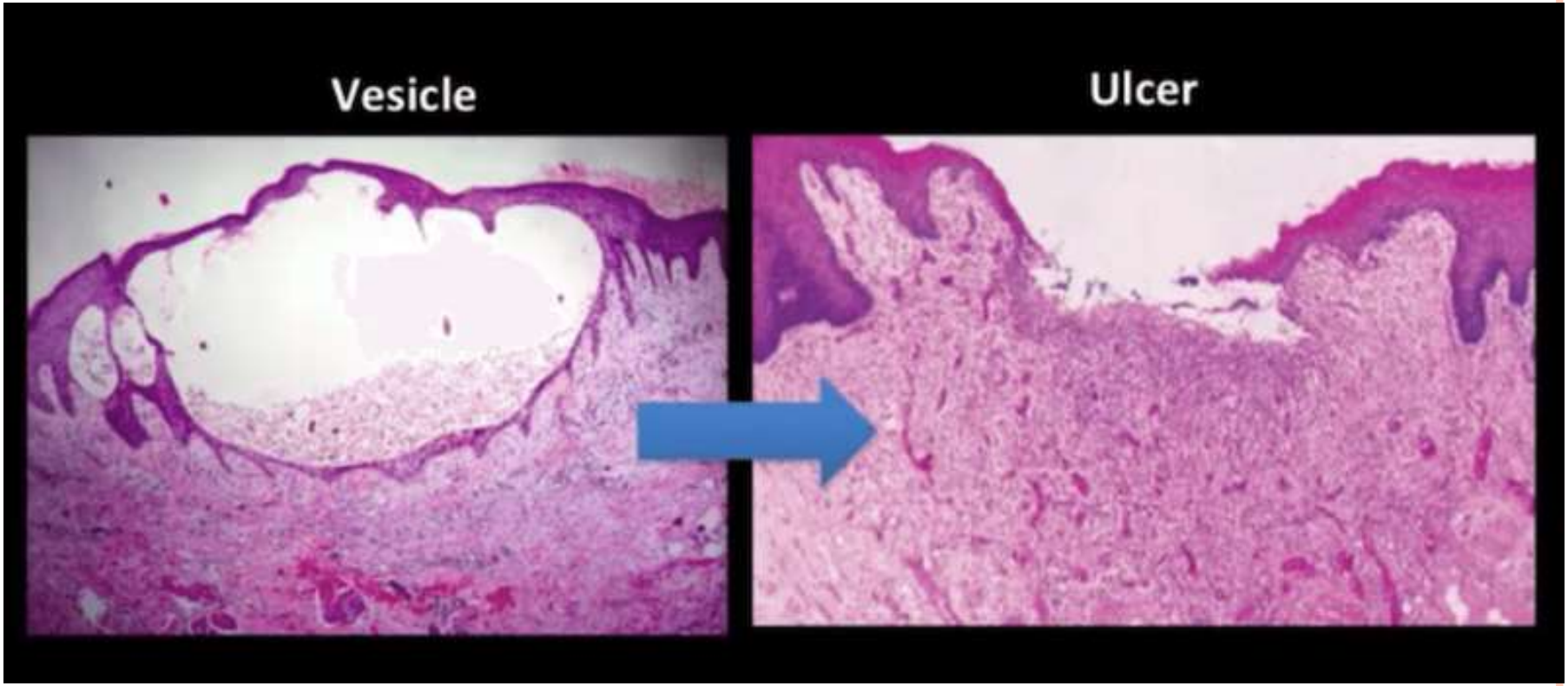
- Ulceration can occur only when tissue necrosis and resultant inflammation exist on or near a surface

- It is most commonly encountered in:
- (1) the mucosa of the mouth, stomach, intestines, or genitourinary tract.
- (2) the skin and subcutaneous tissue of the lower extremities in older persons

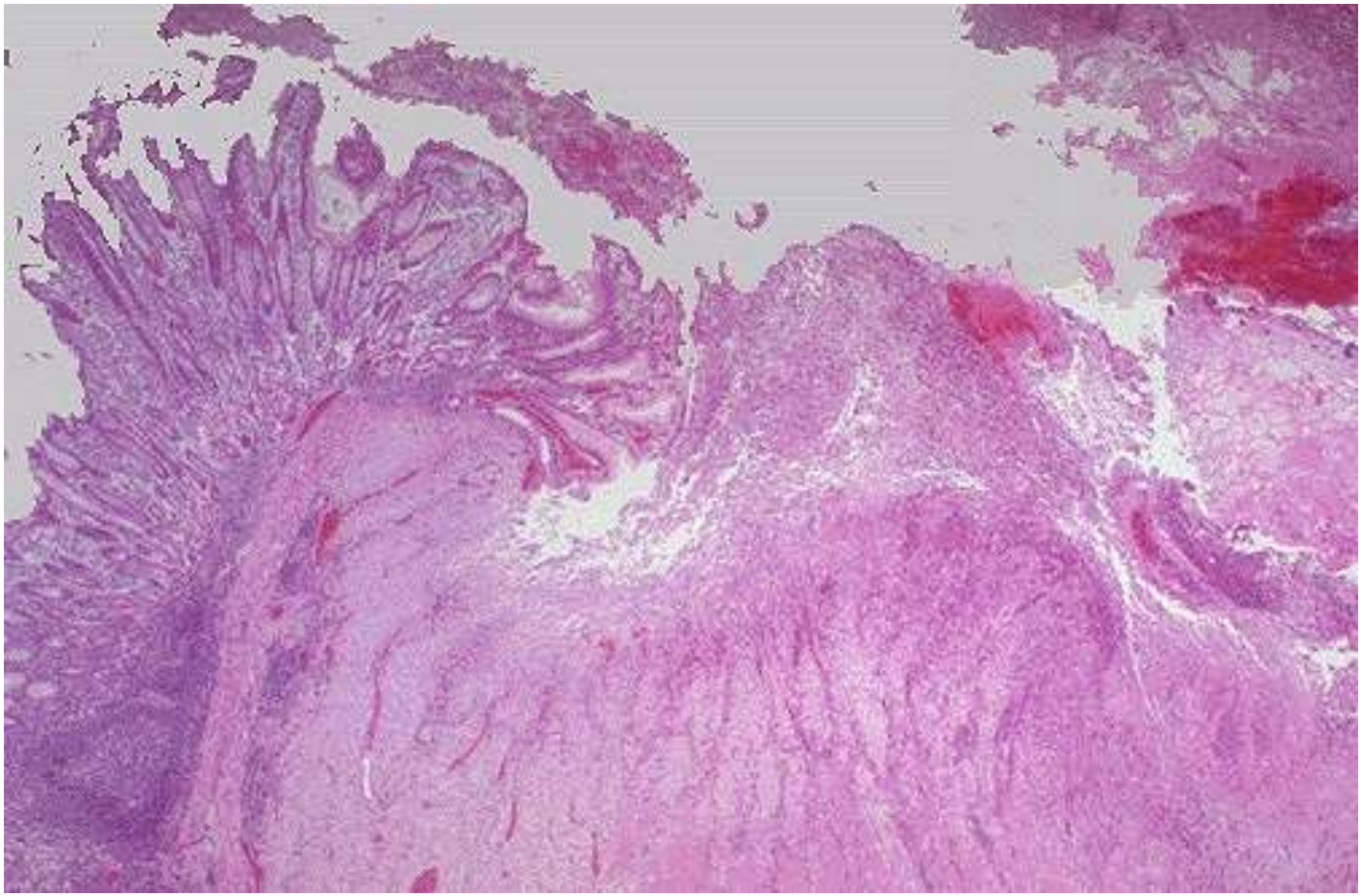




HISTOLOGY



sloughing (shedding) of inflamed necrotic tissue



acute stage there is intense polymorphonuclear infiltration and vascular dilation in the margins of the defect.
With chronicity, the margins and base of the ulcer develop fibroblast proliferation, scarring, and the accumulation of lymphocytes, macrophages, and plasma cells.

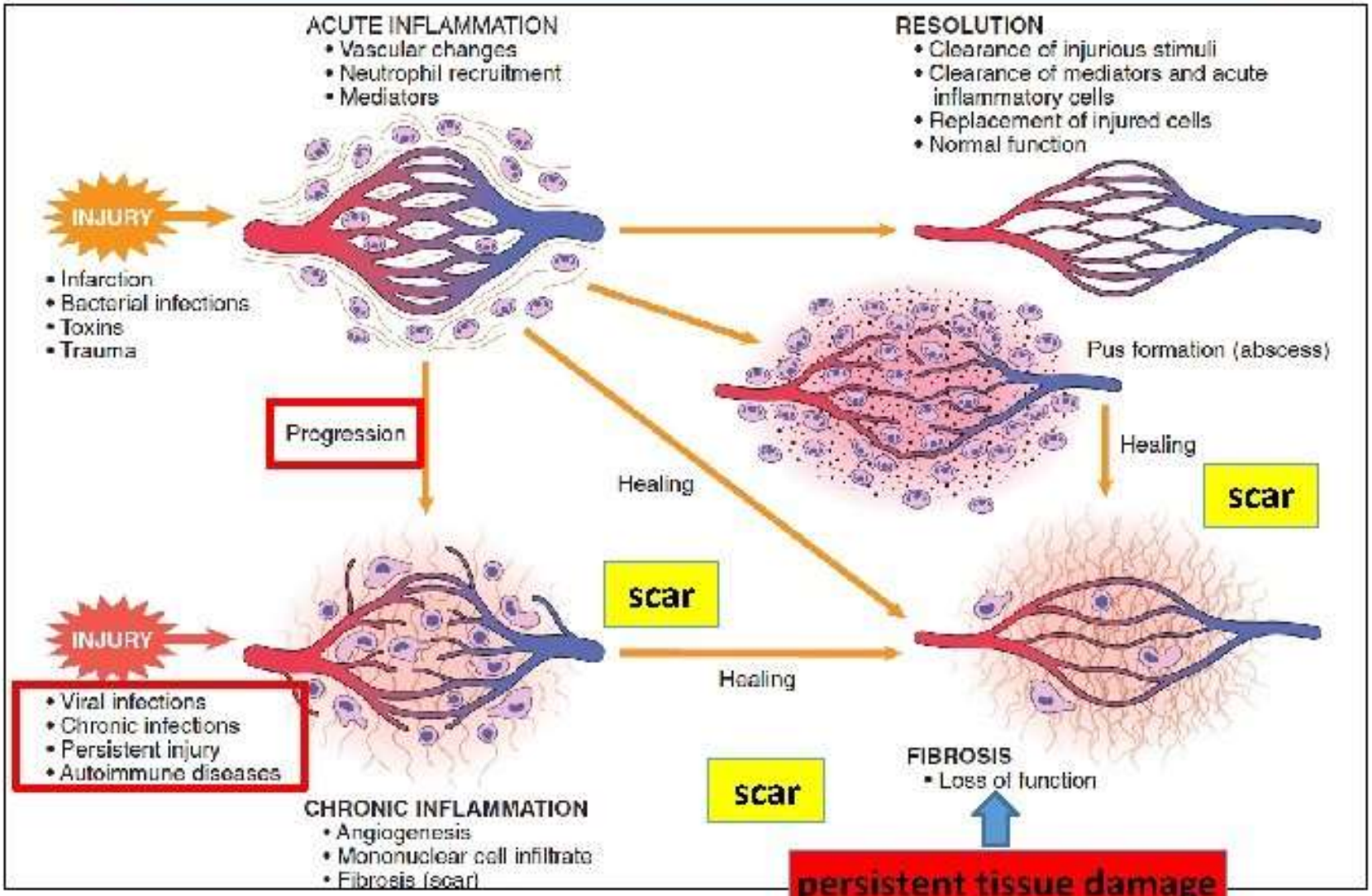
OUTCOMES OF ACUTE INFLAMMATION

- Acute inflammatory reactions typically have one of three outcomes:

- 1. Complete resolution:
- Occur when the injury is limited or short-lived or when there has been little tissue destruction and the damaged parenchymal cells can regenerate.
- Resolution involves removal of cellular debris and microbes by macrophages, and resorption of edema fluid by lymphatics.

- 2. Healing by connective tissue replacement (scarring, or fibrosis).
- occurs after substantial tissue destruction, when the inflammatory injury involves tissues that are incapable of regeneration, or when there is abundant fibrin exudation.
- connective tissue grows into the area of damage or exudate, converting it into a mass of fibrous tissue.
- 3. Progression of the response to chronic inflammation.
- occurs when the acute inflammatory response cannot be resolved, as a result of either :
  - the persistence of the injurious agent
  - or some interference with the normal process of healing, e.g

Outcomes of acute inflammation



CHRONIC INFLAMMATION

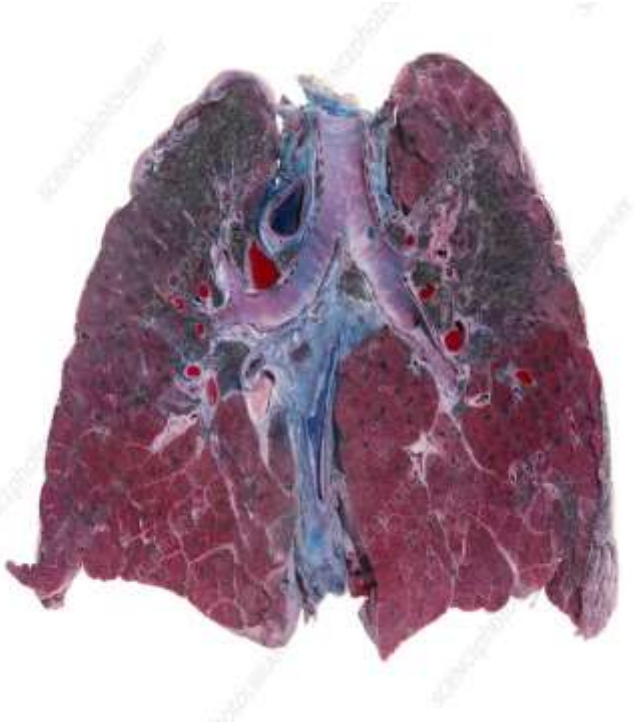
- Chronic inflammation is a response of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations.

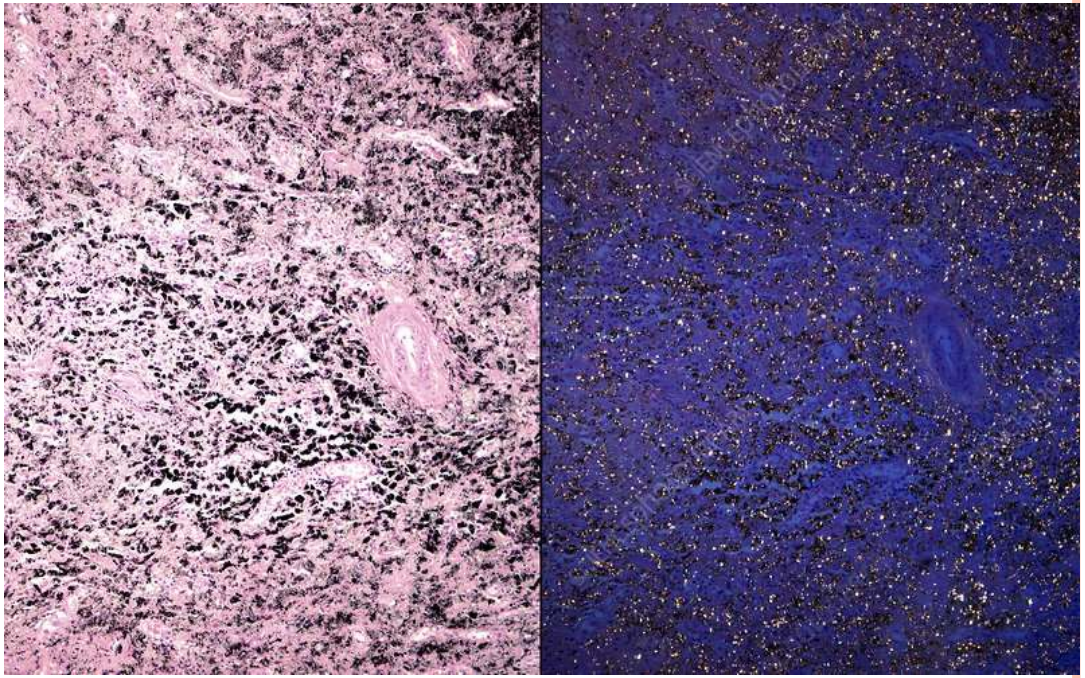
- It may follow acute inflammation, as described earlier, or may begin insidiously,

Causes of Chronic Inflammation

- Persistent infections
- Hypersensitivity diseases,
- autoimmune disease.
- allergic diseases,
- Prolonged exposure to potentially toxic agents, e.g Silica.

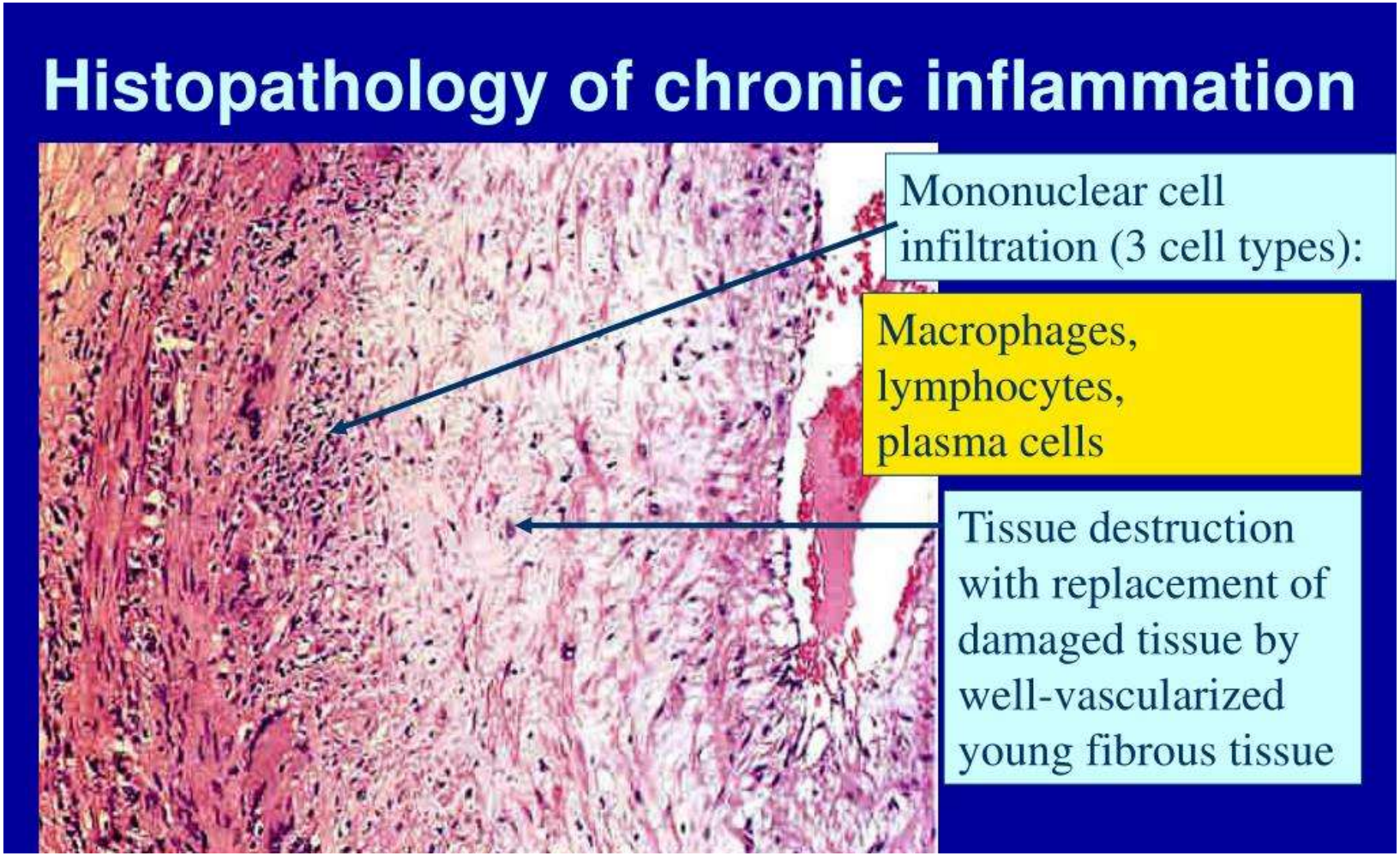
silicosis





The dust particles become permanently embedded into alveoli and smaller respiratory passages and cannot be cleared by mucus or coughing

Silicosis causes inflammation and accumulation of excessive collagen (fibrosis) forming nodular lesions (grey/black)

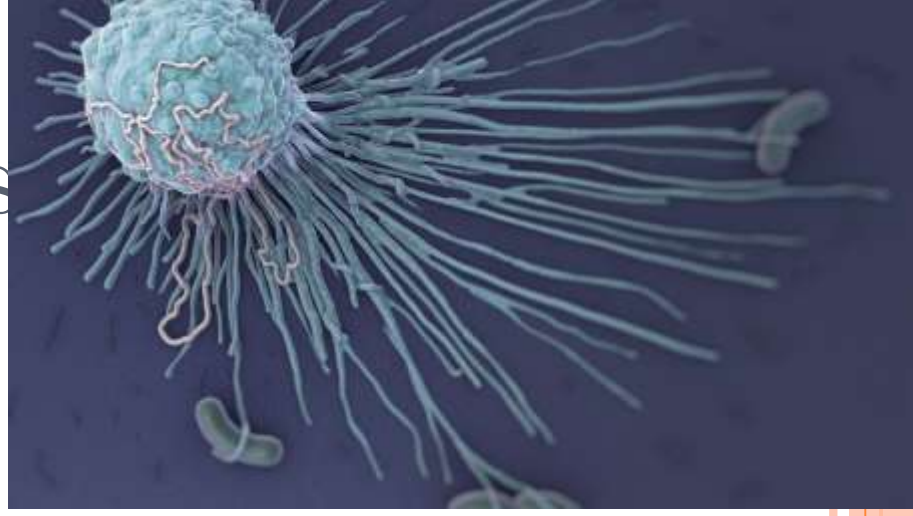


- healing by connective tissue replacement of damaged tissue,

Cells and Mediators of Chronic Inflammation

- Macrophages
- Lymphocytes

1.Role of Macrophages



- The dominant cells in most chronic inflammatory reactions are macrophages, which contribute to the reaction by:

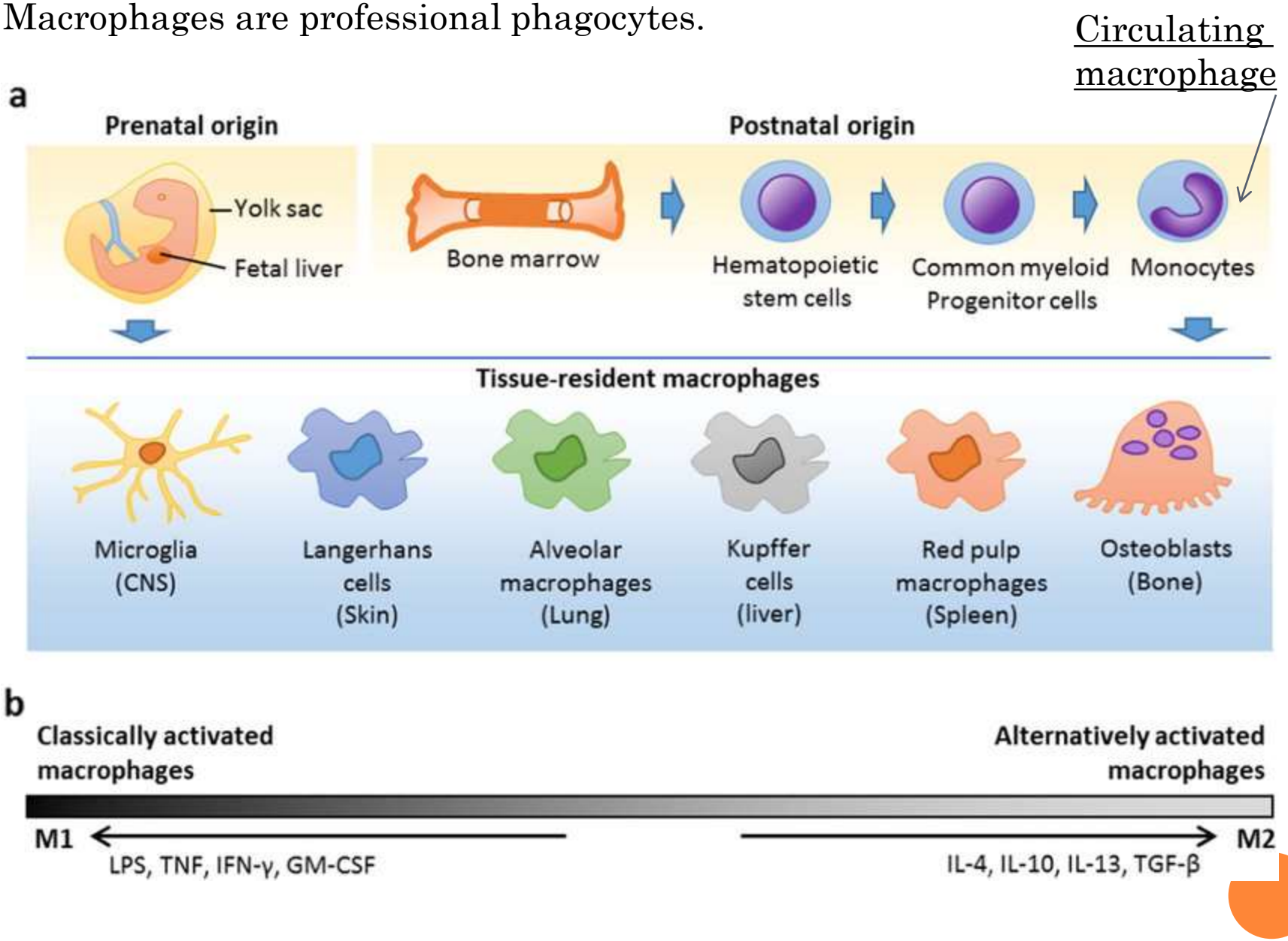
- Secreting cytokines and growth factors that act on various cells.
- By destroying foreign invaders and tissues.
- By activating other cells, notably T lymphocytes.

- Macrophages are tissue cells derived from hematopoietic stem cells in the bone marrow .

- from progenitors in the embryonic yolk sac and fetal liver during early development

- Circulating cells of this lineage are known as monocytes.
- Macrophages are normally diffusely scattered in most connective tissues(tissue resident cells).

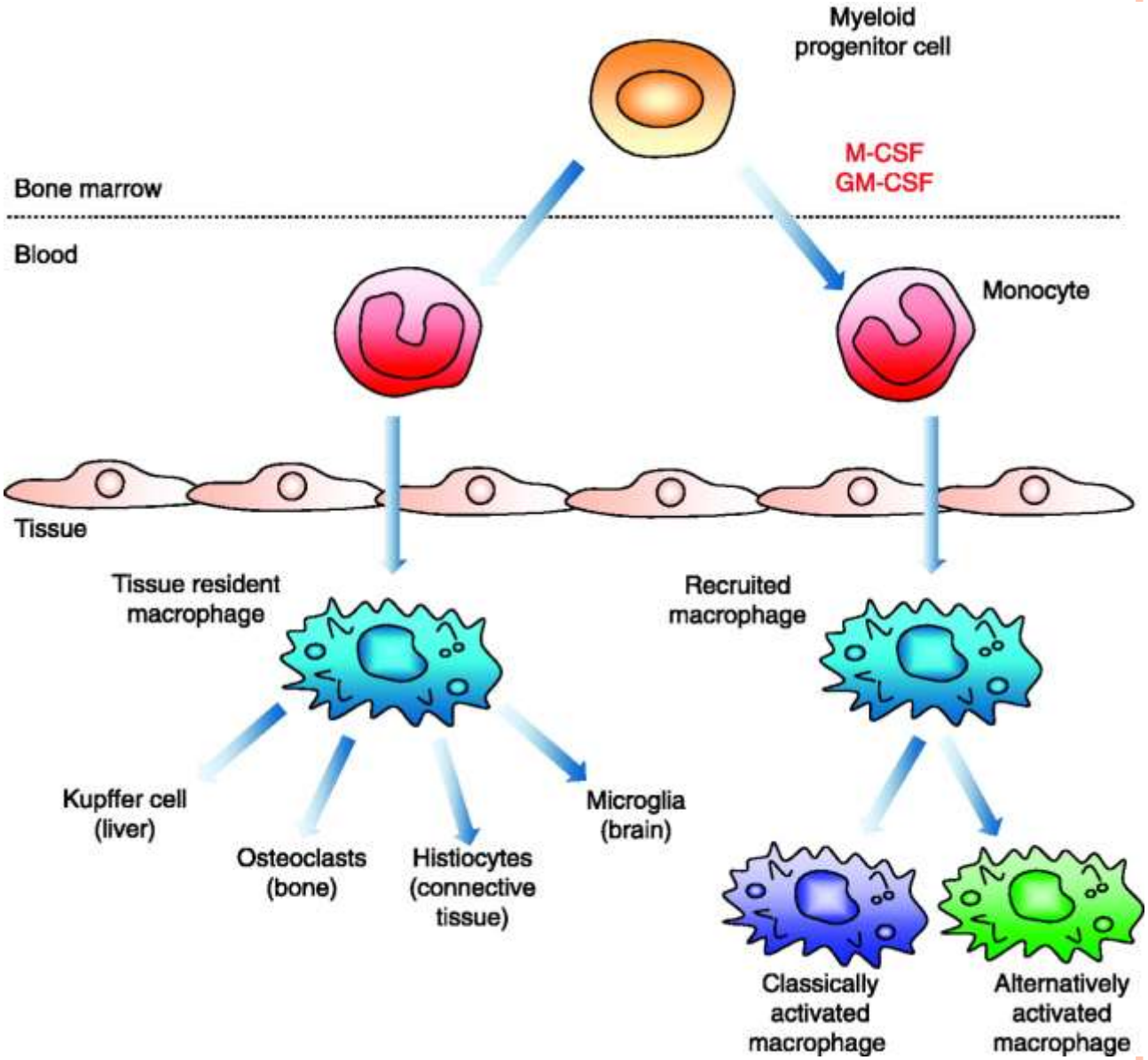
Macrophages are professional phagocytes.



- In inflammatory reactions:
  - progenitors in the bone marrow give rise to monocytes.
    - which enter the blood.
    - migrate into various tissues.
    - differentiate into macrophages.
- Macrophages often become the dominant cell population in inflammatory reactions within 48 hours of onset.

The half-life of blood monocytes is about 1 day

the life span of tissue macrophages is several months or years

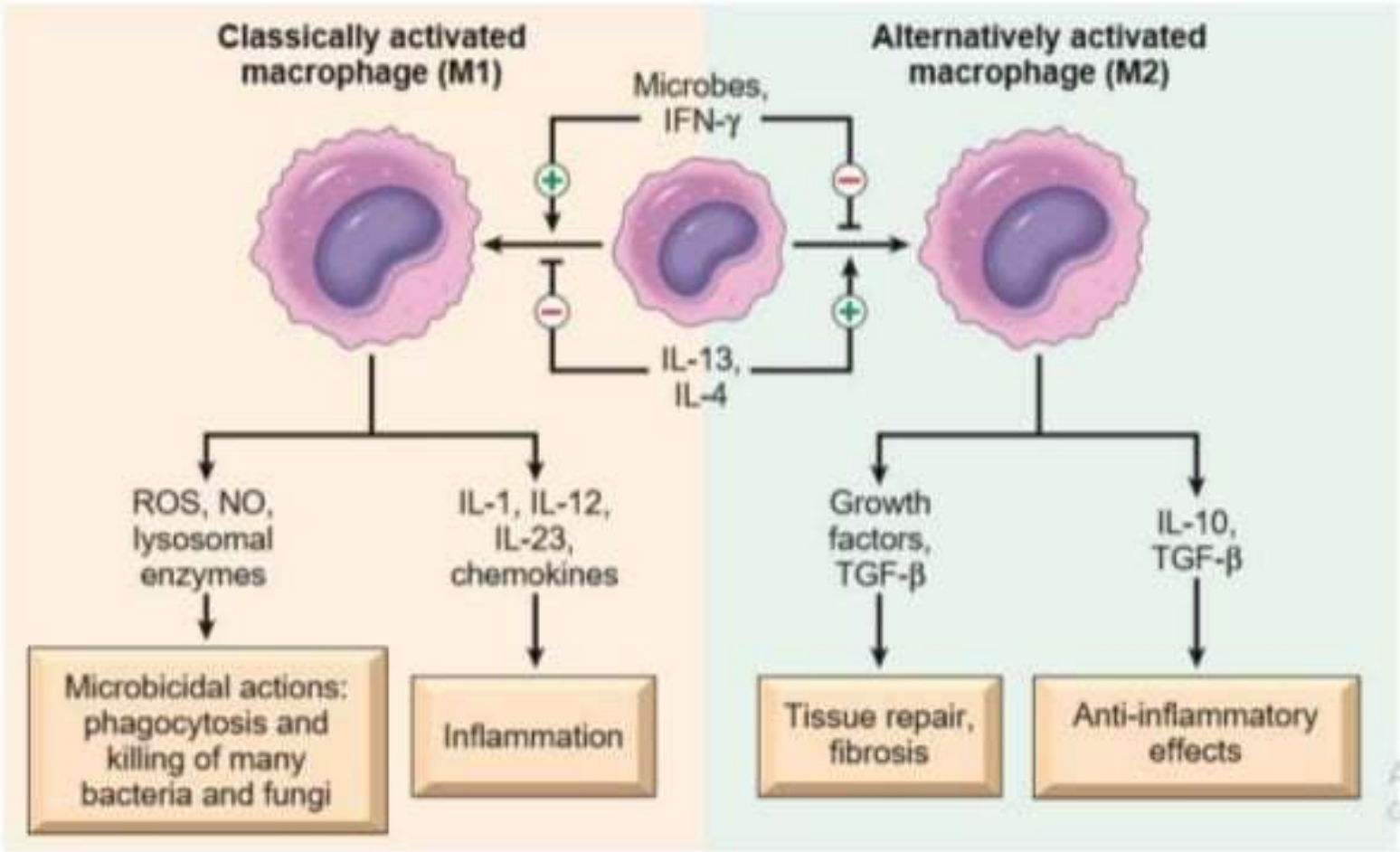


- There are two major pathways of macrophage activation, (depends on the nature of the activating signals):

- Classical:
- designed to destroy the offending agents.

- Alternative :
- initiates tissue repair.

Activation pathways



1.Classical macrophage activation (M1):

- Induced by:
  - Microbial products such as endotoxin.
  - T cell–derived signals, importantly the cytokine IFN-γ.

- Classically activated (also called M1) macrophages produce:
  - NO.
  - ROS.
  - Upregulate lysosomal enzymes.

2.Alternative macrophage activation (M2)

- Is induced by:
- cytokines other than IFN-γ, such as IL-4 and IL-13, produced by T lymphocytes.

- The principal function of alternatively activated (M2) macrophages is in tissue repair.

- They secrete growth factors that promote :
- Angiogenesis.
- activate fibroblasts.
- stimulate collagen synthesis.

- The products of activated macrophages :

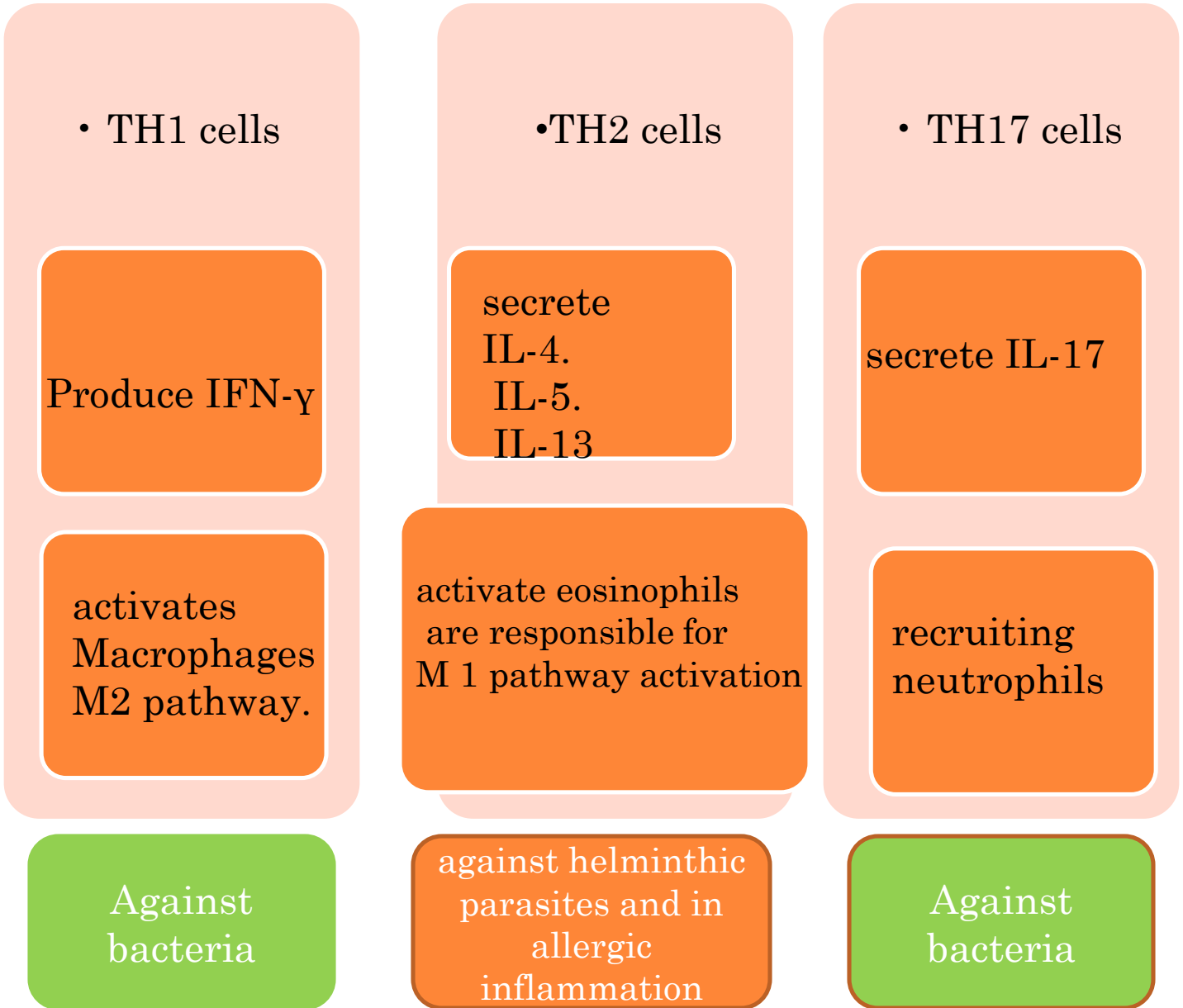
- Eliminate injurious agents such as microbes.
- Initiate the process of repair.
- Responsible for much of the tissue injury in chronic inflammation

2.Role of Lymphocytes

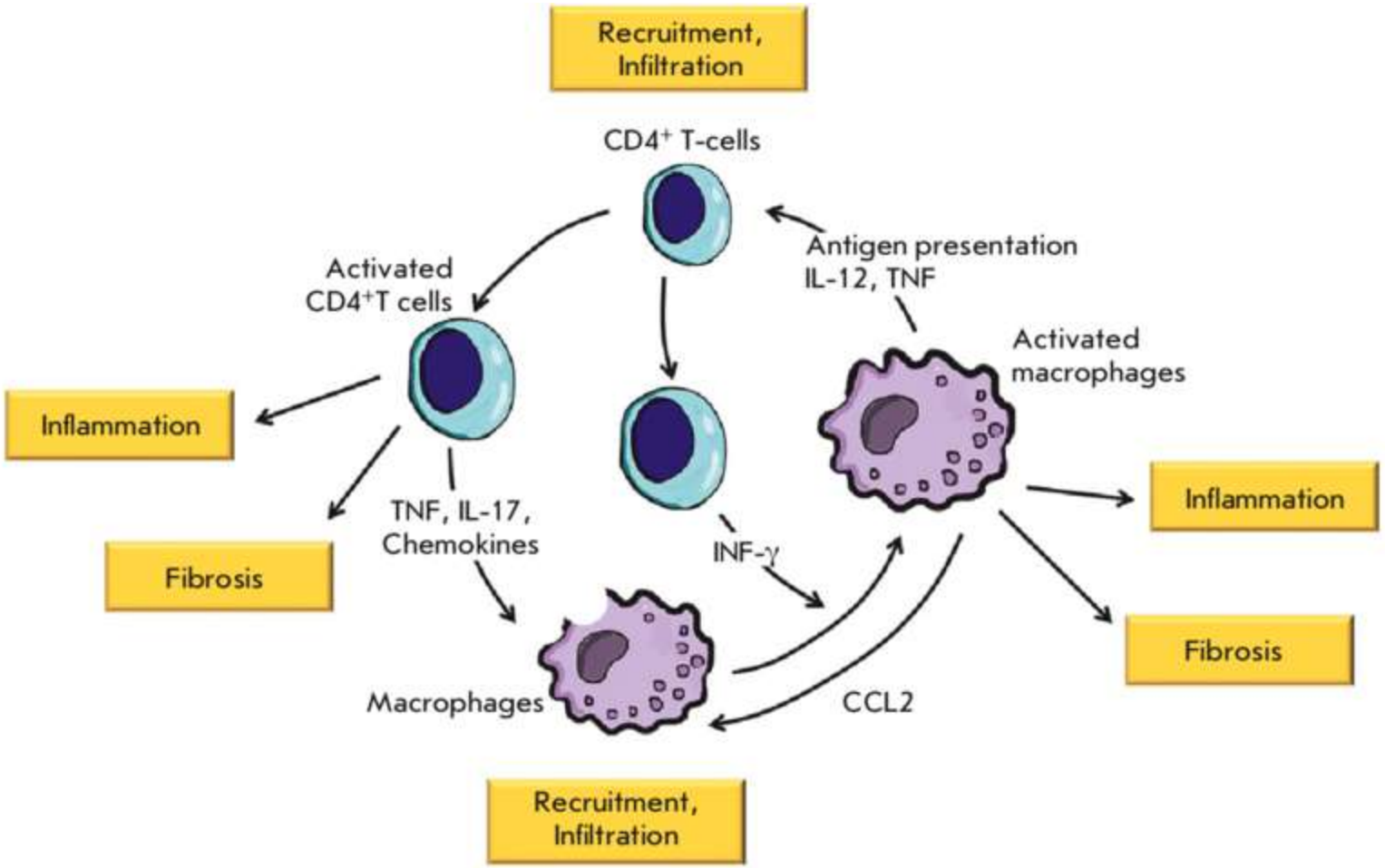
- Microbes and other environmental antigen activate T and B lymphocytes, which amplify and propagate chronic inflammation.

- Some of the strongest chronic inflammatory reactions, such as granulomatous inflammation, are dependent on lymphocyte responses.

❖ CD4+ T lymphocytes promote inflammation



Lymphocytes and macrophages interact in a bidirectional way.

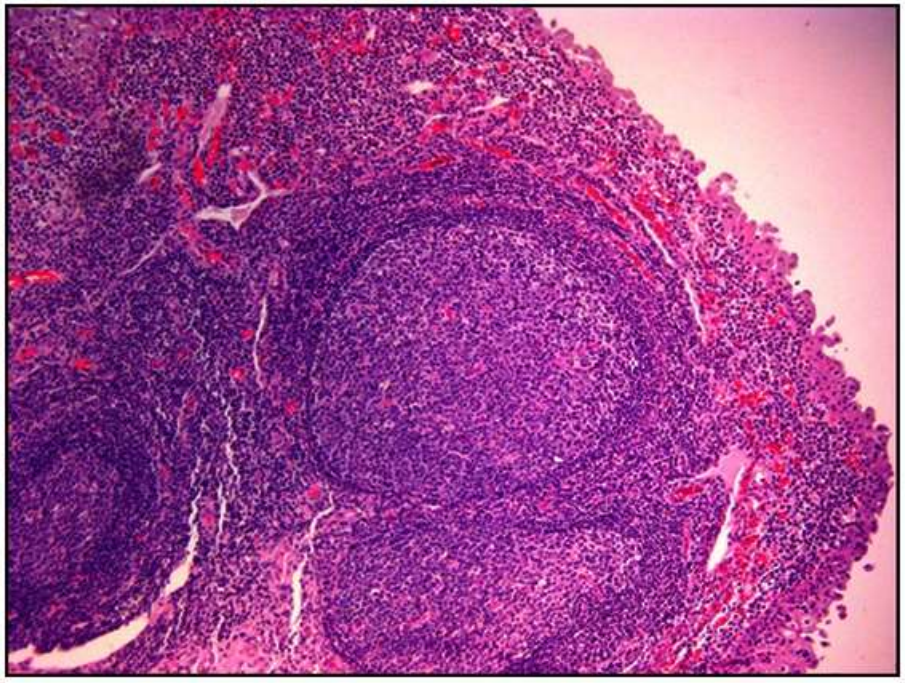


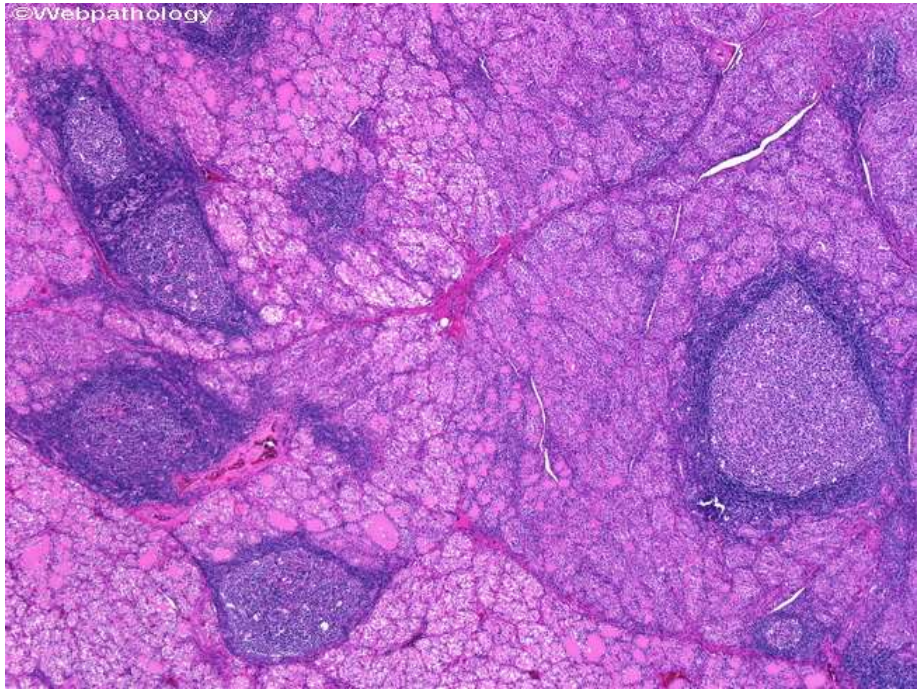
- **cycle of cellular reactions**
- Macrophages:
  - display antigens to T cells, that activate T cells.
  - produce cytokines (IL-12 and others) that also stimulate T cell responses.
- Activated T lymphocytes:
  - produce cytokines, which recruit and activate macrophages.
  - promoting more antigen presentation and cytokine secretion.

These interactions play an important role in propagating chronic inflammation

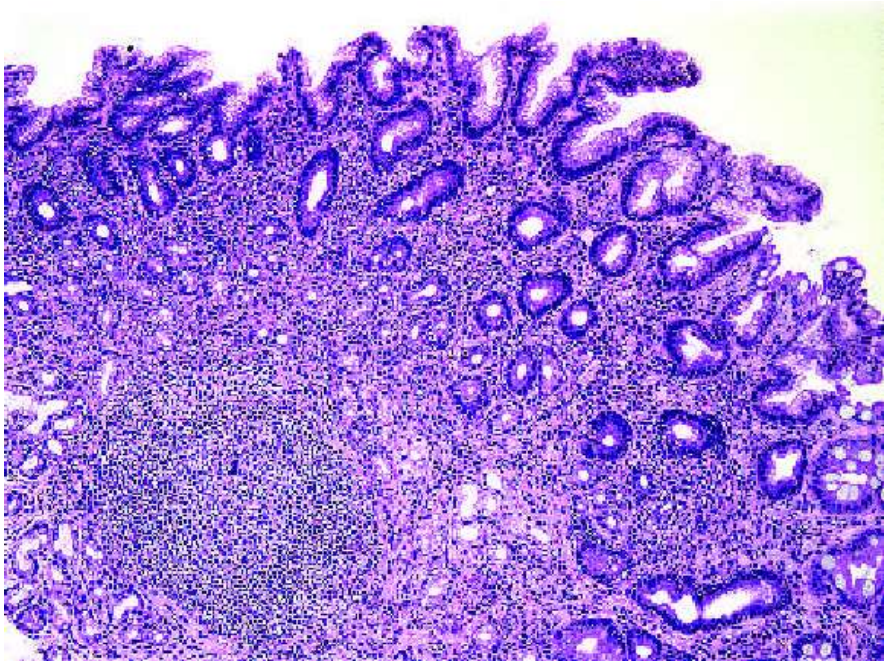
TERTIARY LYMPHOID ORGANS

- Accumulated lymphocytes, antigen-presenting cells, and plasma cells cluster together to form lymphoid structures resembling the follicles found in lymph nodes





Thyroid in Hashimoto thyroiditis



Helicobacter pylori gastritis

Other Cells in Chronic Inflammation

- 1.Eosinophils:

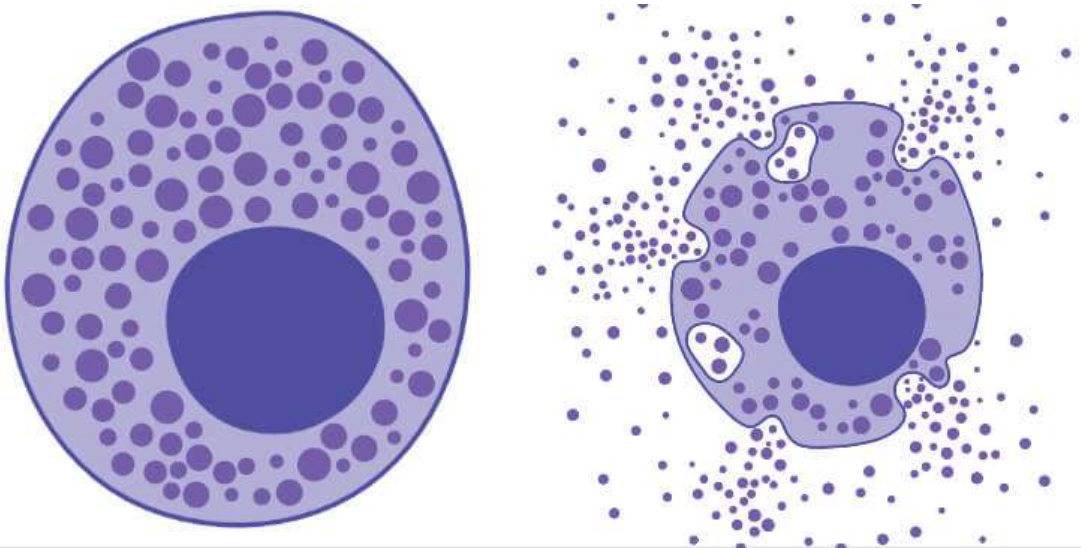
- Are abundant in immune reactions mediated by IgE and in parasitic infections.
- Their recruitment is driven by certain adhesion molecules, and by specific chemokines (e.g., eotaxin).

- Eosinophils have granules that contain major basic protein, a highly cationic protein that is toxic to parasites but also injures host epithelial cells.

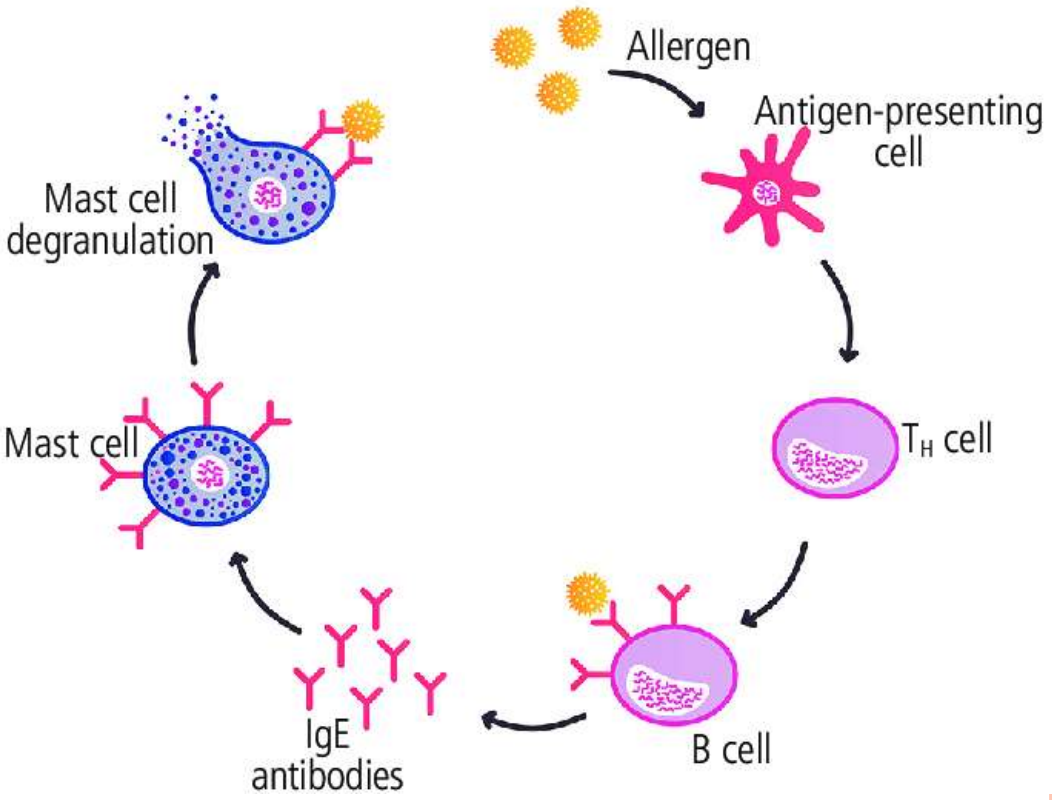
- So eosinophils are of benefit in:
  - controlling parasitic infections.
  - contribute to tissue damage in immune reactions such as allergies

2.Mast cells

- Are widely distributed in connective tissues and participate in both acute and chronic inflammatory reactions.
- Mast cells arise from precursors in the bone marrow.



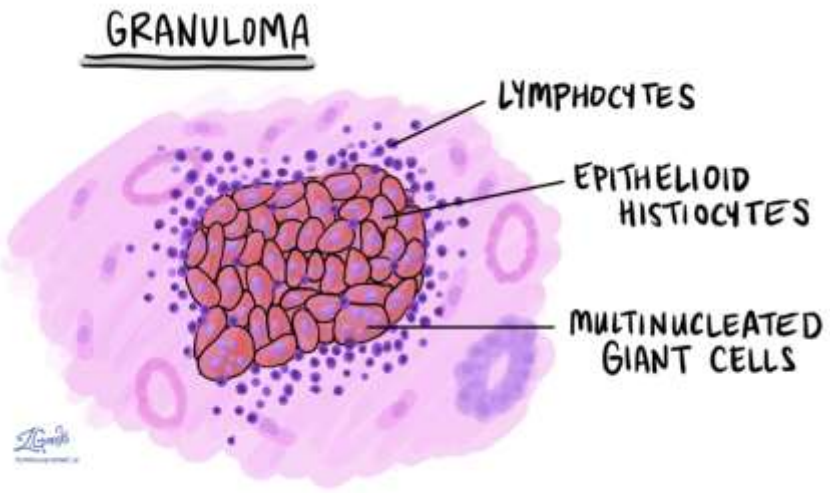
- Mast cells (and basophils) express on their surface the receptor FcεRI, which binds the Fc portion of IgE antibody. In immediate hypersensitivity reactions, IgE bound to the mast cells' Fc receptors specifically recognizes antigen, and in response the cells degranulate and release mediators, such as histamine and prostaglandins

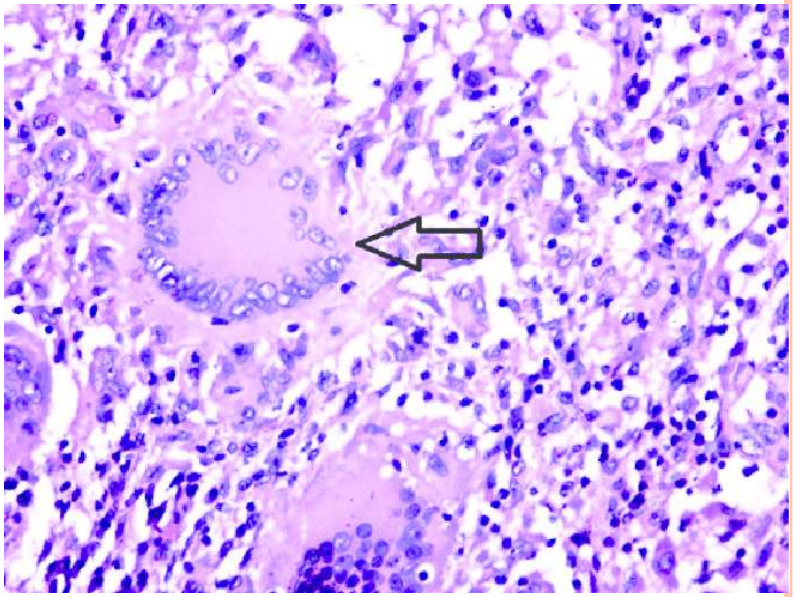


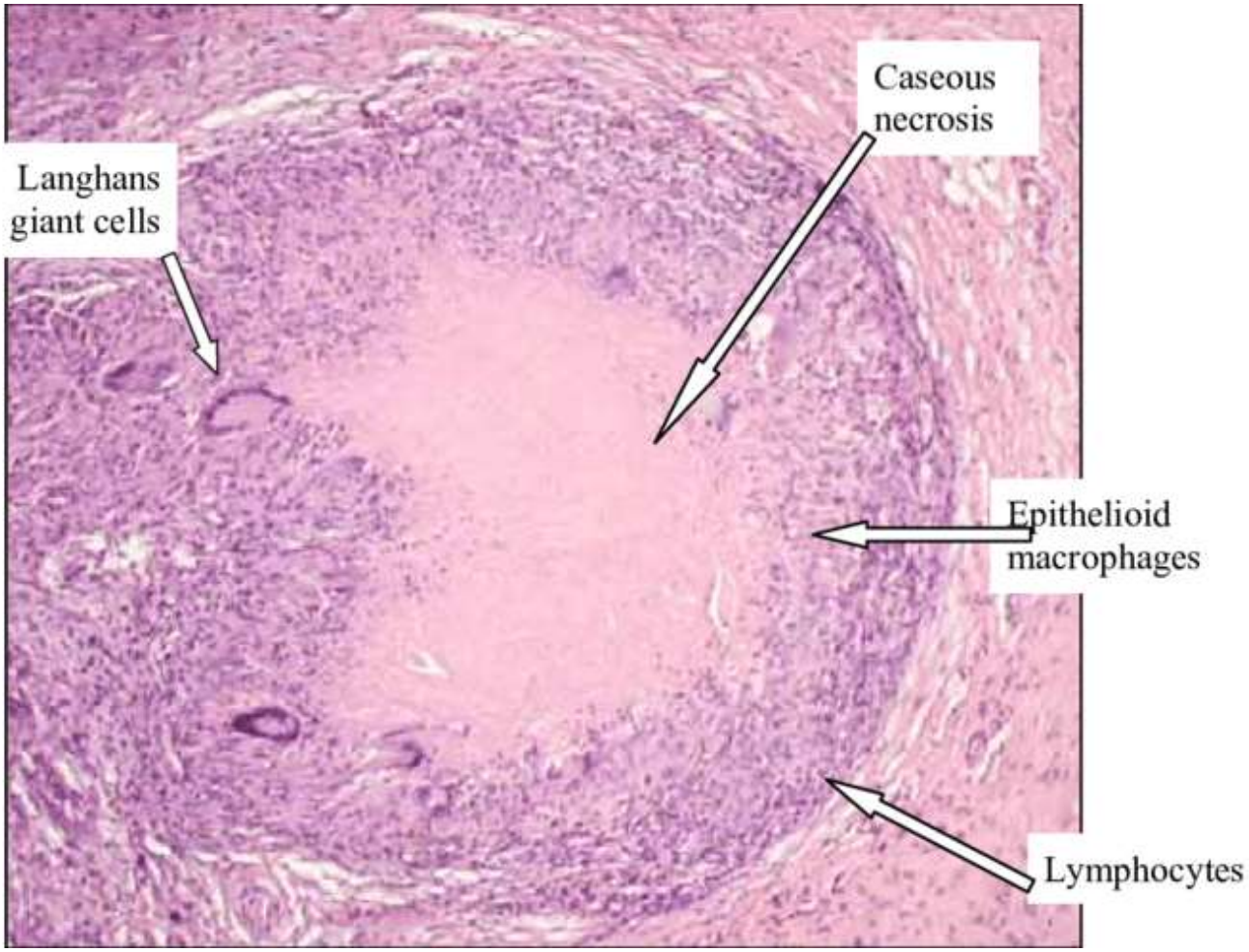
This type of response occurs during allergic reactions

Granulomatous Inflammation

- Granulomatous inflammation is a form of chronic inflammation characterized by collections of activated macrophages, often with T lymphocytes.
- Granuloma formation is a cellular attempt to contain an offending agent that is difficult to eradicate



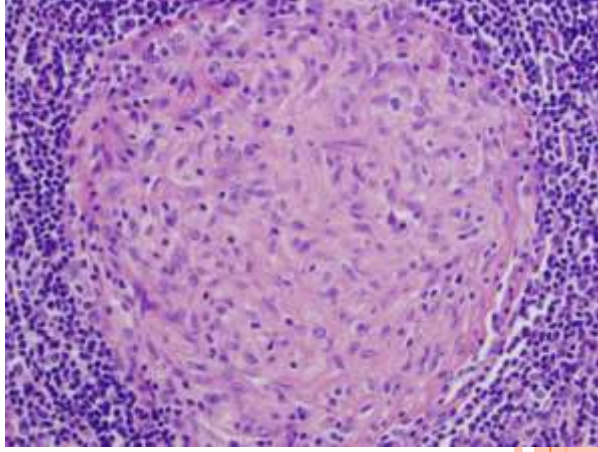




- Epithelioid macrophage: macrophages with abundant cytoplasm and begin to resemble epithelial cells.

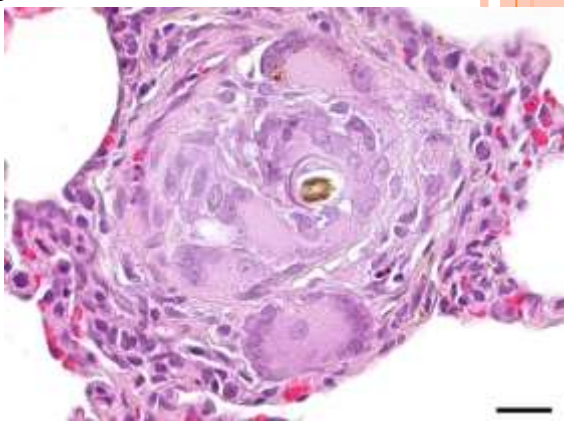
- Multinucleated giant cells: fused activated macrophages .

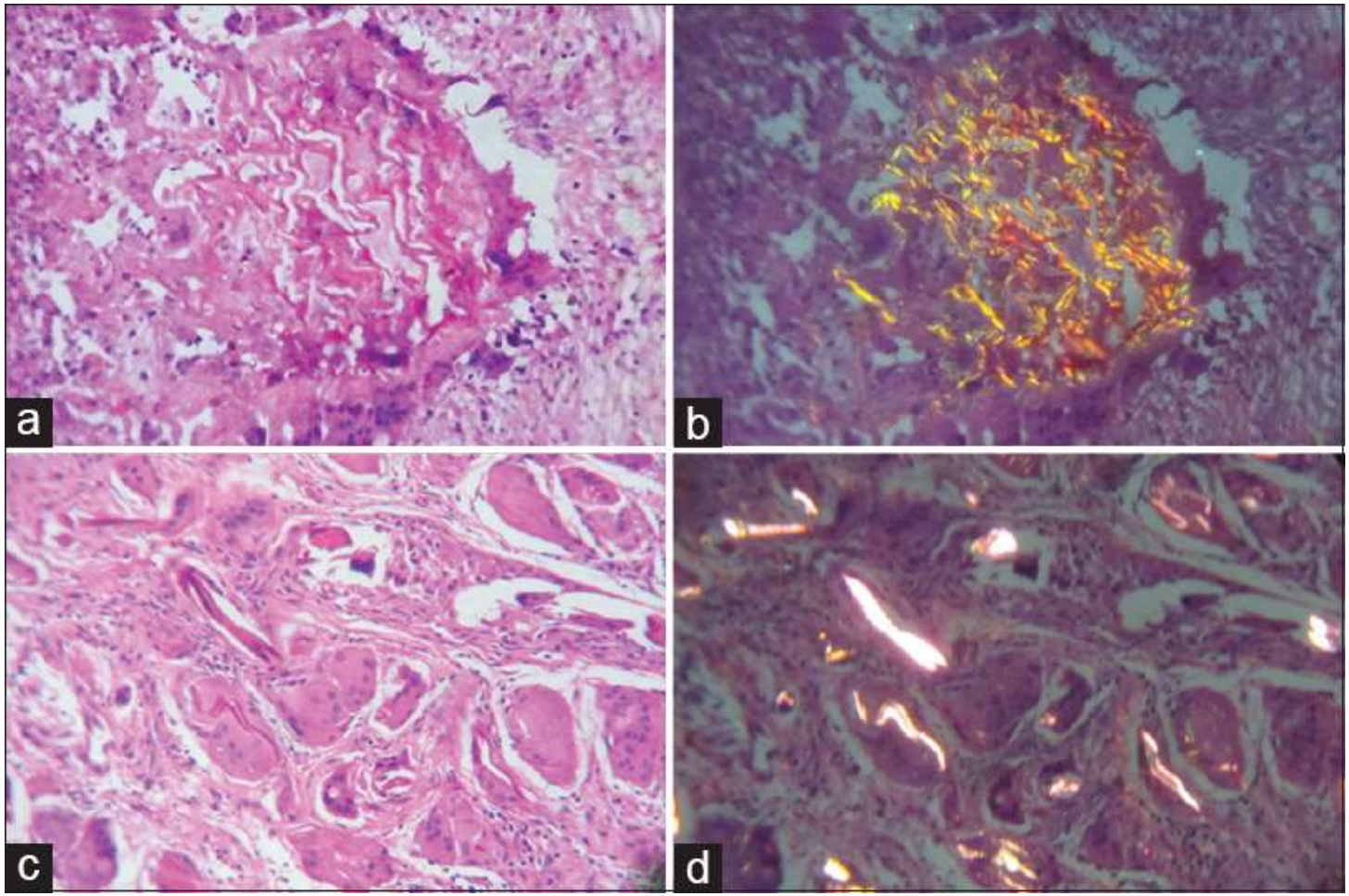
TYPES OF GRANULOMAS;



- 1.Immune granulomas:
- caused by persistent T cell–mediated immune response.
- when the inciting agent cannot be readily eliminated.

- **2.Foreign body granulomas:**
- seen in response to inert foreign bodies, in the absence of T cell– mediated immune responses.
- May form around materials such as talc (associated with intravenous drug abuse), sutures, or other fibers





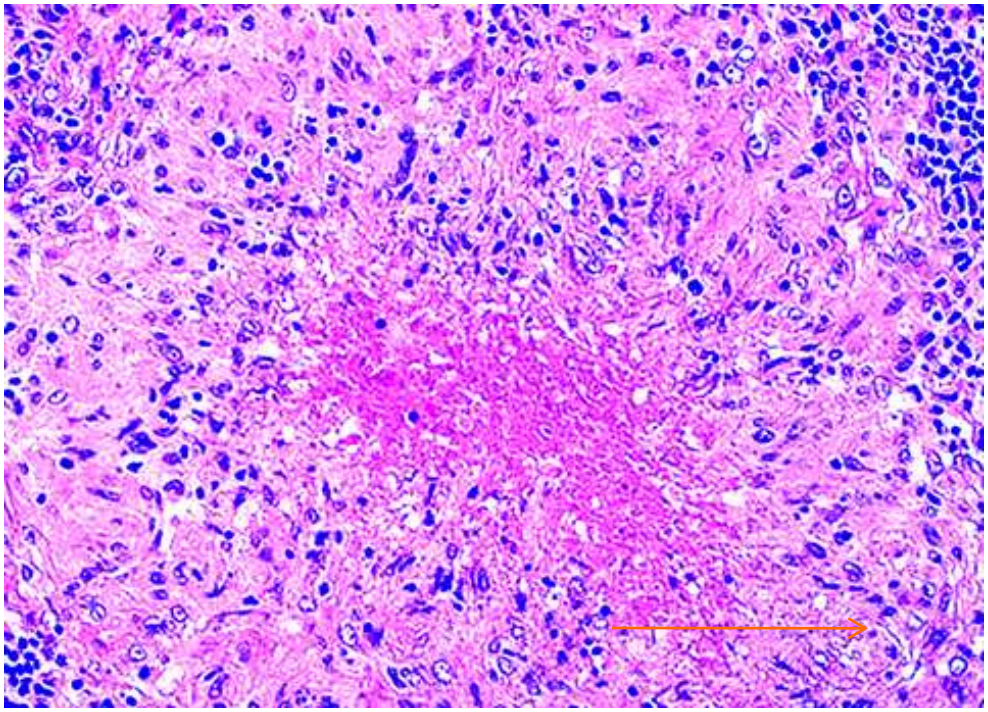
The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it may appear refractile.

Table 3.9 Examples of Diseases With Granulomatous Inflammation

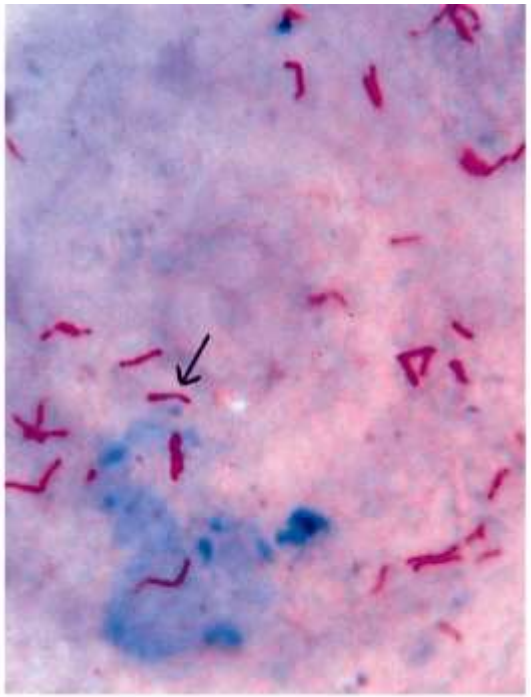
Disease	Cause	Tissue Reaction
Tuberculosis	Mycobacterium tuberculosis	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	Mycobacterium leprae	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	Treponema pallidum	Gumma: microscopic to grossly visible lesion, enclosing wall of macrophages, plasma cell infiltrate; central cells are necrotic without loss of cellular outline; organisms difficult to identify in tissue
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against undefined gut microbes and, possibly, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

It is always necessary to identify the specific etiologic agent by:

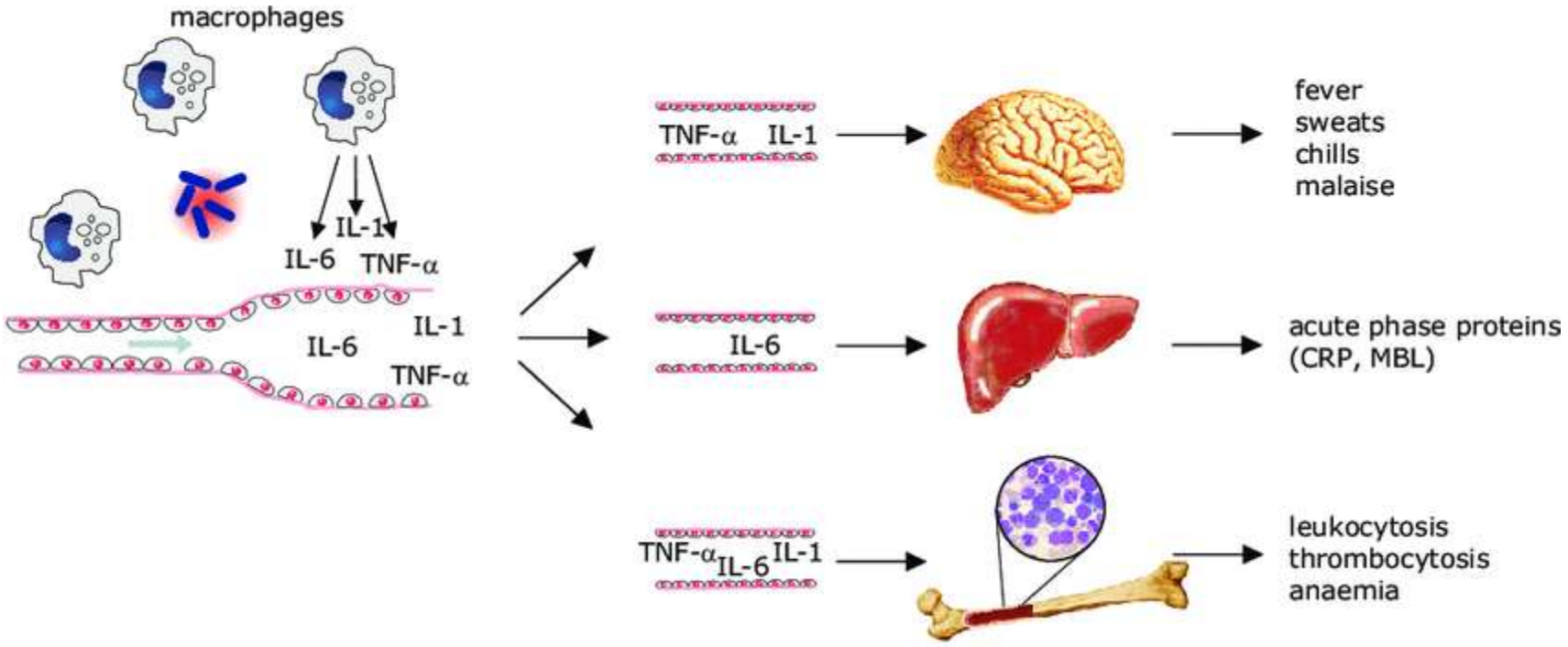
- special stains for organisms (e.g., acid-fast stains for tubercle bacilli).
- culture methods.
- molecular techniques (PCR).



tuberculosis



SYSTEMIC EFFECTS OF INFLAMMATION



SYSTEMIC EFFECTS OF INFLAMMATION

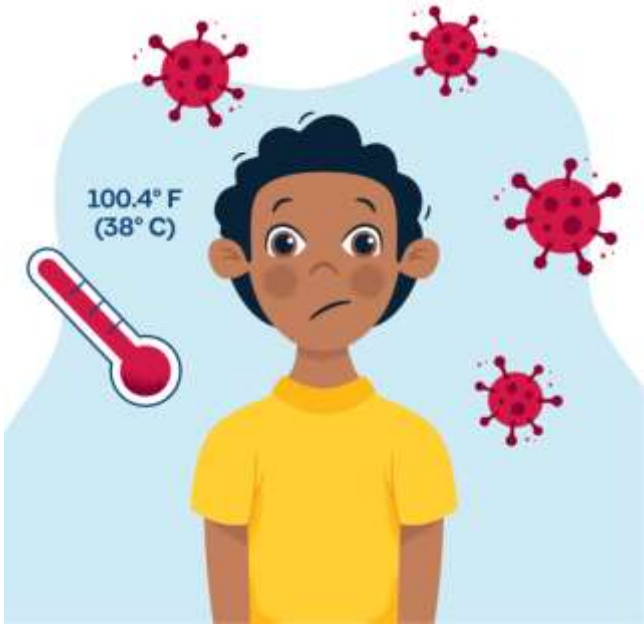
- Inflammation is associated with cytokine-induced systemic reactions that are collectively called the acute-phase response.

- These changes are reactions to cytokines whose production is stimulated by:
  - bacterial products such as LPS.
  - viral double stranded RNA.

- The cytokines TNF, IL-1, and IL-6 are important mediators of the acute phase reaction.

The acute-phase response consists of several clinical and pathologic changes:

- 1.Fever:
- elevation of body temperature, usually by 1° to 4°C,
- Substances that induce fever are called pyrogens.
- caused by prostaglandins that are produced in the vascular and perivascular cells of the hypothalamus.

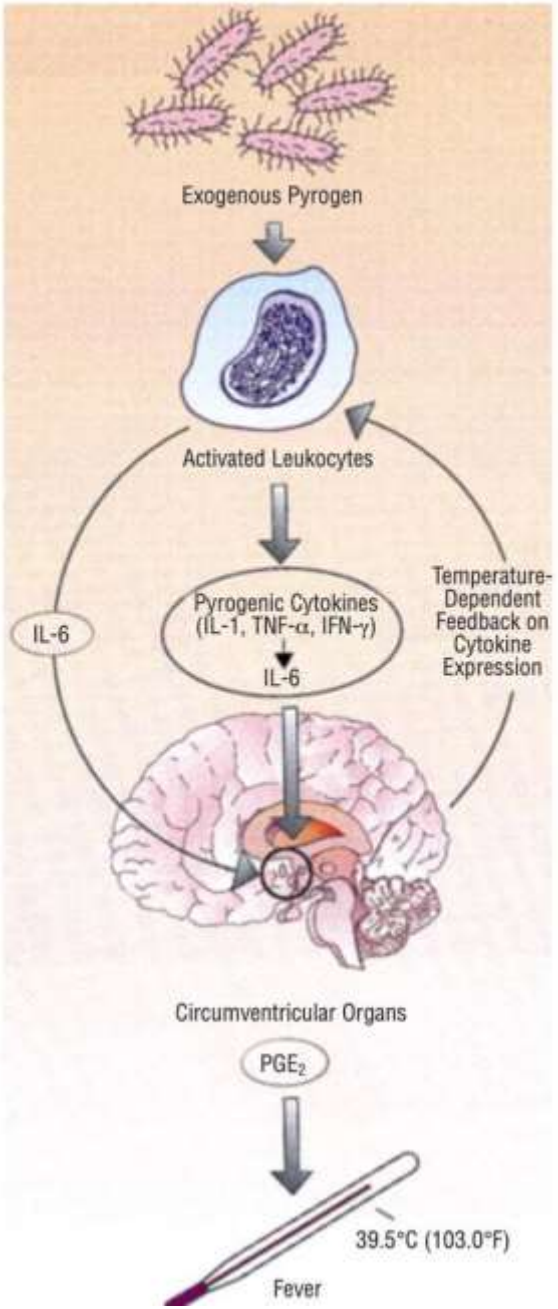


- Bacterial products, such as LPS (called exogenous pyrogens).

- stimulate leukocytes to release IL-1 and TNF (called endogenous pyrogens).

- increase the enzymes (cyclooxygenases) that convert arachadonic acid into prostaglandins.

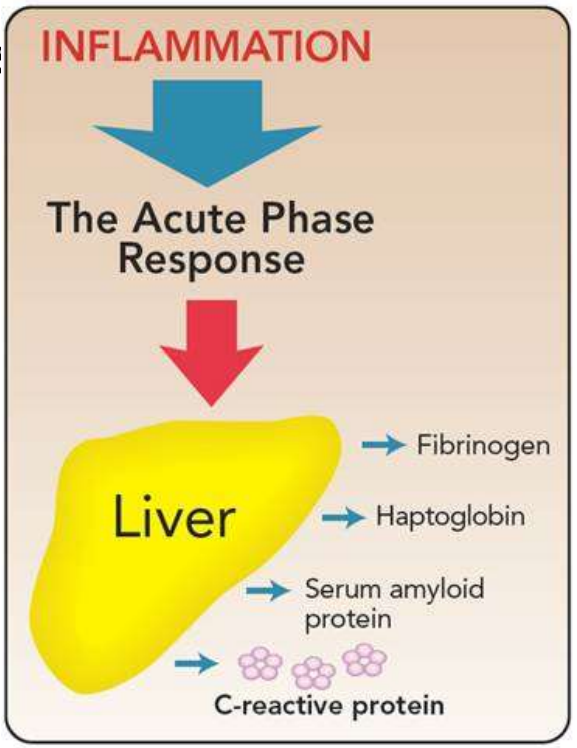
- In the hypothalamus, the prostaglandins, especially **PGE2,** stimulate the production of neurotransmitters that reset the temperature set point at a higher level



2.Acute-phase proteins

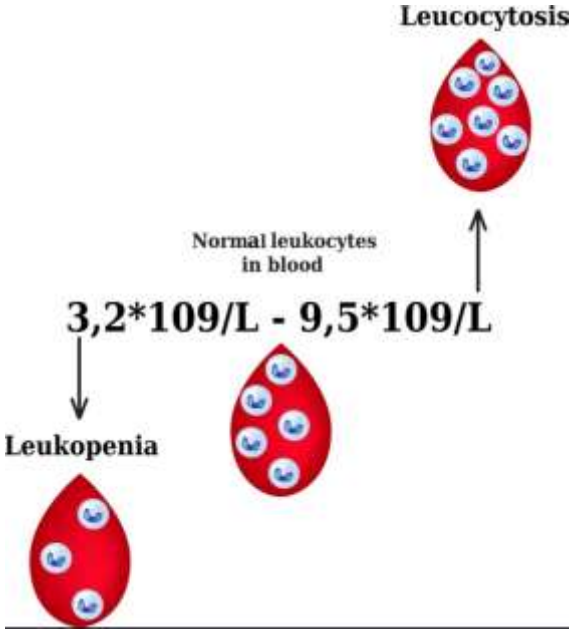
- Are plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of the response to inflammatory stimuli.

- Three of the best-known of these protein
  - C-reactive protein (CRP).
  - fibrinogen.
  - serum amyloid A (SAA) protein.

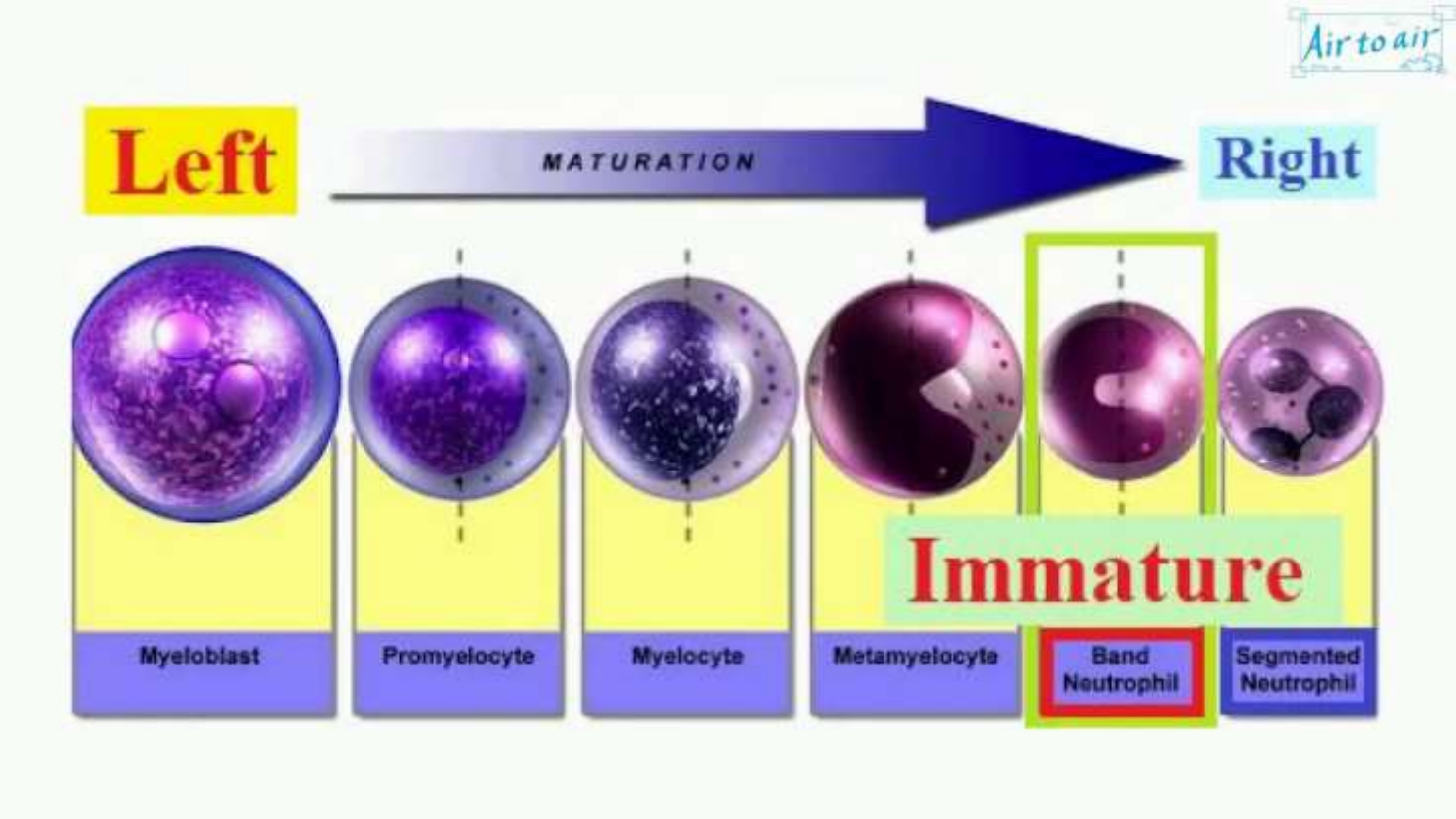


3.Leukocytosis

- Induced by bacterial infections.
- The leukocyte count usually climbs to 15,000 or 20,000 cells/mL, but sometimes it may reach extraordinarily high levels of 40,000 to 100,000 cells/mL.
- These extreme elevations are referred to as leukemoid reactions



- The leukocytosis occurs initially because of accelerated release of cells from the bone marrow and is therefore associated with a rise in the number of more immature neutrophils in the blood, referred to as a shift to the left.



- Most bacterial infections induce an increase in the blood neutrophil count, called neutrophilia.

- Viral infections, such as infectious mononucleosis, mumps, and German measles, cause an absolute increase in the number of lymphocytes (lymphocytosis).

- In some allergies and parasitic infestations, there is an increase in the number of blood eosinophils, creating an eosinophilia.

- Certain infections (typhoid fever and infections caused by some viruses, rickettsiae, and certain protozoa) are associated with a decreased number of circulating white cells (leukopenia).

- **Sepsis** is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs.

- Characterized by clinical triad :
  - disseminated intravascular coagulation.
  - hypotensive shock.
  - metabolic disturbances including insulin resistance and hyperglycemia.

  - systemic inflammatory response syndrome (SIRS):
  - A syndrome similar to septic shock may occur as a complication of noninfectious disorders, such as severe burns, trauma.


ANY
QUESTIONS?