Chronic Inflammation Tissue Repair I

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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,

Chronic Inflammation

- **Characteristics:**

- **Chronic inflammatory cell infiltrate**
  - **Lymphocytes**
  - **Plasma cells**
  - **Macrophages**

- **Tissue destruction**

- **Repair**
  - **Neovascularization**
  - **Fibrosis**

Causes of Chronic Inflammation

- **Persistent infections**

- **Hypersensitivity diseases:**

- autoimmune disease.

- allergic diseases,

- **Prolonged exposure to potentially toxic agents, e.g Silica.**

Inflammation

Acute inflammation

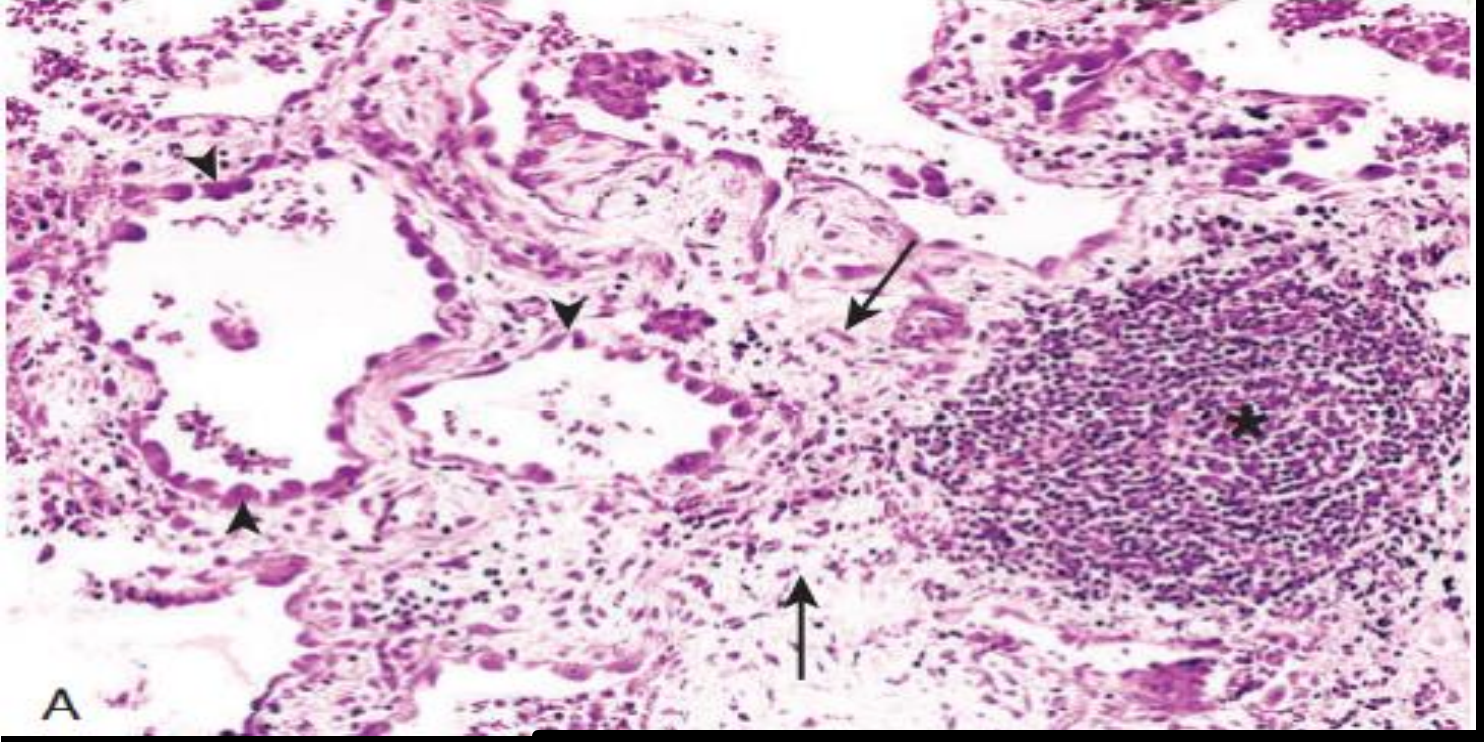
- Duration: minutes to days
- Predominance of neutrophils
- Fluid & plasma protein exudation

Chronic inflammation

- Duration: days to years
- Predominance of lymphocytes and macrphages
- Vascular proliferation and fibrosis

Chronic Inflammation

- **Under what circumstances, does it develop?**
  - **Progression from acute inflammation**
    - **Tonsillitis, osteomyelitis, etc.**
  - **Repeated exposure to toxic agent**
    - **Silicosis, asbestosis, hyperlipidemia, etc.**
  - **Viral infections**
  - **Persistent microbial infections**
    - **Mycobacteria, Treponema, Fungi, etc.**
  - **Autoimmune disorders**
    - **Rheumatoid arthritis, SLE, systemic lupus, etc.**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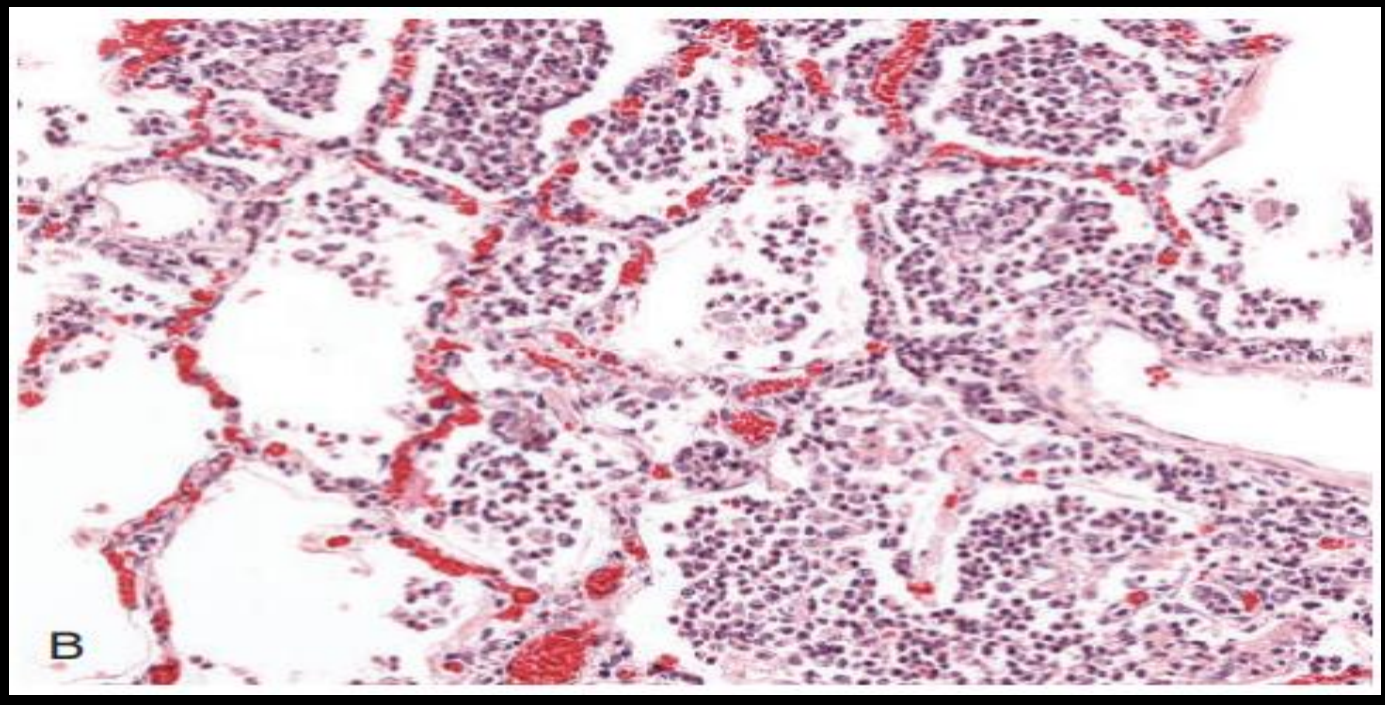
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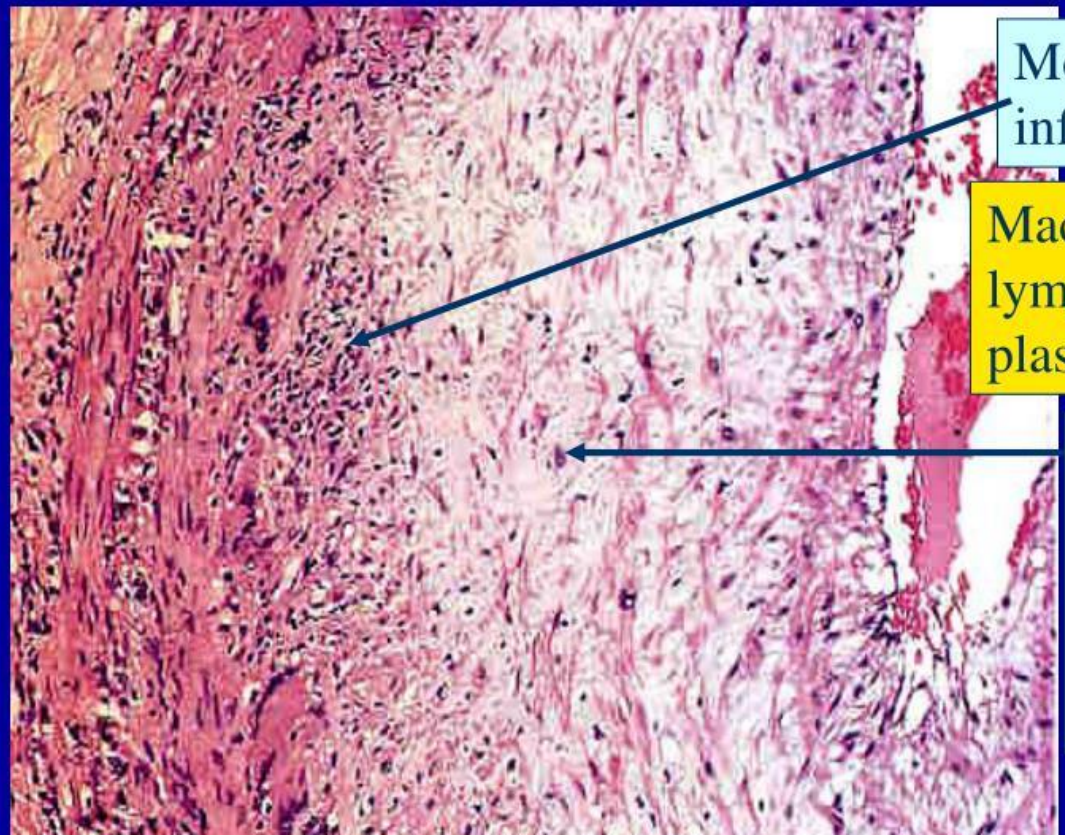
Histopathology of chronic inflammation



Mononuclear cell infiltration (3 cell types):

Macrophages, lymphocytes, plasma cells

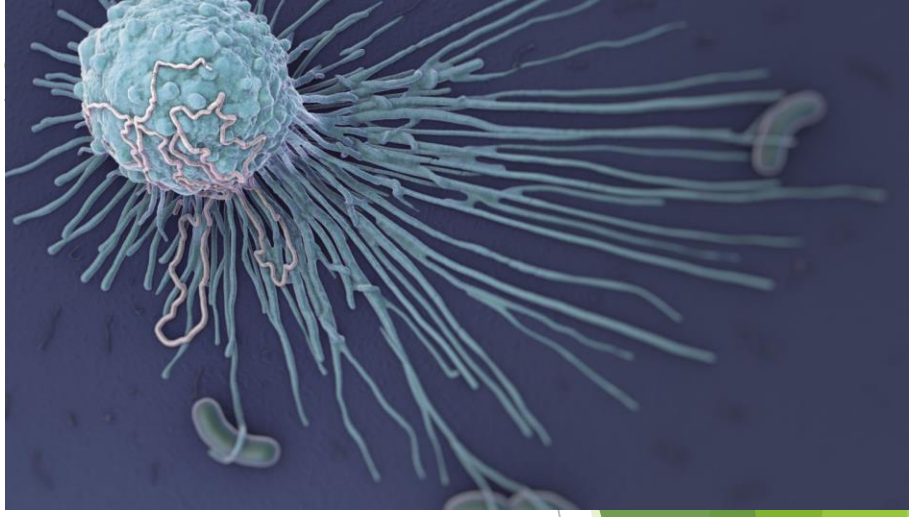
Tissue destruction with replacement of damaged tissue by well-vascularized young fibrous tissue

- healing by connective tissue replacement of damaged tissue,

Cells and Mediators of Chronic Inflammation

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

1.Role of Macrophage



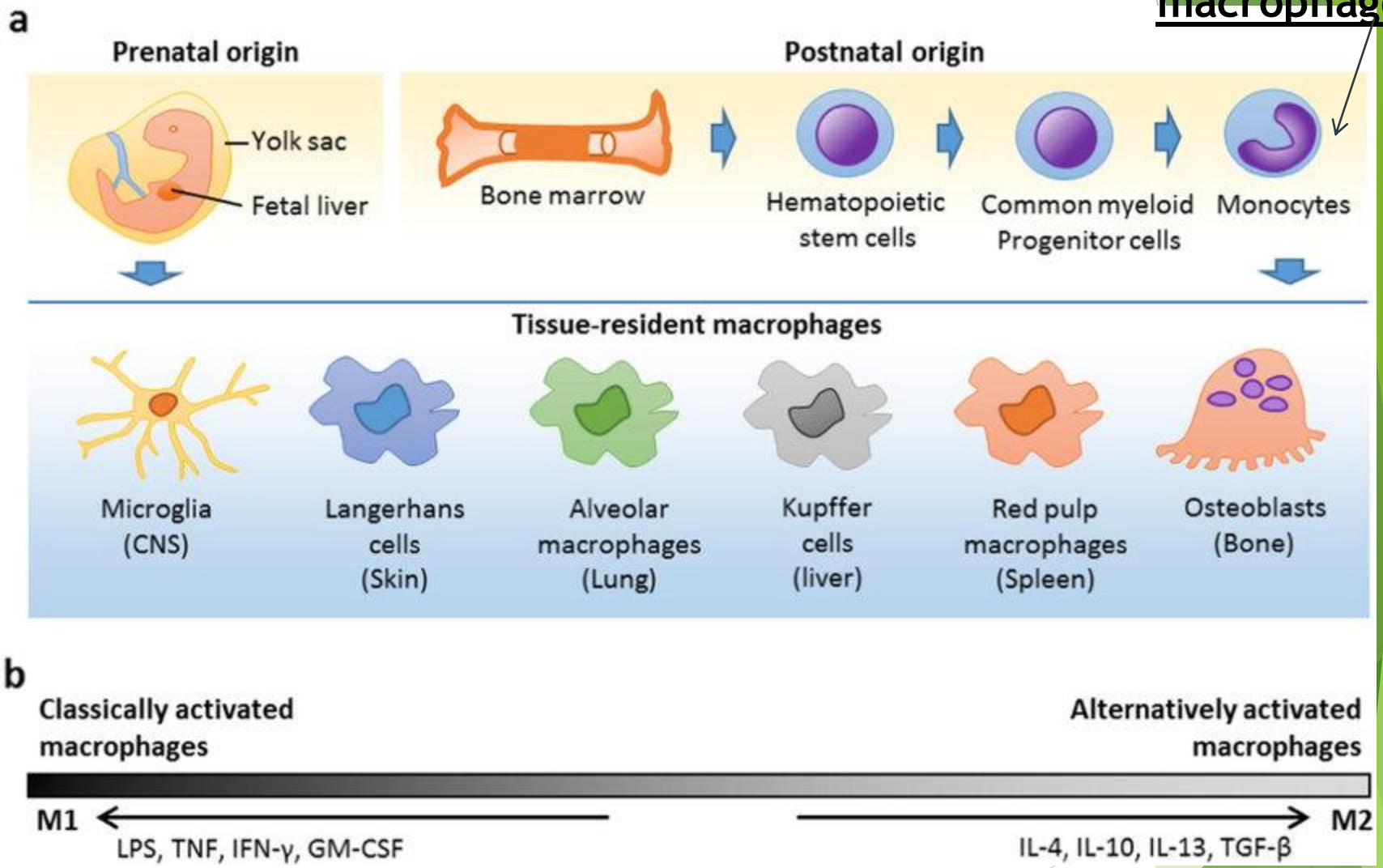
- The dominant cells in most chronic inflammatory reactions are macrophages, which contribute to the reaction by:

- 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.

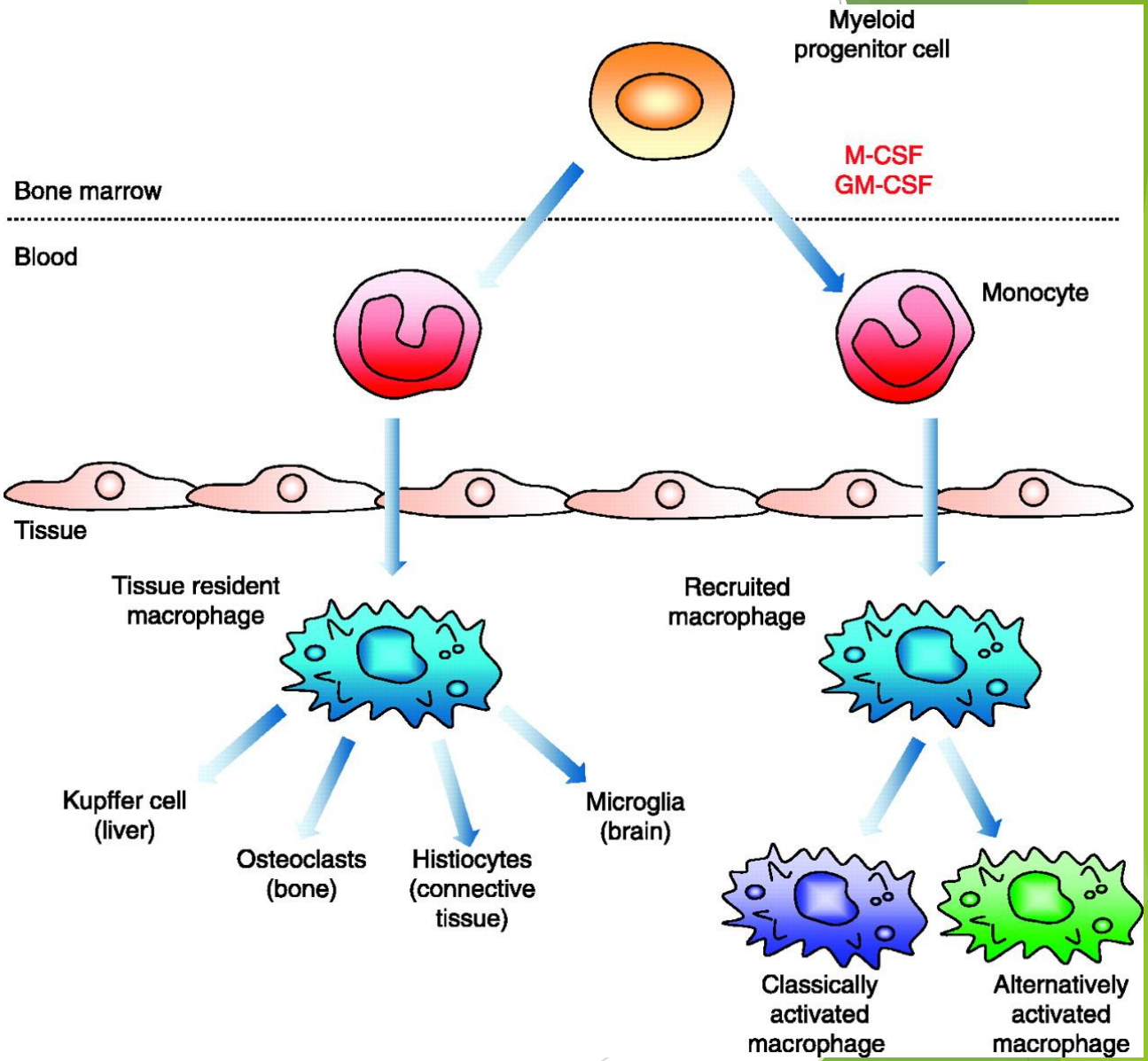
Circulating macrophage



- 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

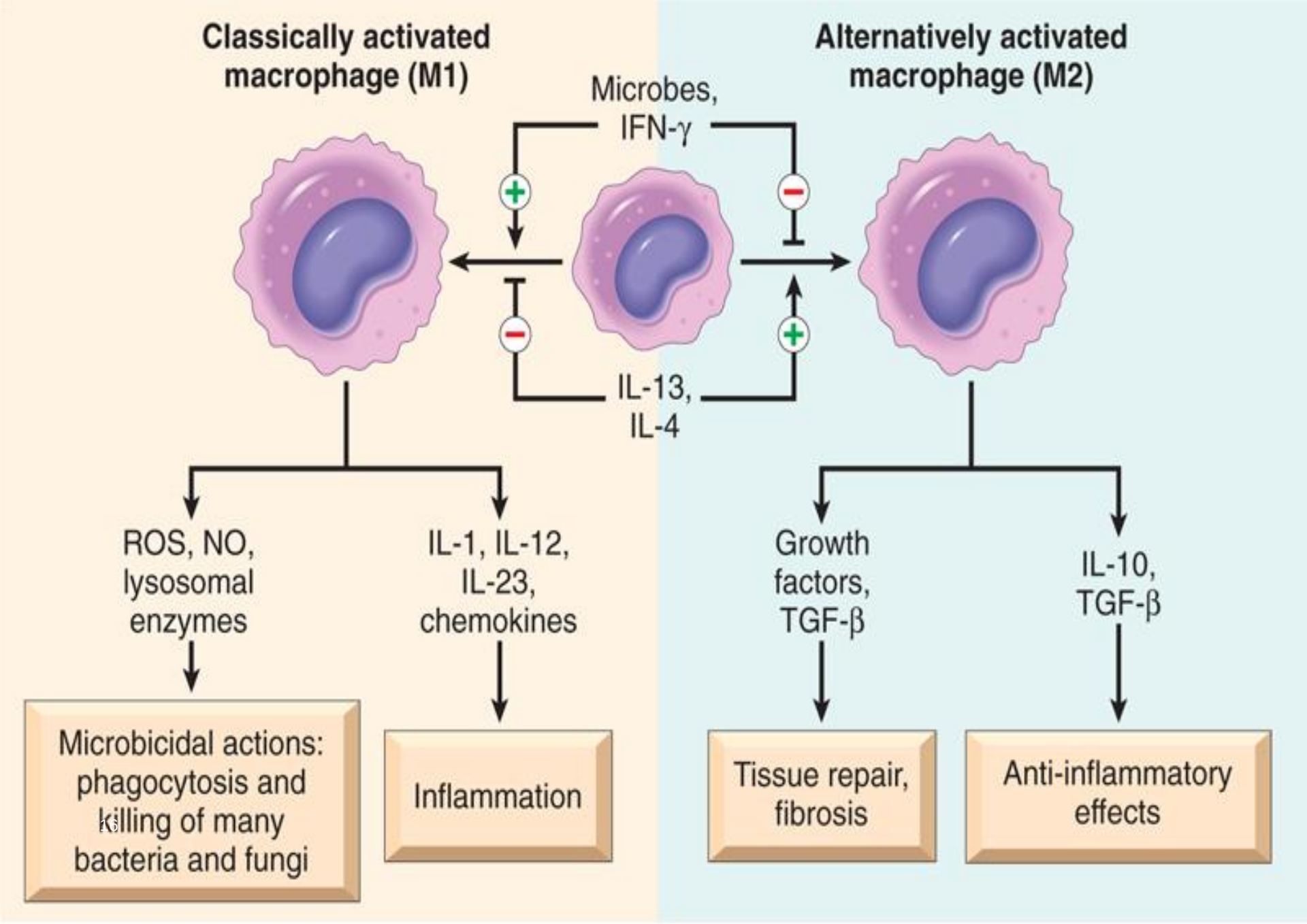
the life span of tissue macrophages is several months or years



- 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.



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)

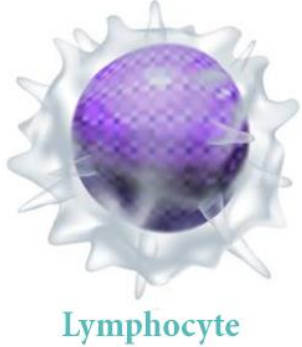
- Is induced by:
- cytokines other than IFN-γ, such as IL-4 and IL-13, produced by T lymphocytes.

- 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

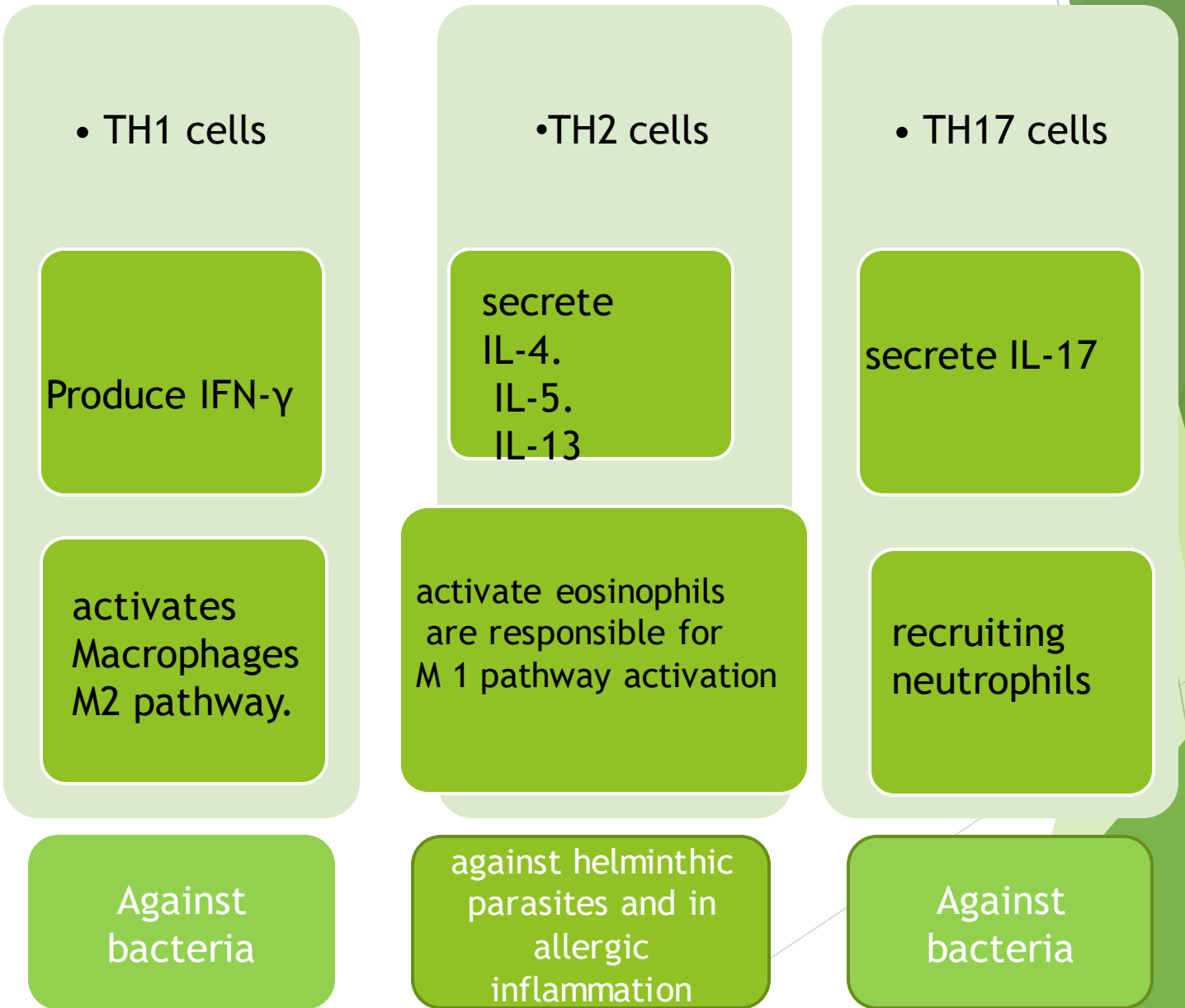
2.Role of Lymphocytes

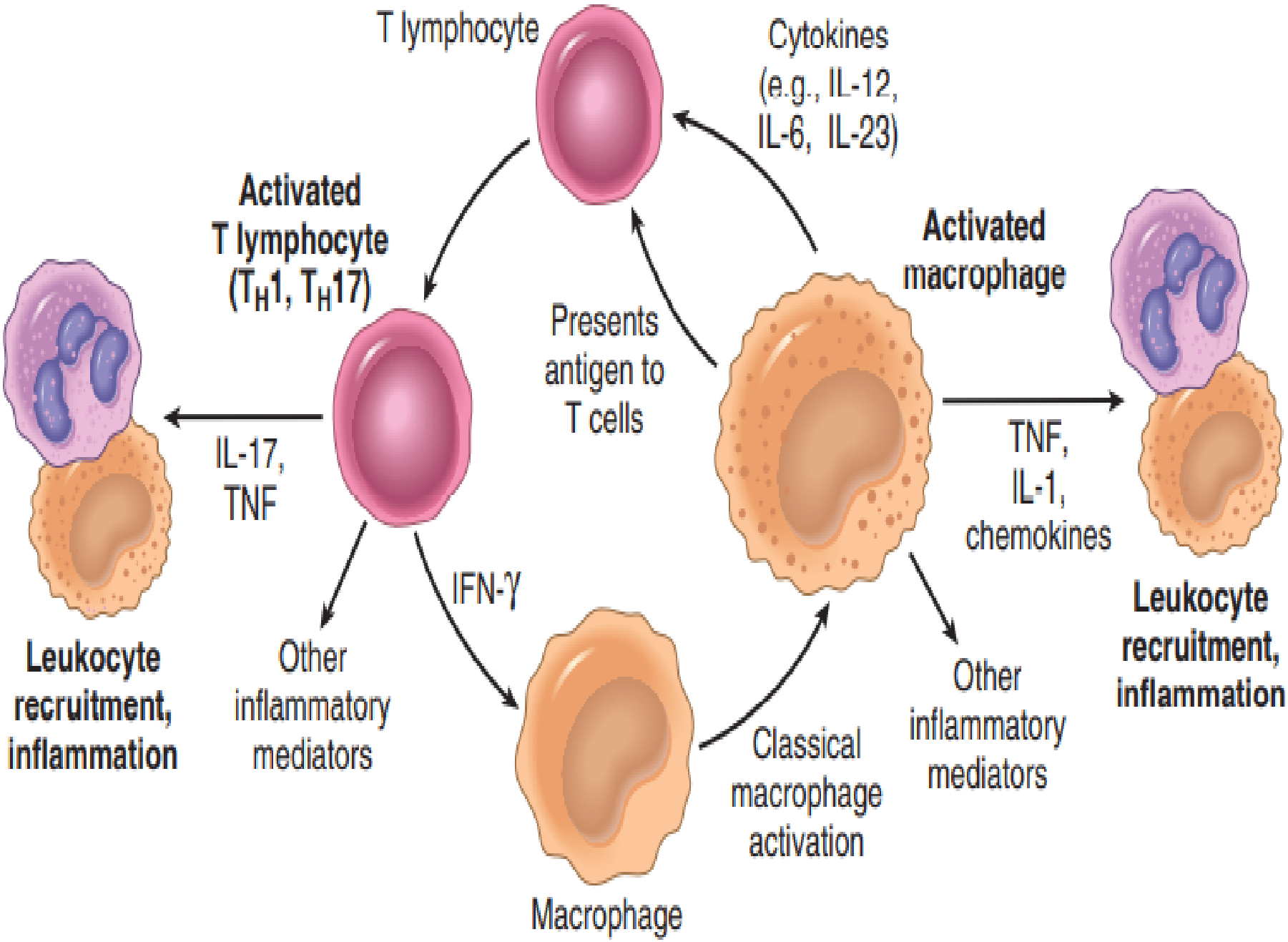


- Microbes and other environmental antigen activate T and B lymphocytes, which **amplify and propagate chronic inflammation.**

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

❖ CD4+ T lymphocytes promote inflammation




T lymphocyte
Cytokines
(e.g., IL-12,
IL-6, IL-23)
Activated
T lymphocyte
(T_H1, T_H17)
Activated
macrophage
Presents
antigen to
T cells
IL-17,
TNF
TNF,
IL-1,
chemokines
IFN-γ
Leukocyte
recruitment,
inflammation
Other
inflammatory
mediators
Classical
macrophage
activation
Other
inflammatory
mediators
Leukocyte
recruitment,
inflammation
Macrophage

cycle of cellular reactions

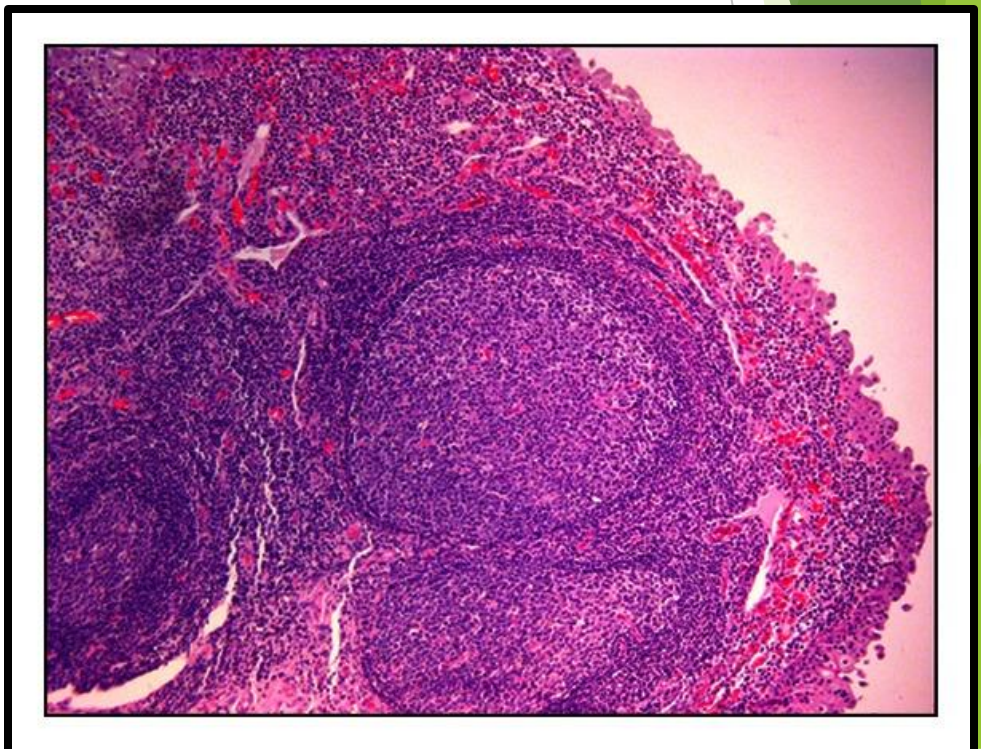
- Macrophages:
  - display antigens to T cells, that activate T cells.
  - produce cytokines (IL-12 and others) that also stimulate T cell responses.

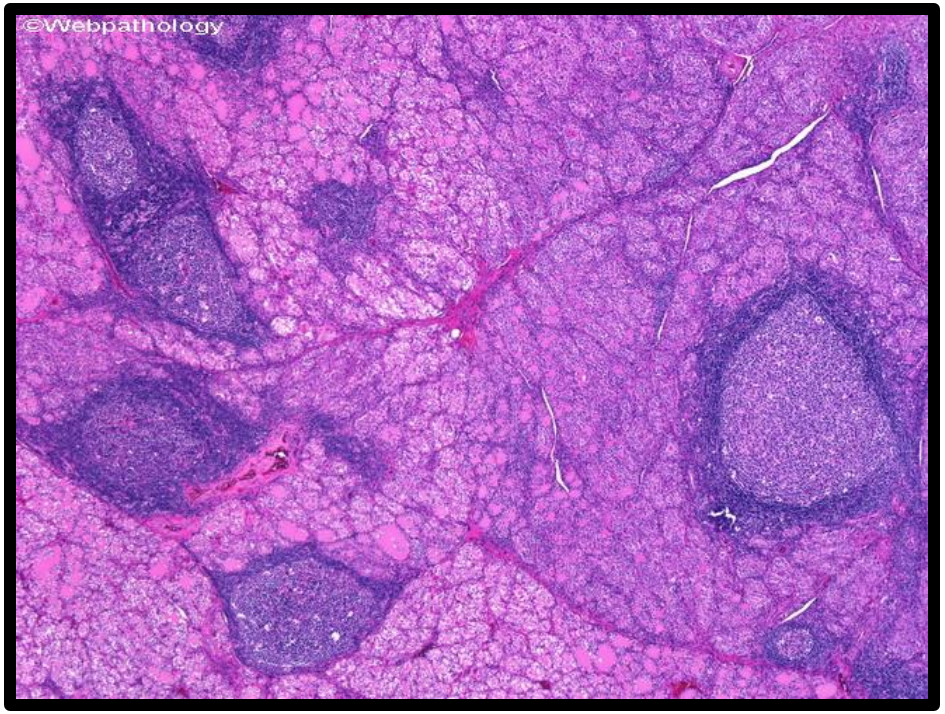
- Activated T lymphocytes:
  - produce cytokines, which recruit and activate macrophages.
  - promoting more antigen presentation and cytokine secretion.

These interactions play an important role in propagating chronic inflammation

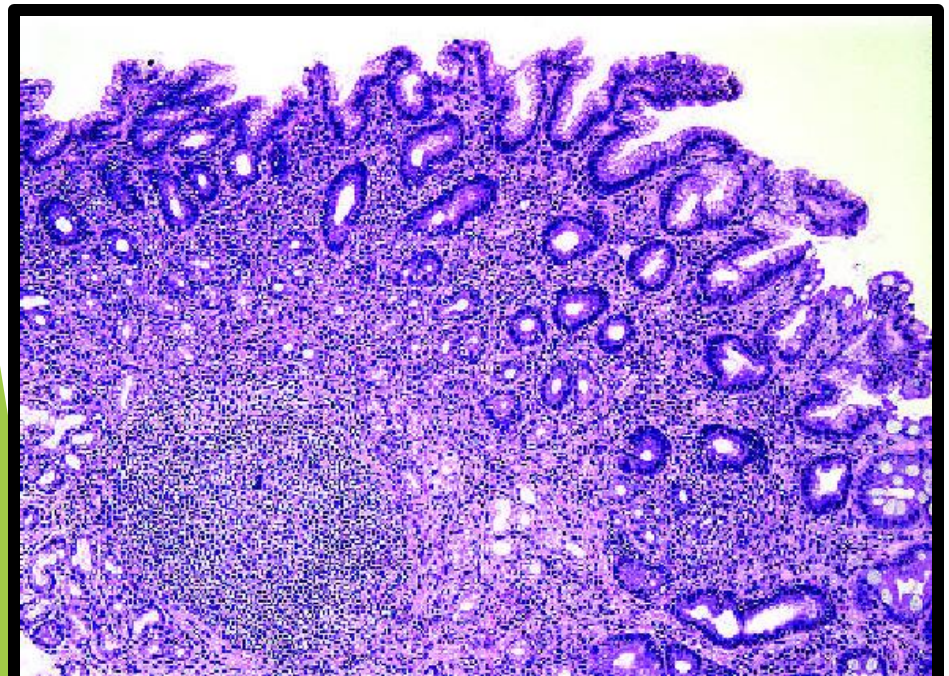
tertiary lymphoid organs

- 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

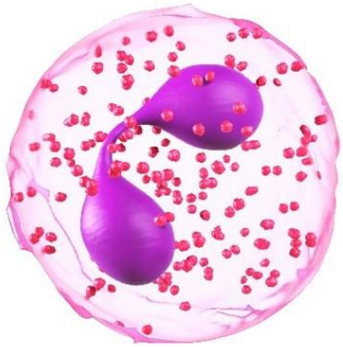


Helicobacter pylori gastritis

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).

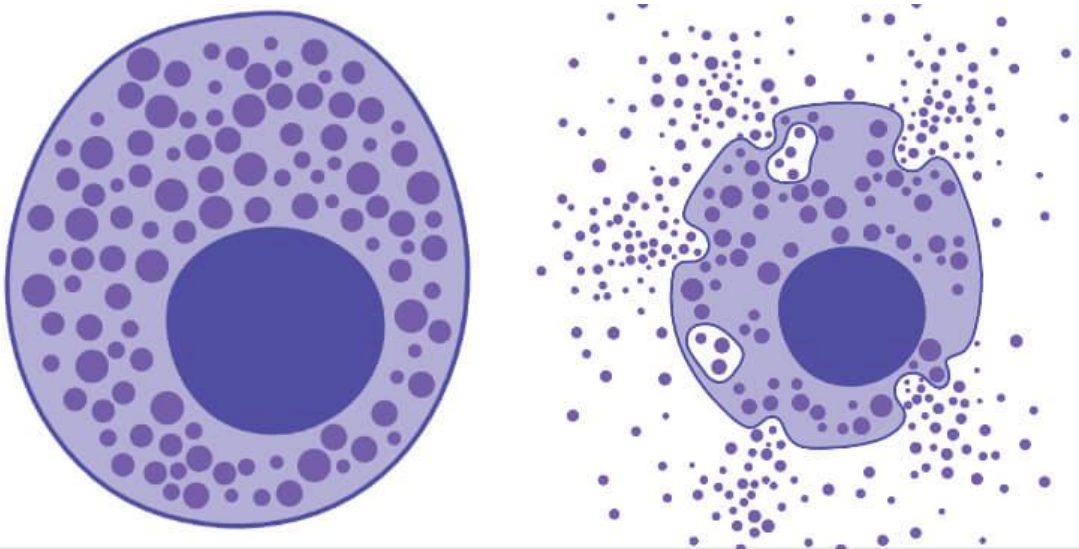


- Eosinophils have granules that contain major basic protein, a highly cationic protein that is toxic to parasites but also injures host epithelial cells.

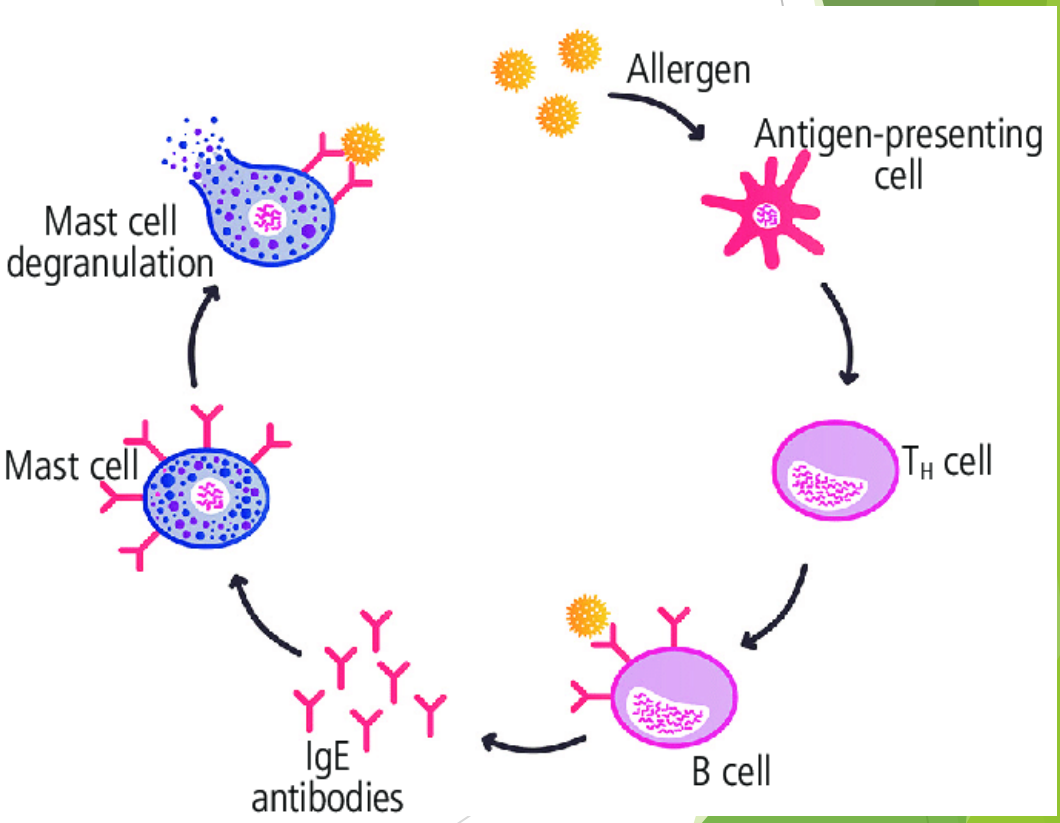
- So eosinophils are of benefit in:
- controlling parasitic infections.
- contribute to tissue damage in immune reactions such as allergies

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.



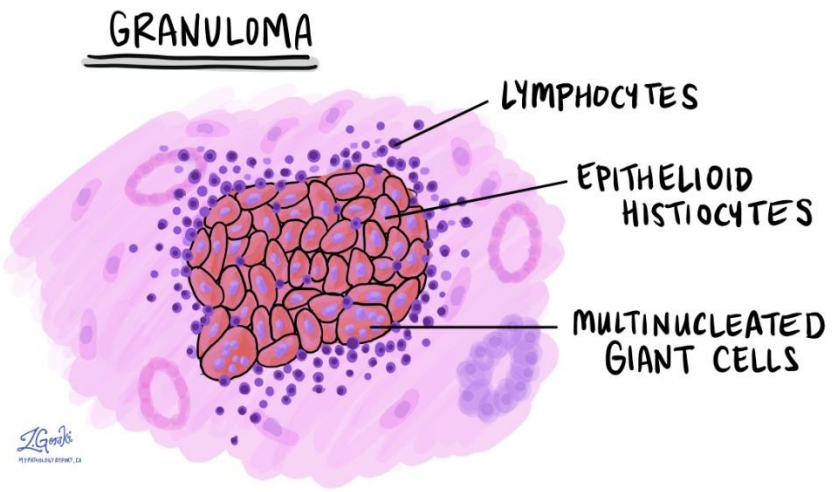
- Mast cells (and basophils) express on their surface the receptor FcεRI, which binds the Fc portion of IgE antibody. In immediate hypersensitivity reactions, IgE bound to the mast cells' Fc receptors specifically recognizes antigen, and in response the cells degranulate and release mediators, such as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

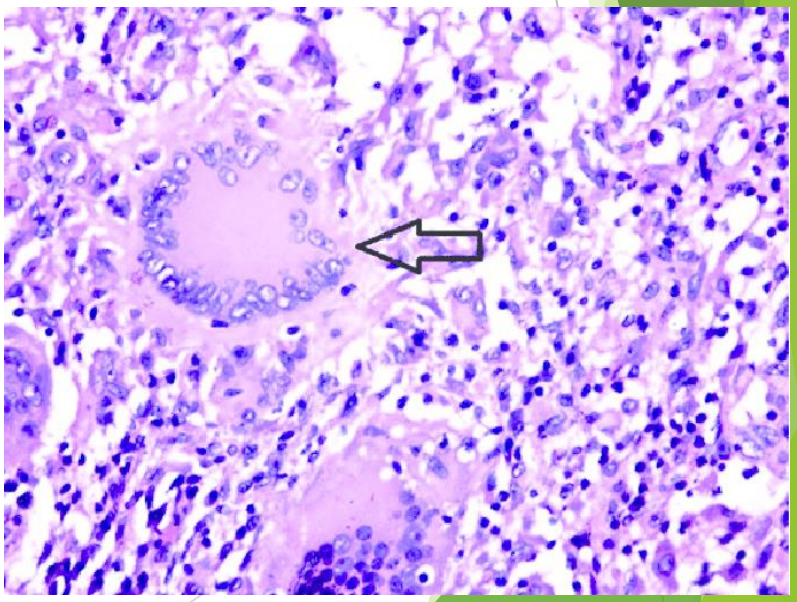


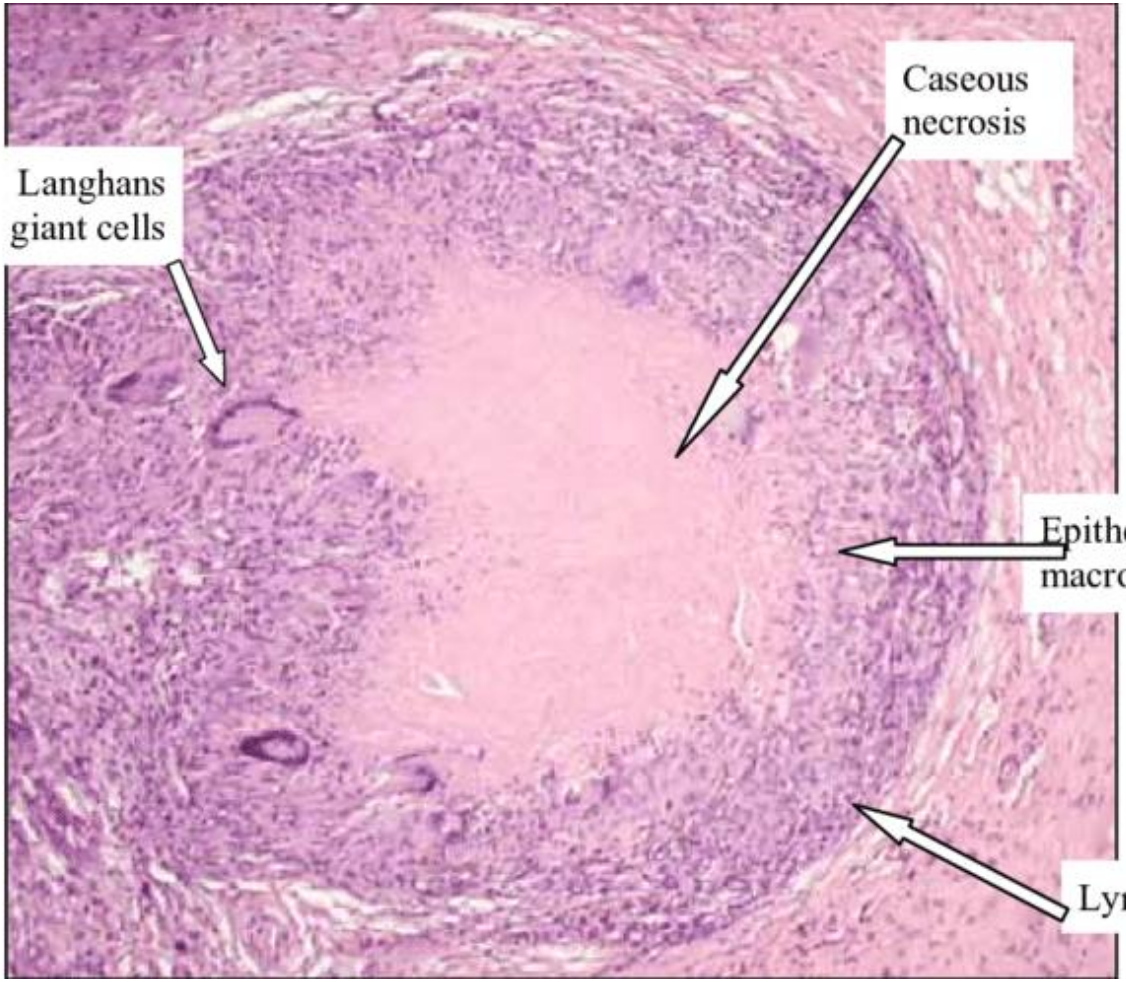
This type of response occurs during allergic reactions

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

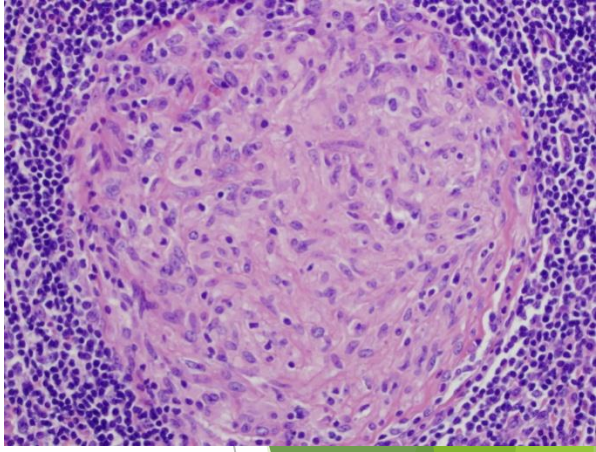






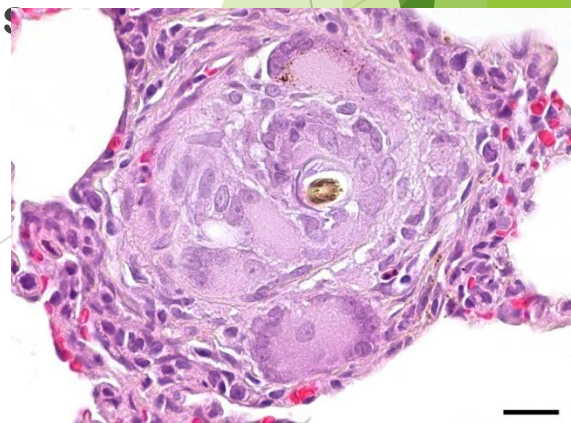
- **Epithelioid macrophage: macrophages with abundant cytoplasm and begin to resemble epithelial cells.**
- **Multinucleated giant cells: fused activated macrophages.**

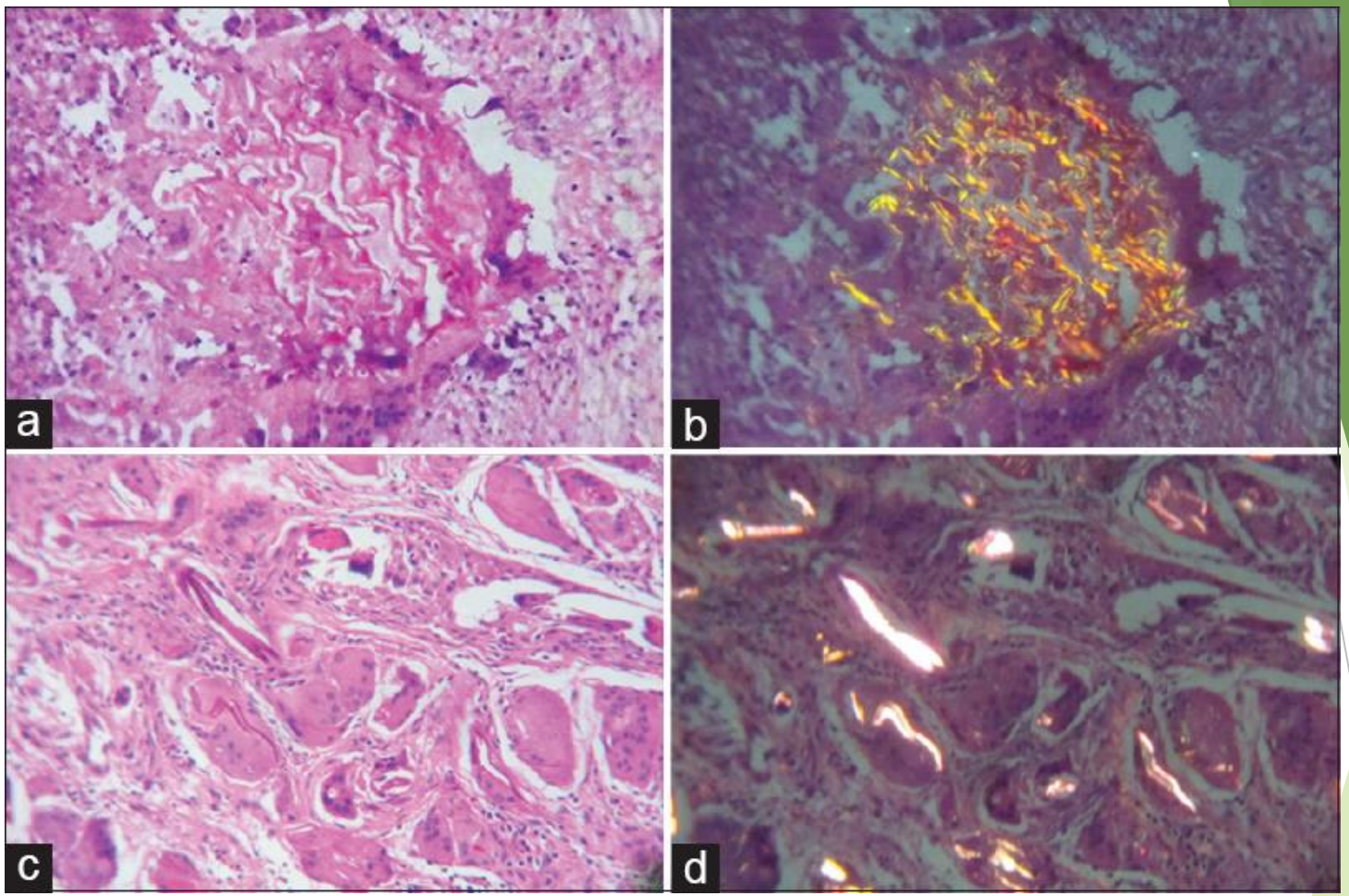
Types of granulomas;



- **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





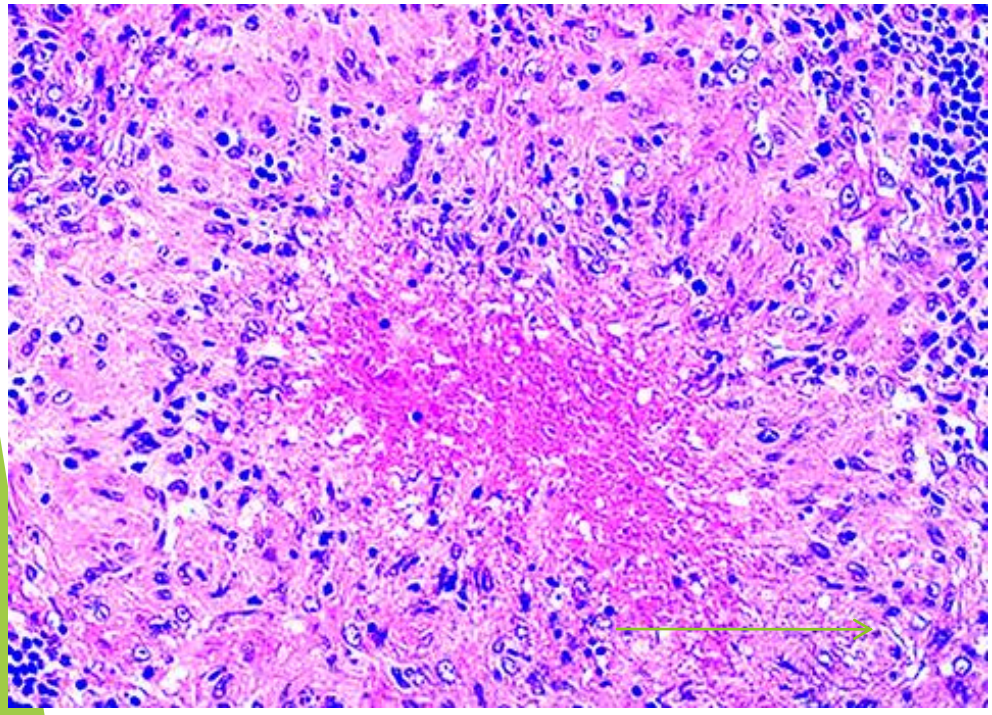
The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it may appear refractile.

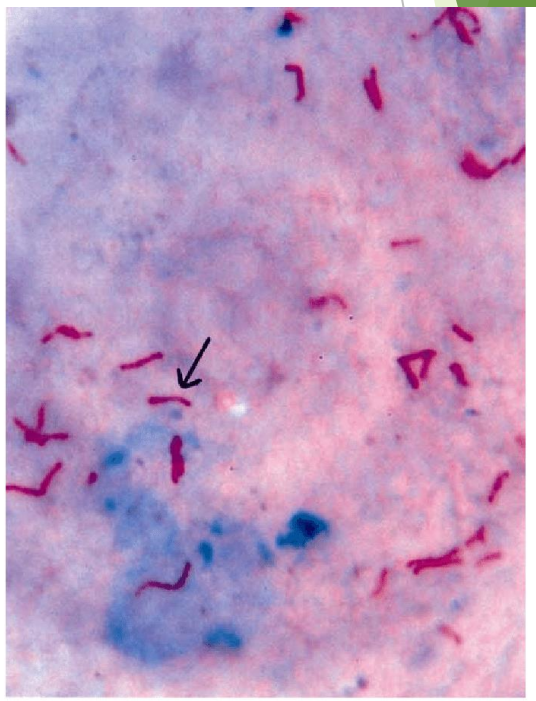
Table 3.9 Examples of Diseases With Granulomatous Inflammation

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:

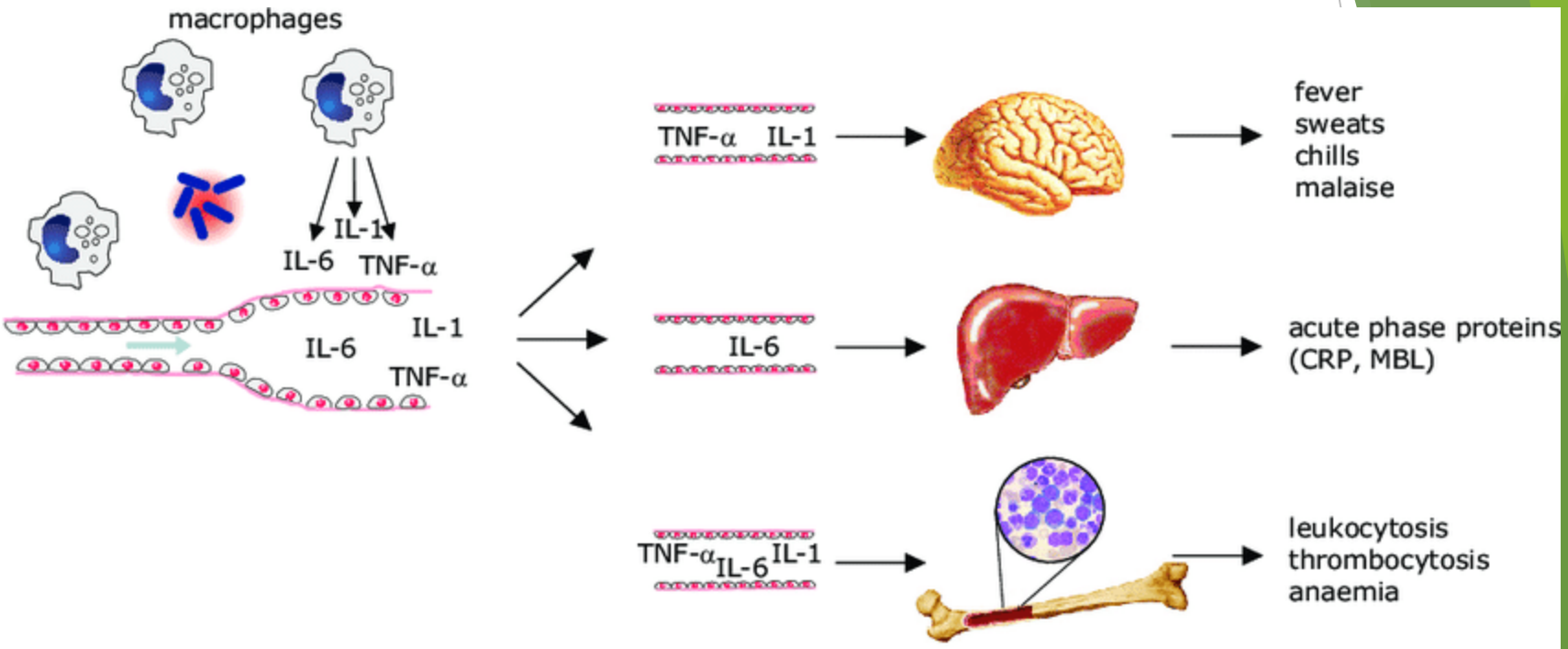
- special stains for organisms (e.g., acid-fast stains for tubercle bacilli).
- culture methods.
- molecular techniques (PCR).





tuberculosis

SYSTEMIC EFFECTS OF INFLAMMATION



SYSTEMIC EFFECTS OF INFLAMMATION

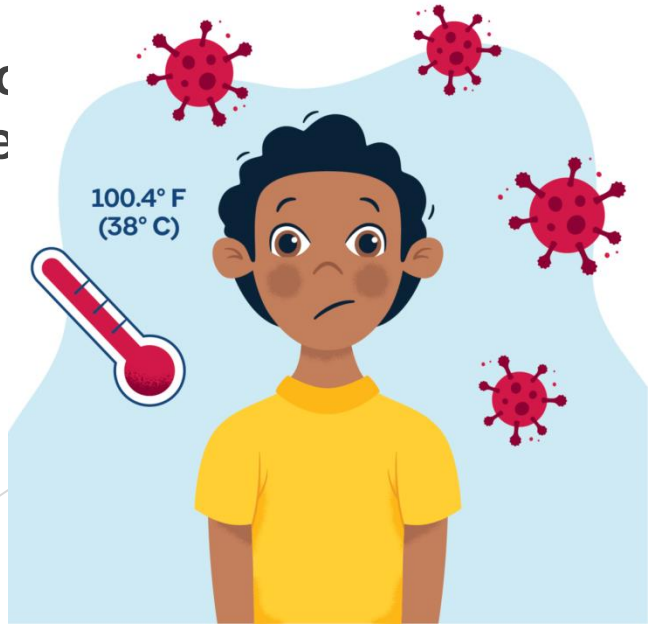
- Inflammation is associated with cytokine-induced systemic reactions that are collectively called the acute-phase response.

- 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 produc the vascular and perivascular cells of the hypothalamus.

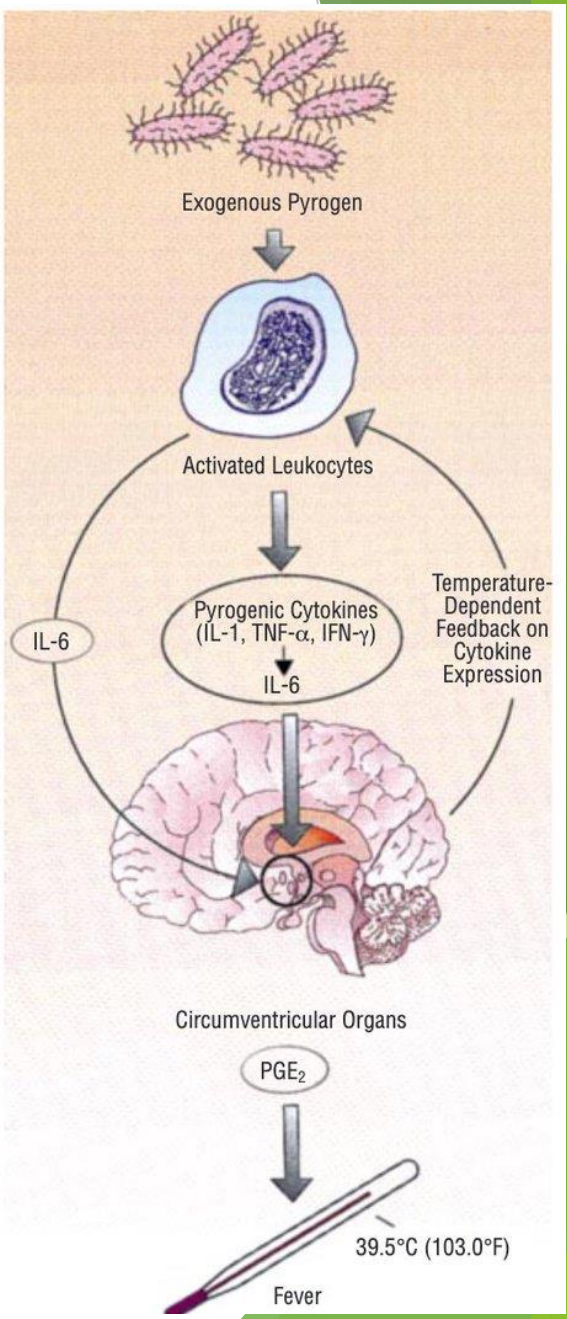


- Bacterial products, such as LPS (called exogenous pyrogens).

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

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

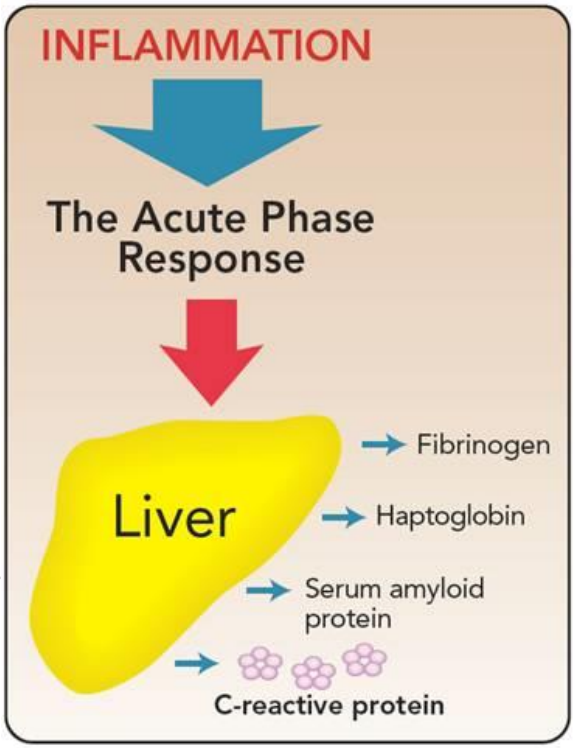
- In the hypothalamus, the prostaglandins, especially **PGE2,** stimulate the production of neurotransmitters that reset the temperature set point at a higher level



2.Acute-phase proteins

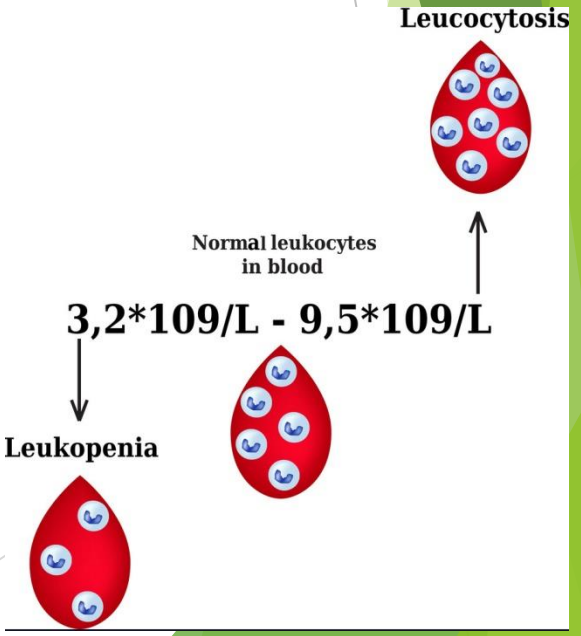
- Are plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of the response to inflammatory stimuli.

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

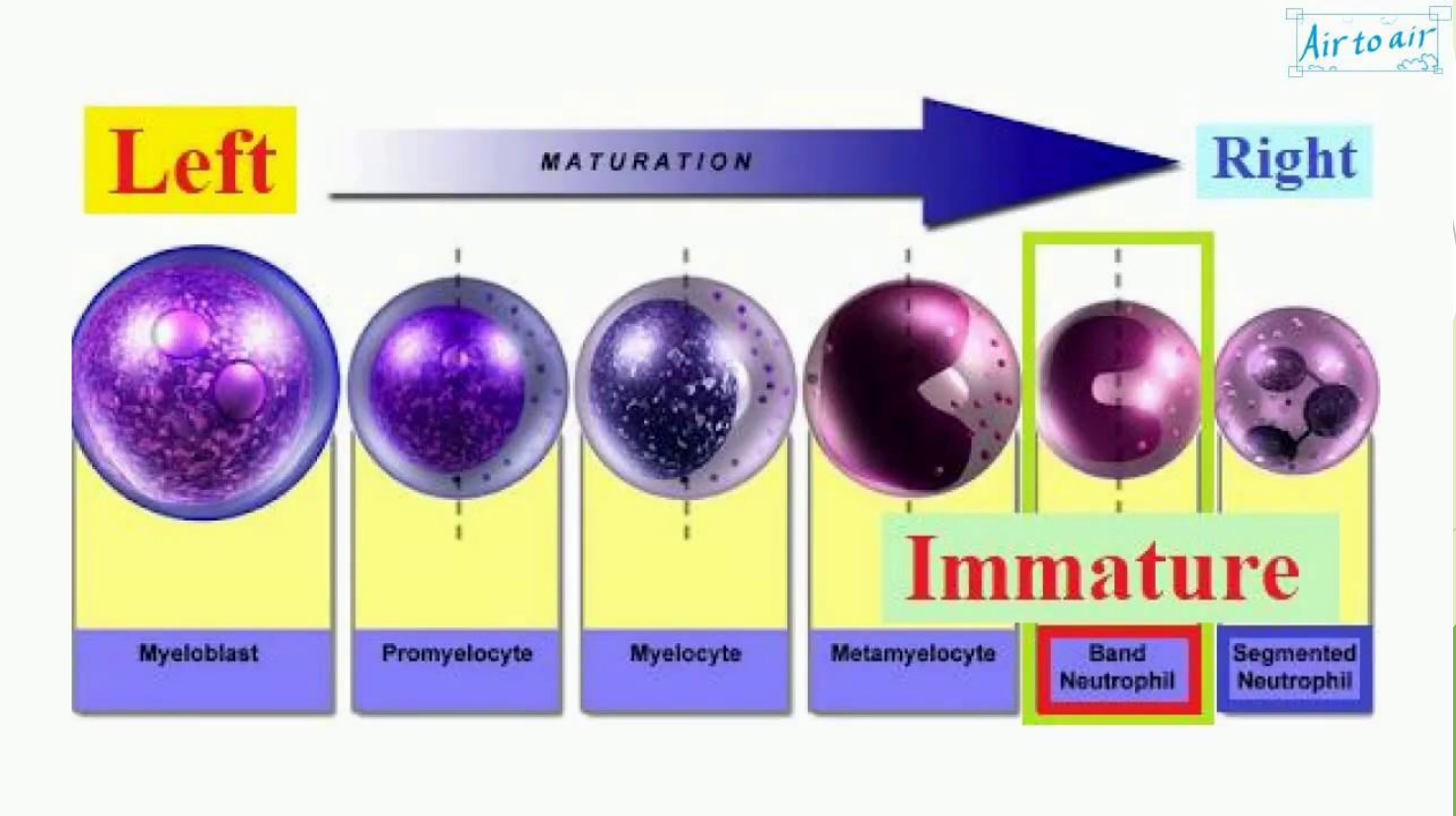


3.Leukocytosis

- 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 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).

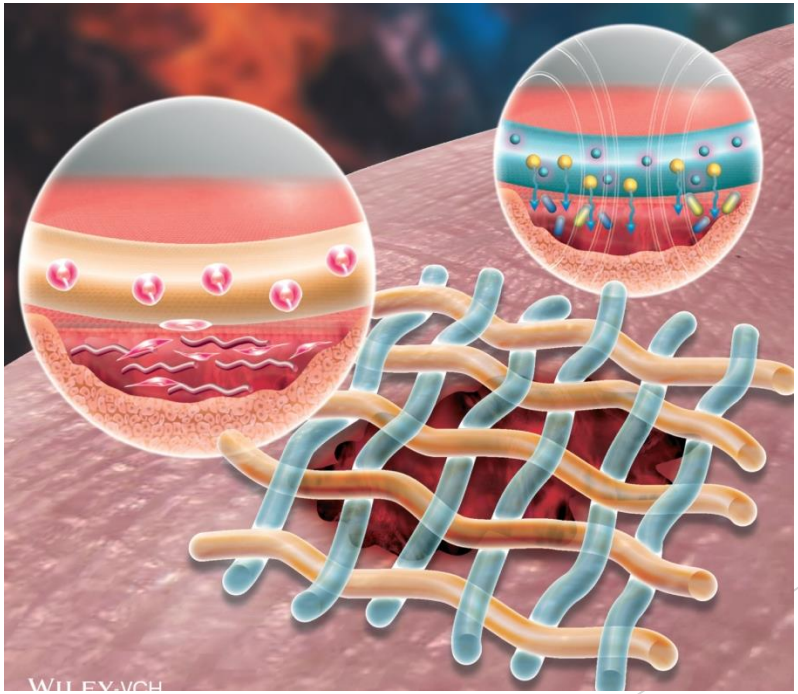
- **Sepsis** is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs.

- 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.

TISSUE REPAIR 1

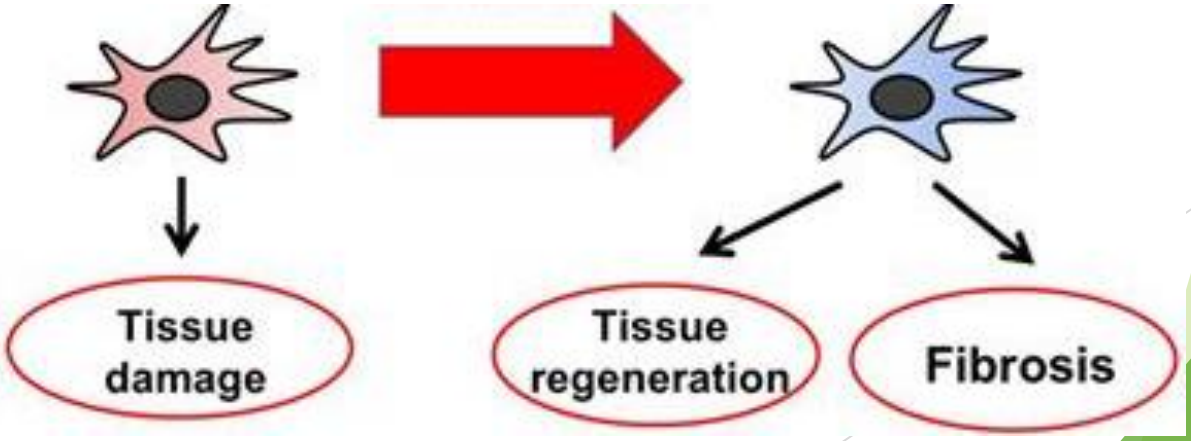
- The ability of an organism to repair the damage caused by toxic insults and inflammation is critical to the survival . In fact, the inflammatory response to microbes and injured tissues not only serves to eliminate these dangers but also sets into motion the process of repair.

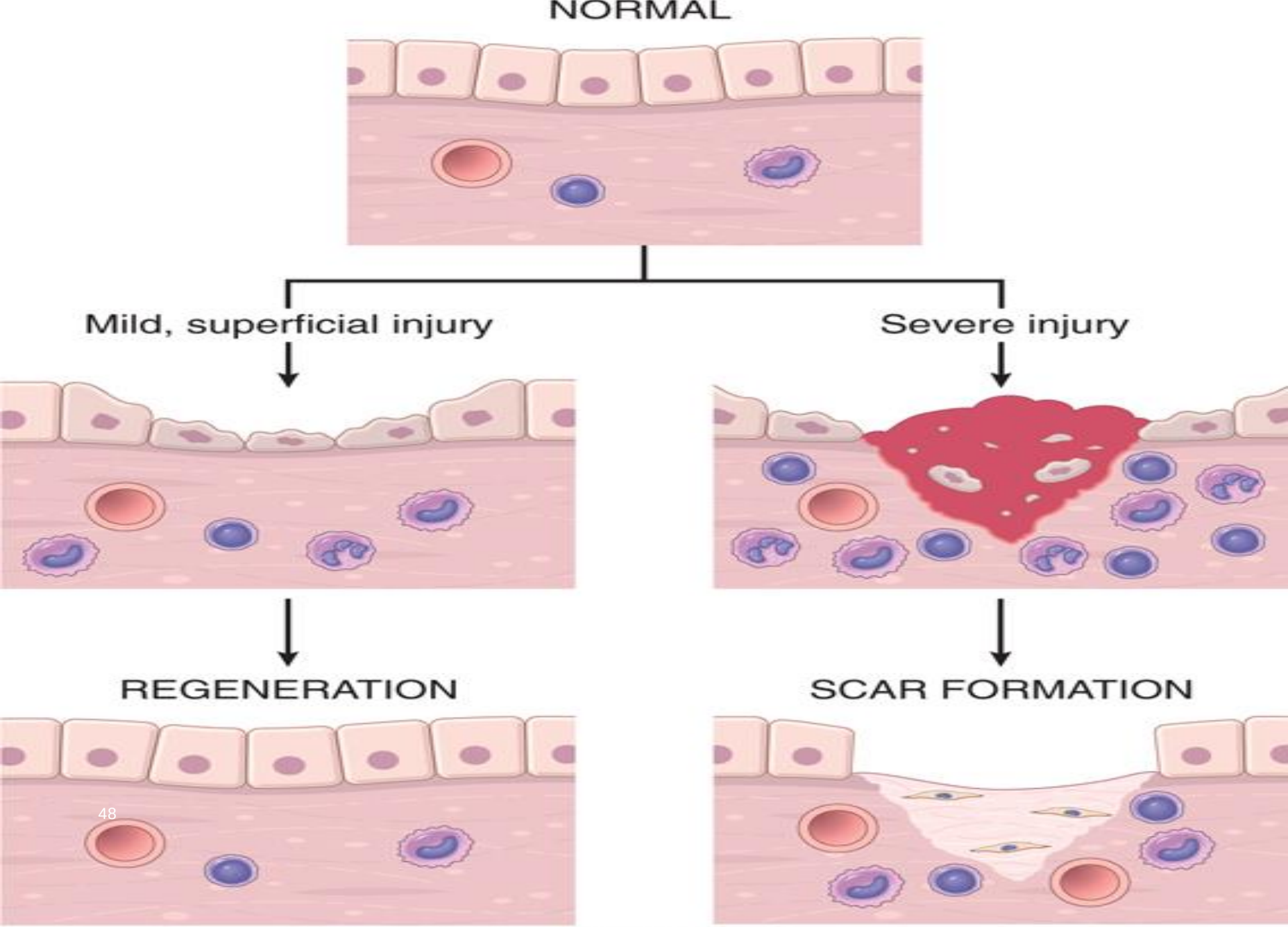


Overview of Tissue Repair

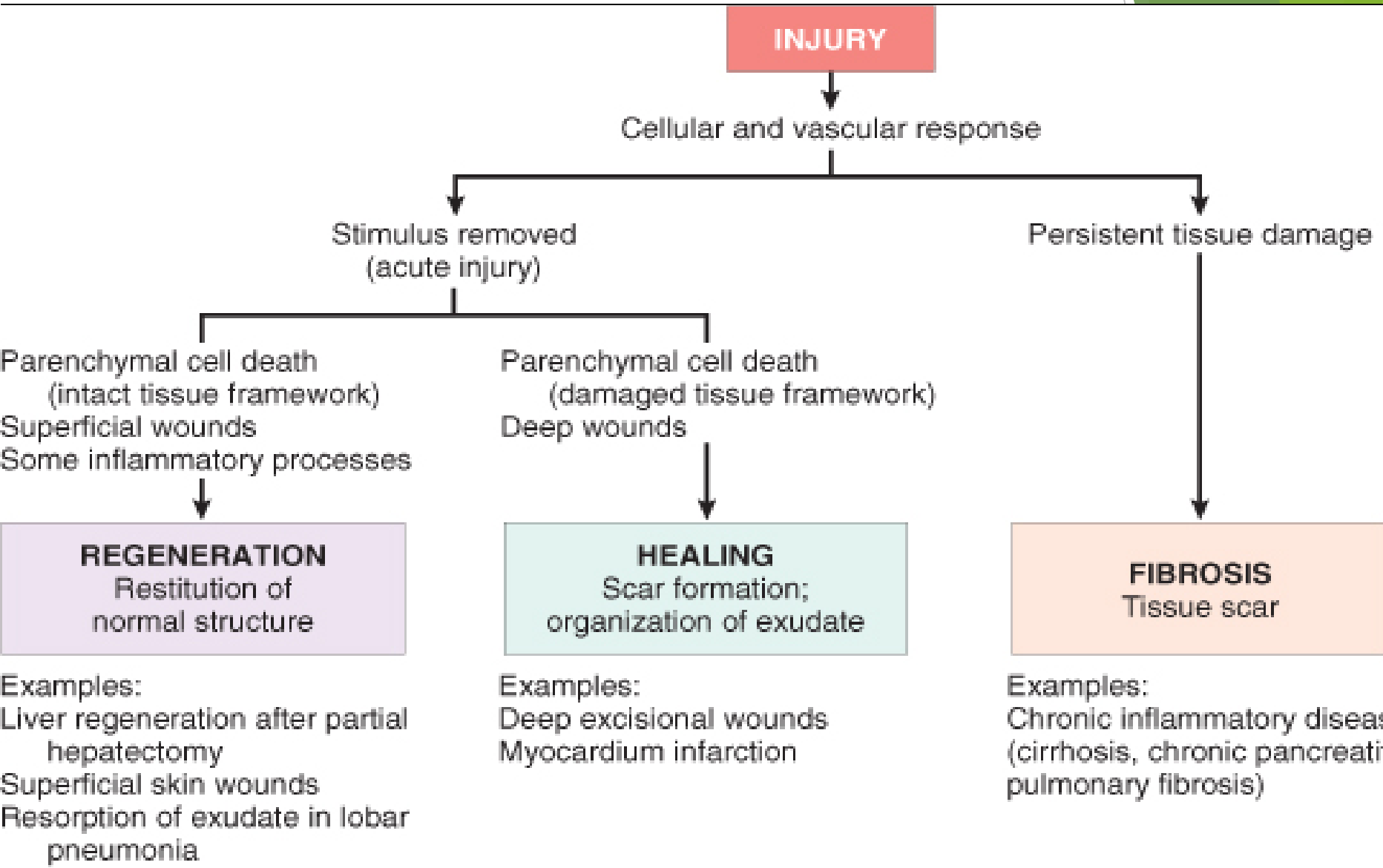
- Repair of damaged tissues occurs by two types of reactions:

- Regeneration by proliferation of residual (uninjured) cells.
- Maturation of tissue stem cells, and the deposition of connective tissue to form a scar.





Repair Outcomes After Injury



The two processes of repair

- **Regeneration**
  - **Replacement of damaged cells by similar parenchymal cells, e.g. liver regeneration**
  - **Requires intact connective tissue scaffold**

- **Fibrosis**
  - **Replacement by connective tissue**
  - **ECM framework is damaged**

Healing is a combination of regenerative and fibrotic processes

1.Regeneration

- Proliferation of cells that survive the injury and retain the capacity to proliferate may contribute to the restoration of damaged tissues, for example:

- In the rapidly dividing epithelia of the skin and intestines.
- In some parenchymal organs, notably the liver.
- Tissue stem cells.

2.Connective tissue deposition (scar formation)

- Repair occurs by the laying down of connective (fibrous) tissue, a process that may result in formation of a scar, it occure in:

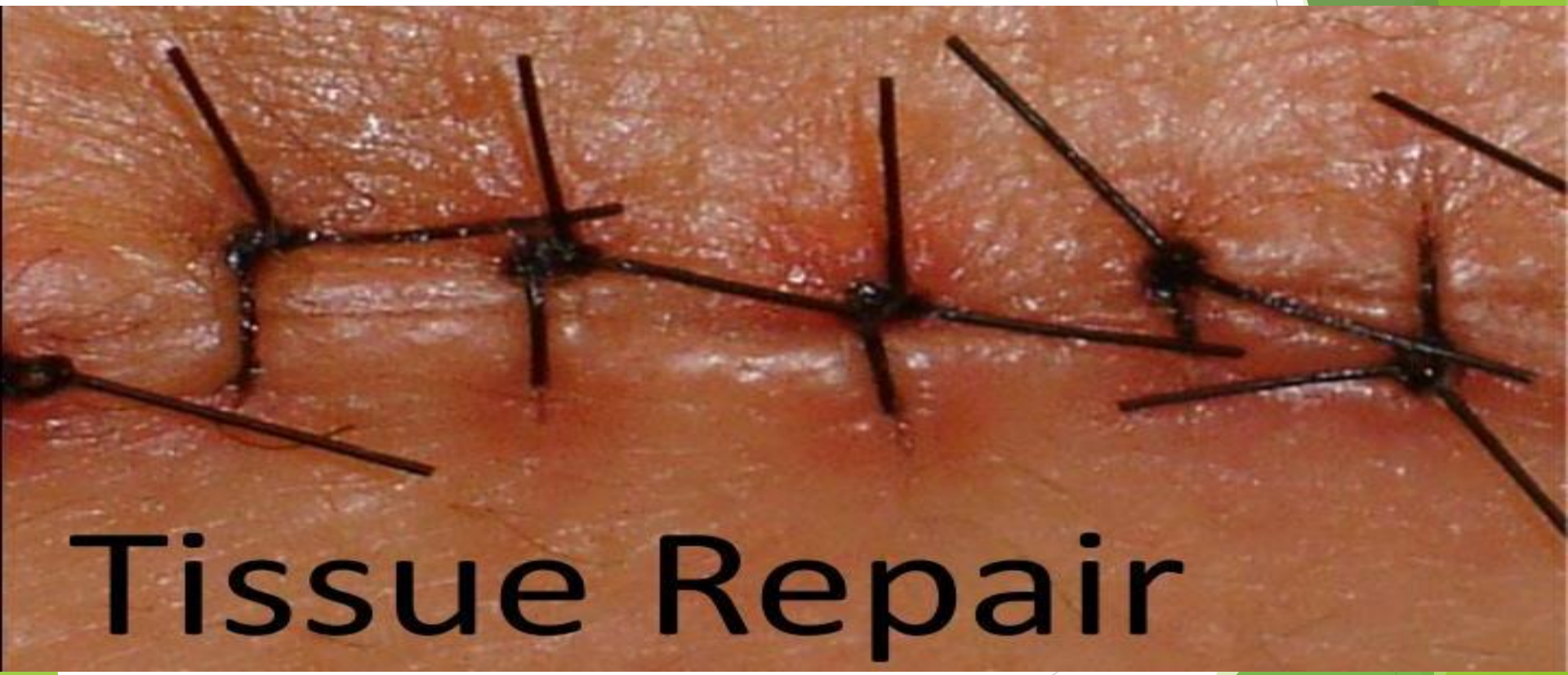
- Injured tissues are incapable of complete restitution.
- If the supporting structures of the tissue are severely damaged

❖fibrosis

- **Extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction).**

➢Although the fibrous scar is not normal, it provides enough structural stability that the injured tissue is usually able to function.

- The ability of tissues to repair themselves is determined, in part, by their intrinsic proliferative capacity.

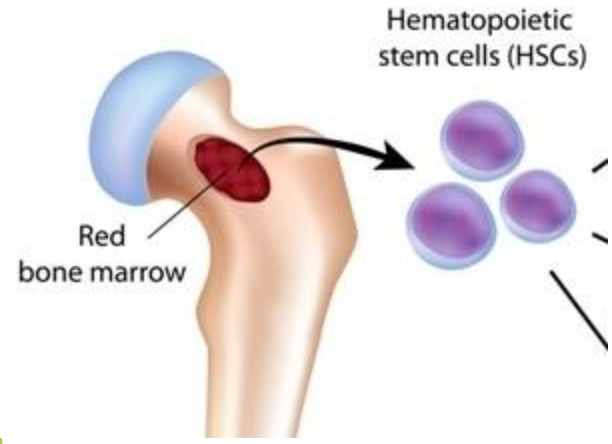


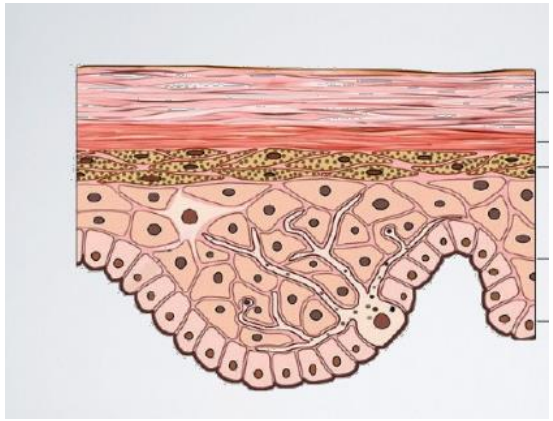
The Proliferative Potential of Different Cell Types

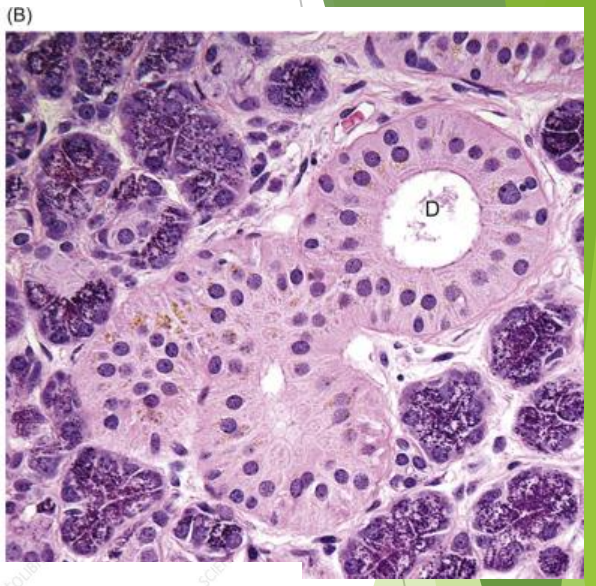
- **Labile cells (continuously dividing & continuously dying)**
  - **Stem cells divide: self renewal and differentiation**
  - **Examples:**
    - **Skin epidermis**
    - **GIT epithelium**
    - **Bone marrow cells**
- **Stable cells (quiescent)**
  - **Examples:**
    - **Liver**
    - **Kidney,**
    - **Smooth muscles.**
- **Permanent (nondividing),**
  - **Examples:**
    - **Cardiac muscle**
    - **Neurones**

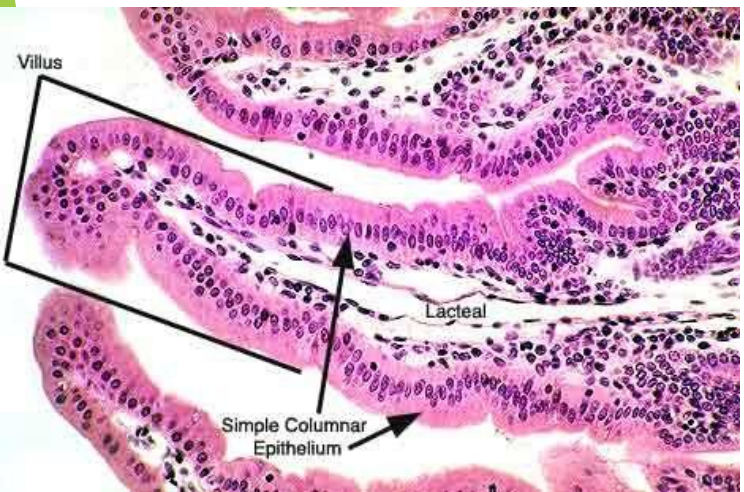
➢ 1.labile tissues

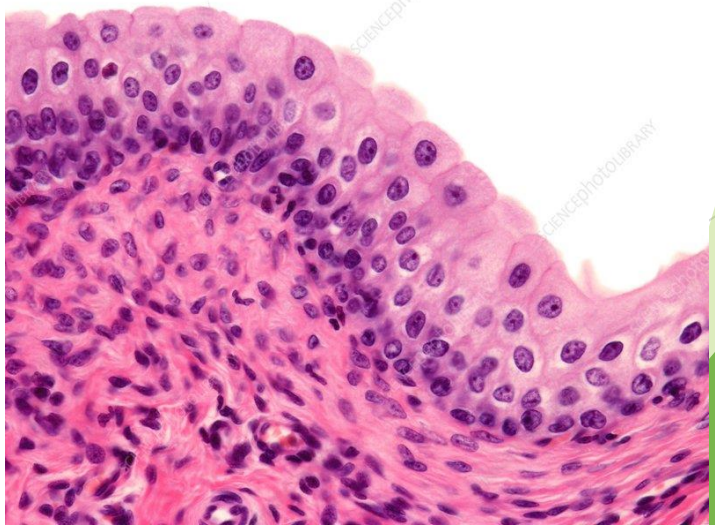
cells are constantly being lost and must be continually replaced by new cells that are derived from tissue stem cells and rapidly proliferating immature progenitors.



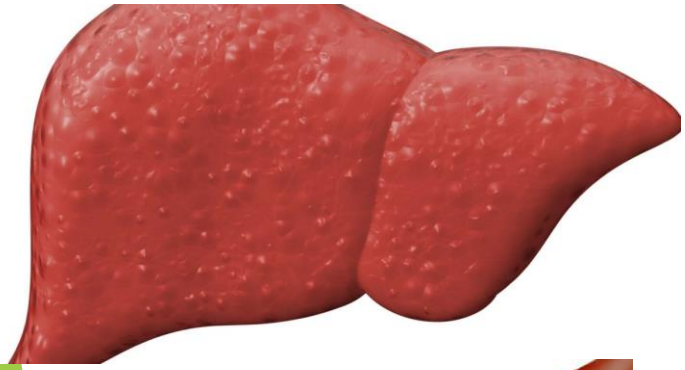


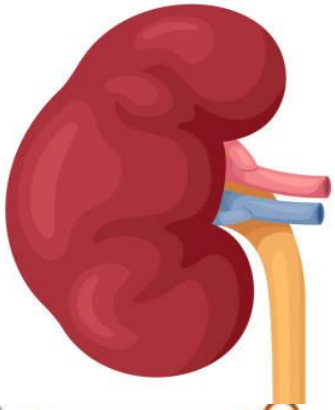


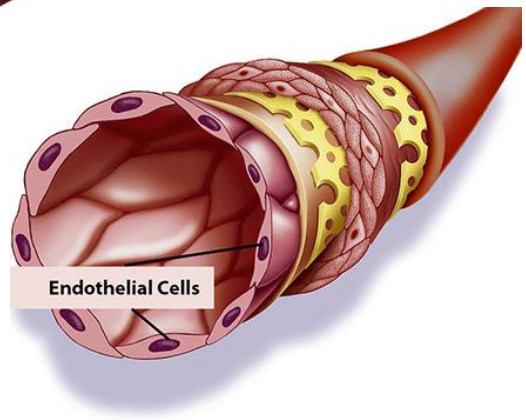


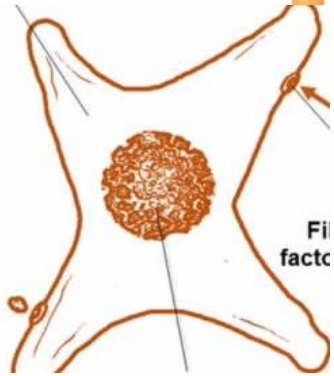


- 2.stable tissues
- are made up of cells that are normally in the G0 stage of the cell cycle and hence not proliferating, but they are capable of dividing in response to injury or loss of tissue mass.

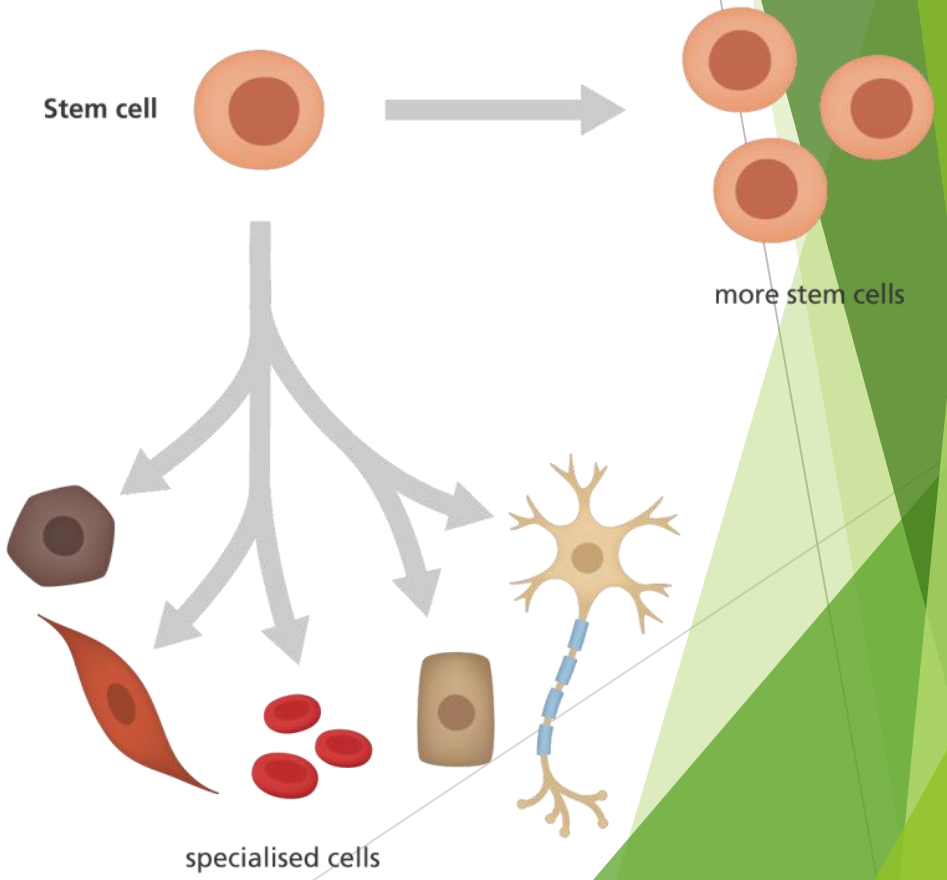








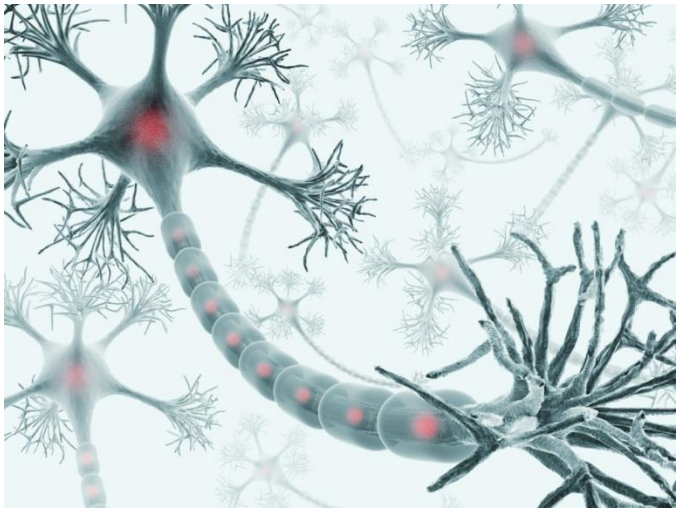
- In the process of regeneration, proliferation of residual cells is supplemented by development of mature cells from stem cells

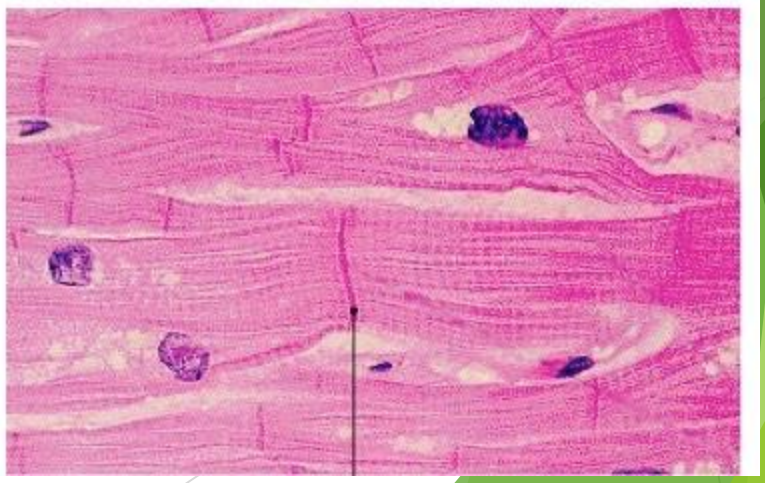


3.permanent tissues

- consist of terminally differentiated nonproliferative cells, such as the majority of neurons and cardiac muscle cells.

- Injury to these tissues is irreversible and results in a scar, because the cells cannot regenerate.



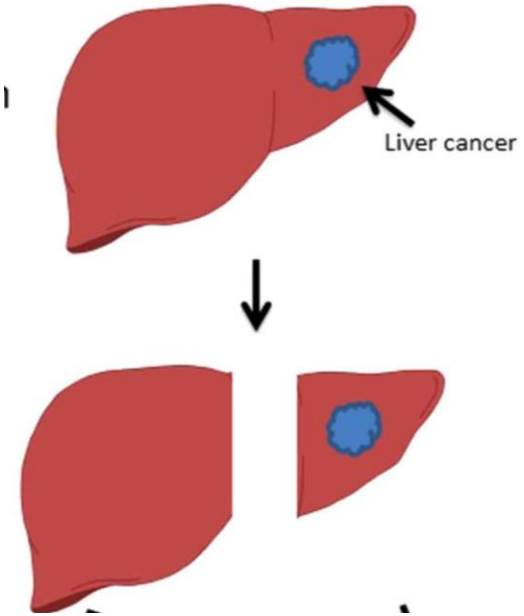


❖Liver Regeneration

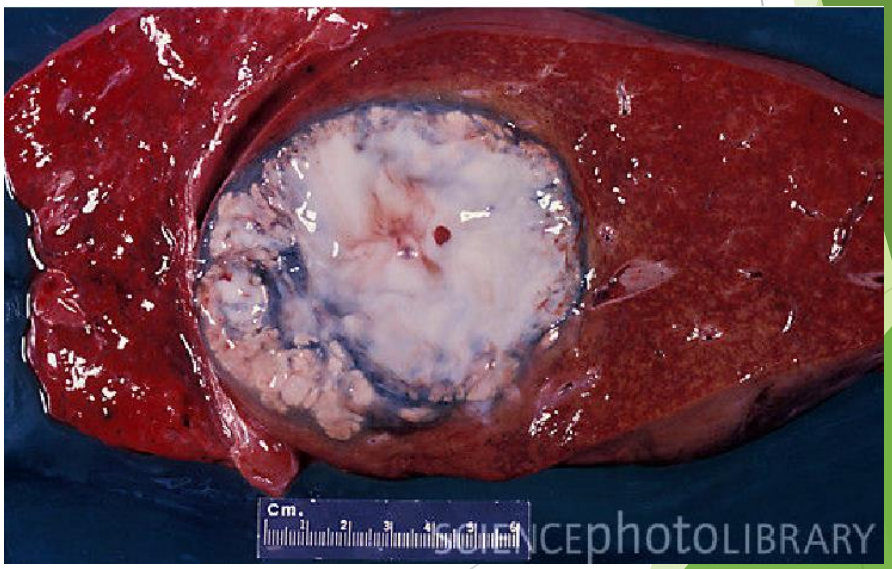
- The human liver has a remarkable capacity to regenerate, as demonstrated by its growth after partial hepatectomy,

- Regeneration of the liver occurs by two major mechanisms:
- proliferation of remaining hepatocytes.
- repopulation from progenitor cells.

- Restoration of normal tissue architecture can occur only if the residual tissue is structurally intact.
- if the entire tissue is damaged, regeneration is incomplete and is accompanied by scarring.



partial surgical resection



liver abscess

- 1.Proliferation of hepatocytes following partial hepatectomy.

- In humans, resection of up to 90% of the liver can be corrected by proliferation of the residual hepatocytes.

- This process is driven by
  - cytokines such as IL-6 produced by Kupffer cells,
  - hepatocyte growth factor (HGF) produced by many cell types.

- **2.Liver regeneration from progenitor cells.**

- In situations in which the proliferative capacity of hepatocytes is impaired, progenitor cells in the liver contribute to repopulation, such as:

  - After chronic liver injury.

  - Inflammation.

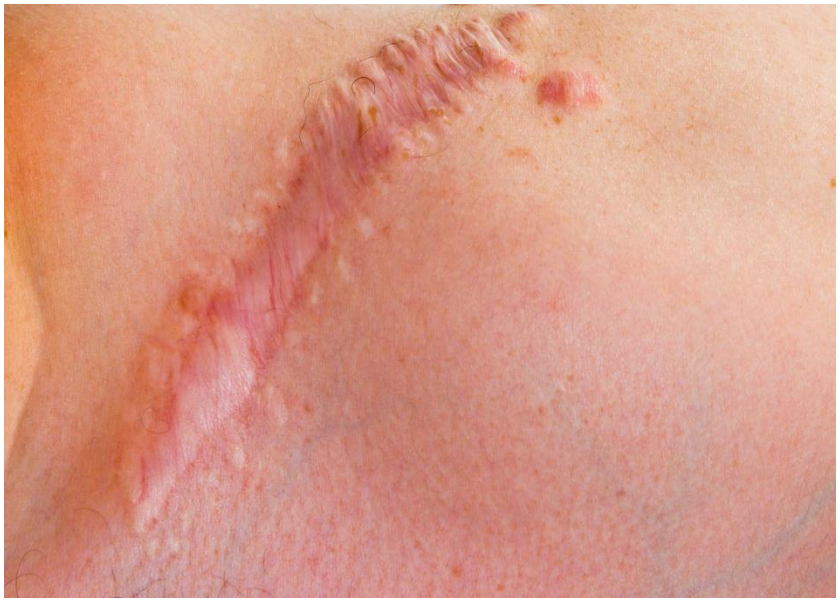
Repair by Scarring

- if repair cannot be accomplished by regeneration alone, it occurs by:

- replacement of the injured cells with connective tissue, leading to the formation of a scar, or by a combination of regeneration of some residual cells and scar formation.

- The term scar is most used in connection to wound healing in the skin.

- Replacement of parenchymal cells in any tissue by collagen, as in the heart after myocardial infarction.



Steps in Scar formation

Injury

Hemostatic plug → Inflammation → Cell proliferation → Formation of **granulation tissue**

Stops bleeding, provides scaffold for deposition of fibrin

To eliminate offending agent

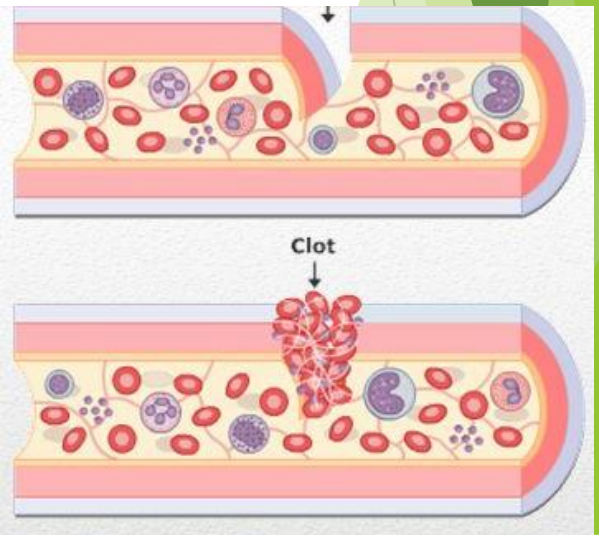
Remnants of injured tissue	Vascular Endothelial cells	Fibroblasts
Attempt to restore normal tissue	Creates blood vessels for nutrition during repair	Forms scar For defects which cannot regenerate

Deposition of **connective tissue (SCAR)**

Steps in Scar Formation

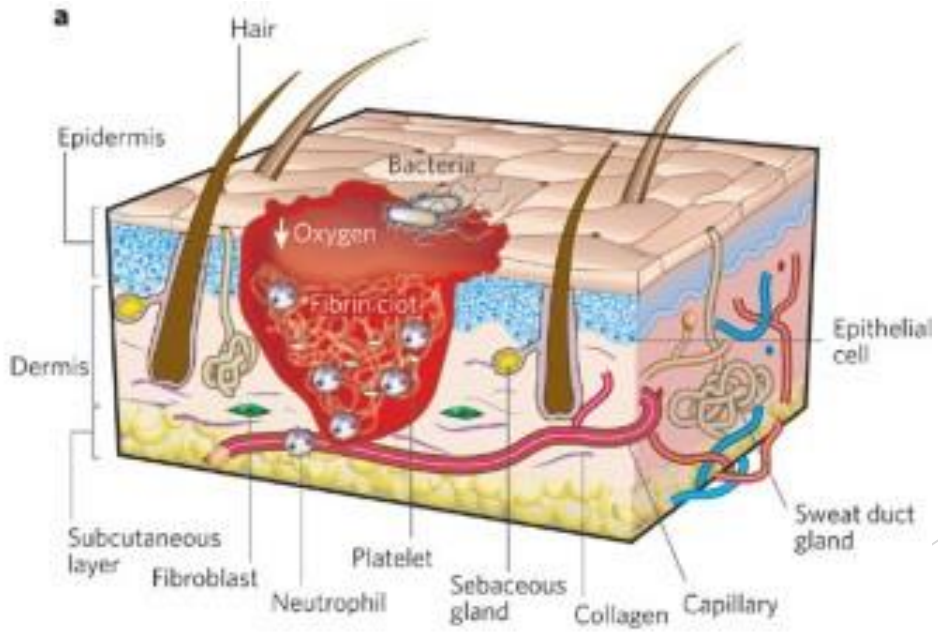
- **1. Within minutes after injury, a hemostatic plug comprised of platelets is formed:**

- **stops bleeding .**
- **provides a scaffold for infiltrating inflammatory cells.**



- 2.Inflammation:

- Include acute and chronic inflammatory responses.
  - The inflammatory cells:
    - eliminate the offending agents
    - clear the debris



The End

Questions