Pathology

Second Year - First Semester Course

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Lecture 9

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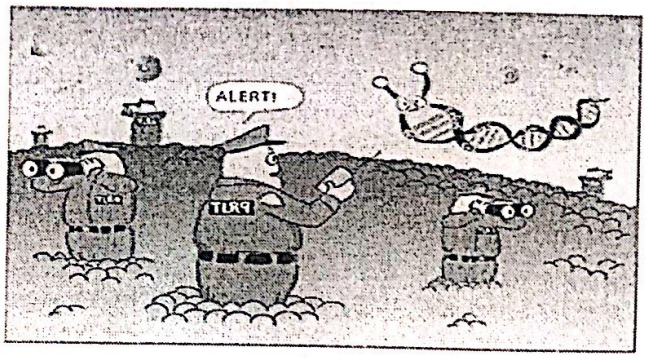
Acute Inflammation 3



Acute inflammation regarding activation of leukocytes (so they can go to the injury site).

mainly neutrophils

←Leukocyte Activation

- leukocytes use various receptors to sense the presence of microbes, dead cells, and foreign substances.
- Engagement of these cellular receptors induces a number of responses in leukocytes and are grouped under the term *leukocyte activation.*

leukocytes → Inflammation site → Activation of leukocytes

① margination
② rolling
③ adhesion
④ transmigration
⑤ chemotaxis

① recognition of abnormal stimulus

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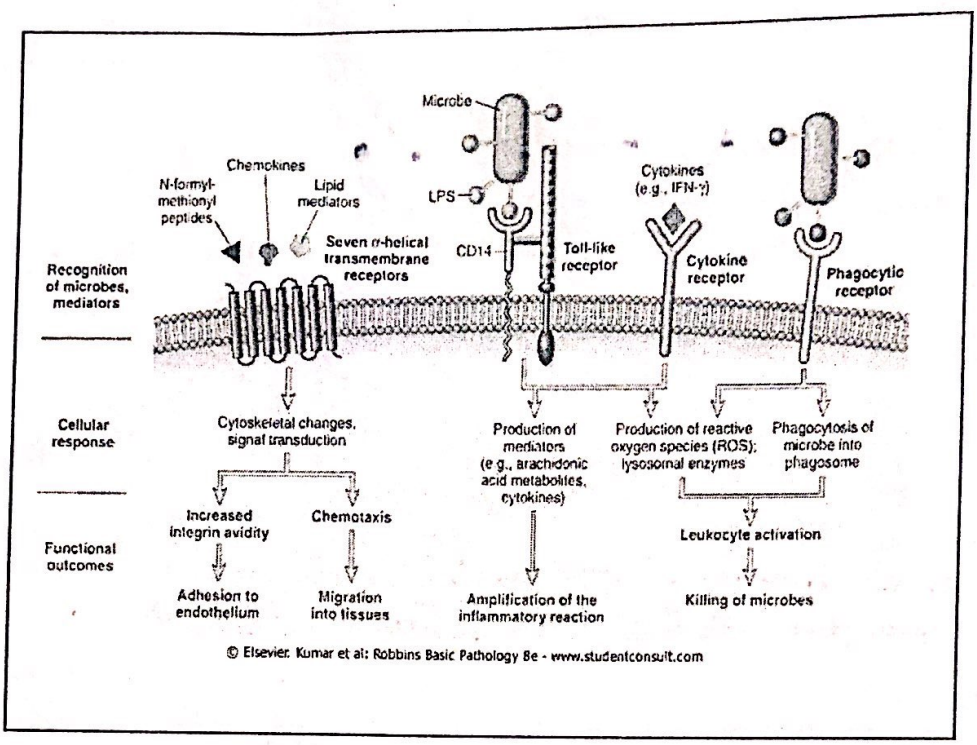

- Leukocyte activation results in enhancement of:
- **Phagocytosis** of particles
- Intracellular **destruction** of phagocytosed microbes and dead cells
- Liberation of substances that **destroy extracellular microbes and dead tissues(Extracellular "traps.")**
- Production of mediators, including arachidonic acid metabolites and cytokines, that **amplify the inflammatory reaction**, by recruiting and activating more leukocytes

substances that are created inside cells and are expelled

mediators that accelerate the process of getting rid of the inflammation

=getting rid of the initiating factor for inflammation

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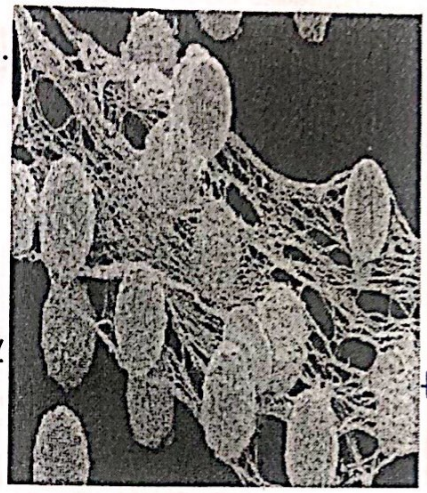
Neutrophils expel net-like structures which are composed of nuclear chromatin and granular protein. This limits the microbes to one area and makes them easier to get rid of. It also starts the process of microbal lysis even outside of the neutrophil.

Neutrophilic Extracellular Traps (NETs):

- Are extracellular fibrillar networks.
- Contains a frame work of nuclear chromatin with granule protein.
- Provides a high concentration of antimicrobial substances and **prevent the spread of the microbes by trapping them in the fibrils.**

https://www.youtube.com/watch?v=03pKHPqeNj8



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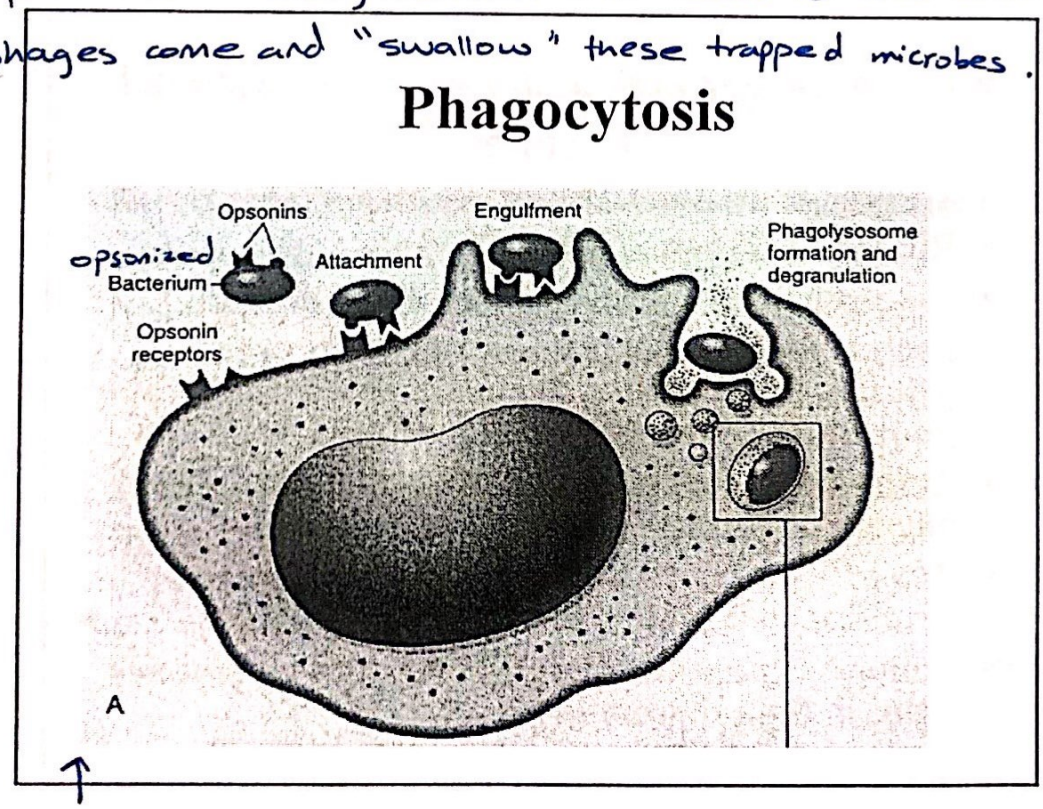
This method can sometimes lead to autoimmune diseases. Macrophages sometimes destroy the body's neutrophils.

(1) engulfing of microbes by phagocytosis

(2) lysis and some of the chromatin from the nucleus leaves along with fibrillar proteins = sticky material that leads to the entrapment of more microbes.

(3) macrophages come and "swallow" these trapped microbes.



opsonins: molecules that attach to the surface of the bacteria labels them for phagocytic cells (macrophages, neutrophils). Now, they are recognized. opsonins now attach to opsonin receptors on phagocytic cells. Bacteria is engulfed and once it is inside, it fuses with lysosomes and is destroyed. Its contents are reused by the cell.

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- Leukocytes have receptors recognize components of the microbes and dead cells
- Other receptors recognize host proteins, called ***opsonins***, that coat microbes and target them for phagocytosis (the process called *opsonization*).

- The most important opsonins are :

1- Immunoglobulin G (IgG) class.

2- Complement protein C3.

3- Plasma carbohydrate-binding lectins called collectins.

~~pathogen is ingested~~

① pathogen is recognized

② phagocytic vacuole is generated and it fuses with the lysosome = phagolysosome

③ Bacteria is killed by ROS

Killing and degradation of phagocytosed microbes

The most impotant microbicidial substances are:

- Reactive Oxygen Species (ROS)
- Lysosomal enzymes: Myeloperoxidase (MPO)
- Bactericidal permeability-increasing protein (causing phospholipase activation and membrane phospholipid degradation)
- Lysozyme (causing degradation of bacterial coat oligosaccharides)
- Major basic protein (an important eosinophil granule constituent, cytotoxic for parasites)
- Defensins (peptides that kill microbes by creating holes in their membranes).

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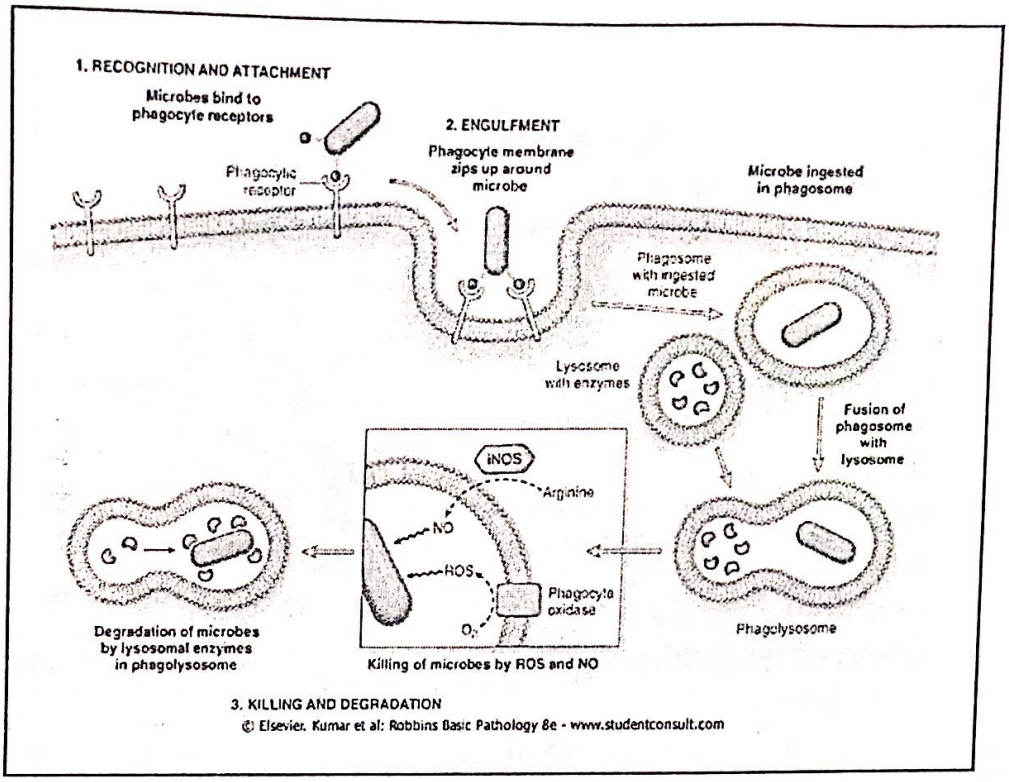

Oxidative burst (Respiratory burst) :

- Rapid activation of a leukocyte NADPH oxidase, (Phagocyte oxidase) which oxidizes NADPH (reduced nicotinamide adenine dinucleotide phosphate) and, in the process, converts oxygen to superoxide ion.
- Superoxide is then converted into hydrogen peroxide .

Inside the neutrophil's lysosomes

NADPH —oxidation→ oxygen free radicles generation —super oxide dimutase→ hydrogen peroxide H_2O_2 —MPO→ hypochloride $HOCl^-$ (very Toxic)

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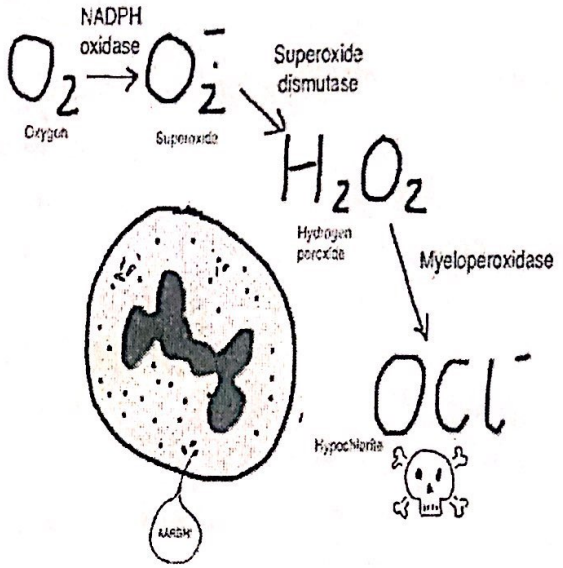
- Myeloperoxidase (MPO), in the presence of a halide such as Cl^-, converts H_2O_2 to $HOCl^\bullet$ (hypochlorous radical).

- $HOCl^\bullet$ is a powerful oxidant and antimicrobial agent that kills bacteria .

- The dead microorganisms are then degraded by the action of lysosomal acid hydrolases.



Defects in Leukocytes function

- Acquired causes : *not gene – related*

- **Bone marrow suppression** caused by tumors or treatment with chemotherapy or radiation (Decreased leukocyte numbers) → *neutropenia*

- **Metabolic diseases** such as diabetes (Abnormal leukocyte functions). *exact mechanism unknown*

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- Genetic causes:

1- Defects in leukocyte **adhesion** (LAD): :

- **Type 1** (LAD-1): defective synthesis of the CD18 β subunit of the leukocyte **integrins** LFA-1 and Mac-1 .
- **Type 2** (LAD-2) : Defect in fucose metabolism resulting in the absence of **sialyl–Lewis X**, the oligosaccharide on leukocytes that binds to selectins. they lack proper rolling and adhesion

= Abnormalities in white blood cell adhesion.
= cannot transmigrate to infection sites

Their symptoms include recurrent bacterial infections.
Can lead to death.

2- Defects in **microbicidal** activity:

Chronic granulomatous disease:

- Genetic deficiency in one of the several components of the **phagocyte oxidase enzyme.**
- In an attempt to control these infections, the microbes are surrounded by activated macrophages, forming the "granulomas". → center surrounded by macrophages

= Abnormal phagocytic function
= granulomas in multiple places, organs

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3- Defects in **phagolysosome formation:**

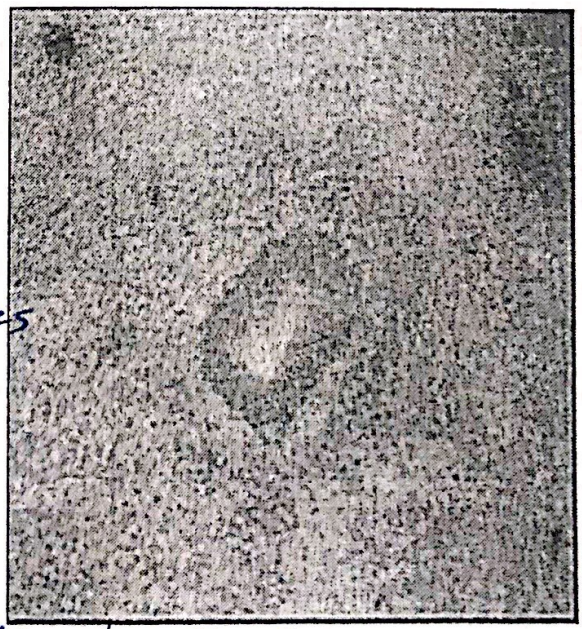
- **Chédiak-Higashi syndrome**
  - inherited
  - immuno-defiency
  - neuronal system abnormalities

= Abnormalities in phagolysomal activity

MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

1. Serous inflammation (clear liquid) :

- Characterized by a watery, protein-poor fluid (in cavities)
- Example: skin blister resulting from a burn or viral infection. (herpes)



seperating of skin layers + fluid collection

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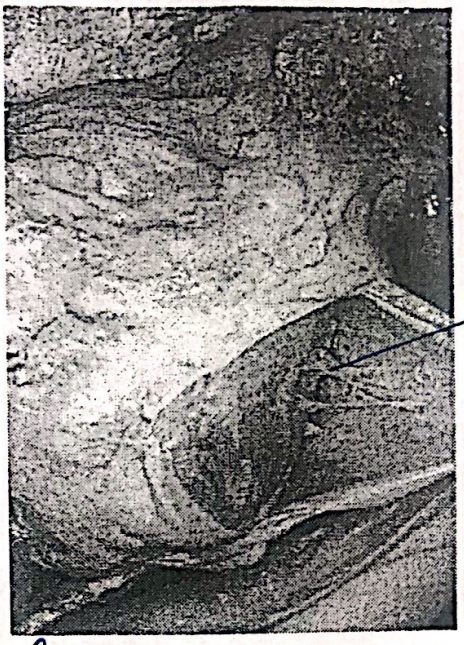
2. Fibrinous inflammation

- Occurs as a consequence of more severe injuries, resulting in greater vascular permeability that allows large molecules (such as fibrinogen) to pass the endothelial barrier.
- Histologically: the accumulated extravascular fibrin appears as an eosinophilic meshwork of threads



fibrin bands (adhesive bands)

- high concentration of fibrin in extracellular spaces. fibrinogen / fibrin proteins leave the vascular spaces. = adhesion of structures to one another because fibrin makes fibrin bands.
- Happens due to edema fluid generation which ~~[illegible]~~ is rich in big proteins like fibrinogen.

3. Suppurative (purulent) inflammation and abscess formation:

- Collection of large amounts of pus consisting of many neutrophils, necrotic cells, and edema
- Organisms (such as staphylococci) cause suppuration and are referred to as pyogenic (pus-forming).
- Abscess: Focal collection of Pus, usual outcome is scarring.

Pus: neutrophils + necrotic tissue (cell remenants)

- mostly due to bacteria

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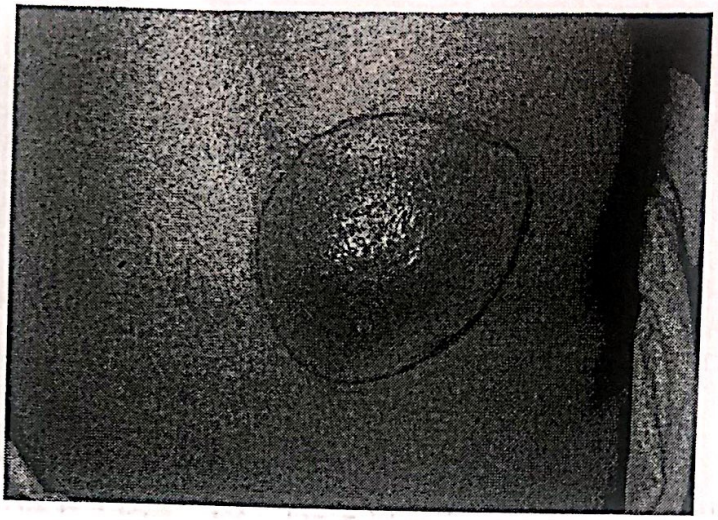
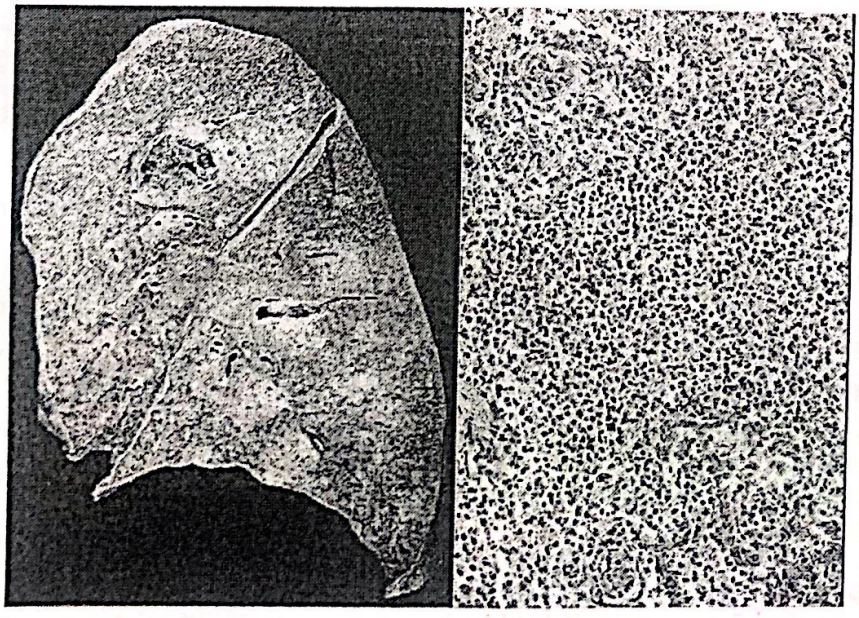
(below skin layers)

Subcutaneous Abscess



→ puss collection under the skin
→ very red, inflamed

Lung Abscess



→ cavities generated which used to contain puss

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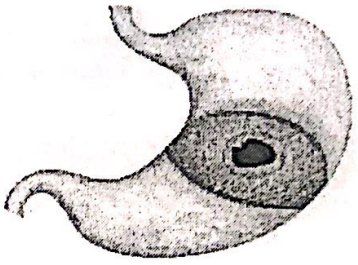
cyst :
has a very well formed defining, confining wall

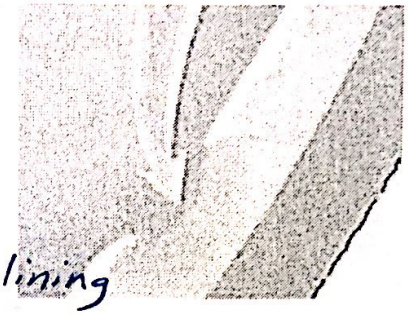
abscess :
does not have a wall, only tissue surrounding the area

4- Ulcer:

- Local defect of the surface of an organ or tissue that is produced by necrosis of cells and sloughing (shedding).
- Most commonly encountered in: Mucosa of the mouth, stomach, intestines, or genitourinary tract

STOMACH ULCER





. defect in an epithelial lining
. acute inflammation ⇒ cell death ⇒ focal area where the surface is lost (ulcer)

Outcomes of Acute Inflammation

1. ◆Resolution : Regeneration and Repair
2. ◆Progression to chronic inflammation
3. ◆Scarring

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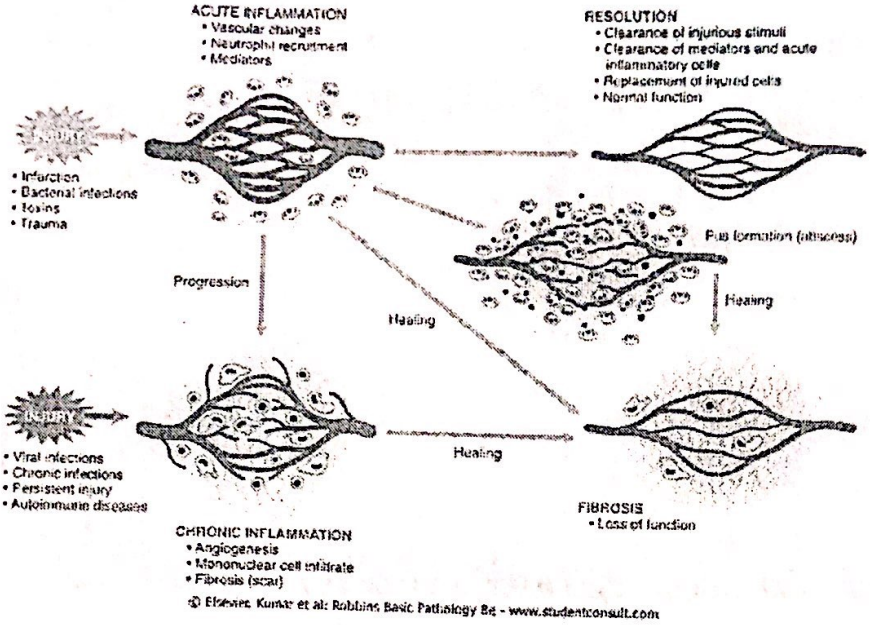
Outcome of acute inflammation



Outcomes of Acute Inflammation

- **Resolution**
  - Occurs when the injury is limited or short-lived, when no or minimal tissue damage and when the tissue is capable of regeneration:
    - Neutralization and removal of chemical mediators
    - Normalization of vascular permeability
    - Halting of leukocyte emigration with subsequent death by apoptosis.
    - Leukocytes begin to produce mediators that inhibit inflammation. (anti-inflammatory factors)
    - Clearance of edema (lymphatic drainage) , inflammatory cells and necrotic debris (macrophages).

= Total regeneration

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Outcomes of Acute Inflammation

Progression to chronic inflammation

- If the offending agent is not removed
- Depending on the extent of the initial and continuing tissue injury, as well as the capacity of the affected tissues to re-grow
- Chronic inflammation may be followed by restoration of normal structure and function or may lead to scarring.

Outcomes of Acute Inflammation

- **Scarring:**
  - Occurs when
    - There is substantial tissue destruction.
    - When the inflammation occurs in tissue not capable of regeneration.

(or)

= scar, fibrous tissue

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