3.Killing & Degradation

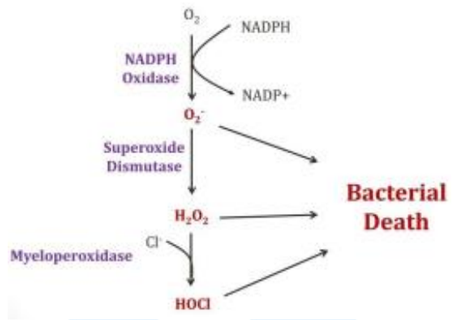
- The **key step** is the formation of **phagolysosome** & exposing the ingested particles to **microbicidal substances.**
- the most important **microbicidal substances are**:

1.Reactive oxygen species **2.Lysosomal enzymes**.

1. Phagocytosis stimulates an oxidative burst characterized by:

1.Sudden **increase in O2 consumption.**
2.**Glycogenolysis.**
3. ↑↑ glucose **oxidation.**
4. ↑↑ production **ROS.**

- The generation of the oxygen metabolites is due to rapid activation of **a leukocyte NADPH oxidase**, called the **Phagocyte Oxidase**, which oxidizes NADPH (reduced nicotinamide adenine dinucleotide phosphate) and, in the process, converts **oxygen to superoxide ion (O2 -) .**
- Superoxide is then converted by spontaneous dismutation into **hydrogen peroxide (O2- +2H+ → H2O2).**



2.Lysosmal enzymes as:

a. **Oxidase**
b. **Myeloperoxidase** (HOCl)
c. **Elastase** (**the most important lysosomal enzyme involved in bacterial killing**)
d. Acid **hydrolase** (degradation of M.O)

- **Other leukocytic killing granules:**

1. **Bactericidal Permeability** → increasing protein which causes **phopholipase stimulation** → degradation membrane phopholipids.
2. **Lysozyme**: degradation of bacteria coat **oligosaccharides**.
3. **Major basic protein:** eosinophil **granule cytotoxic for parasites.**
4. **Defensins**: Peptides kill bacteria by **creating holes in their membranes**.

Leukocyte Induced Tissue Injury:

1. Part of **normal defense against infectious M.O.**
2. **Host response against** some infection that are **difficult to eradicate as TB or some viral infections.**
3.**Reperfusion Injury:** After **MI inflammation may prolong** & **exacerbate the injury**
4. **Autoimmune disease**
5. **Allergic disease** E.g. asthma

- Leukocytes may release toxic products into the **extra-cellular spaces** as well as **within phagolysosme.**

- The most important substance are:

1. **Lysosmal enzymes** 2. **ROS**

- Mechanisms

1. Phagocytic vacuole **remains transiently open** to the outside before complete closure of the phagolysosme.
2. If **the cells encounter material** **cannot be easily ingested** such **as immune complexes** deposited on flat fixed surfaces as **glomerular B.M.**
3. Following phagocytosis of **potentially injurious substances** such as urate crystals which **damage the membrane** of the phagolysosome.

Leukocytes Induced injury / Underlying Human disease

✓ **Acute Disorders**

1.Acute respiratory distress syndrome (**Neutrophils**)
2.Acute transplant rejection (**Lymphocytes, Abs & complement**.)
3.Asthma (**eosinophils, IgE**)
4.Glomerulonephritis (**Ab, complement**)
5.Septic shock (**cytokines**)
6.Vasculitis (**Ab, complement, Neutrophils**)

✓ **Chronic disorders**

1-Arthritis (**lymphocytes, macrophages, Ab**)
2-Asthma (**eosinophils, other WBC, IgE**)
3-Atherosclerosis (**Macrophage, lymphocytes**)
4-Chronic transplant rejection (**Lymphocyte, cytokines**)
5-Pulmonary fibrosis (**Macrophages, Fibroblasts**)

Defects in Leukocyte Function

- MCC of defective inflammation are:

1- **bone marrow suppression** caused by **tumors** and **chemotherapy** or **radiation** (→ **decreased leukocyte numbers**)

2-**metabolic diseases** such as diabetes (causing **abnormal leukocyte functions**).

Inherited defects in leukocyte function

1. Defects in Leukocyte Adhesion

a. LAD type 1 (**defective integrins** LFA-1 and Mac-1)

b. LAD type 2 (**absence of sialyl-Lewis X**)

2. Defects in Microbicidal Activity

e.g **Chronic Granulamatous Disease**

- a genetic **deficiency** in one of the several components of the **phagocyte oxidase responsible for generating ROS**.
- **engulfment** of bacteria **does not result in oxidative burst**.
- in an attempt to control these infections**, the microbes are surrounded by activated macrophages**, forming the **"GRANULOMAS"**.

3. Defects in Phagolysosome formation

e.g **Chediak-Higashi disease** aut.recessive immune deficiency disorder

4. Defects in Toll-like receptor signaling pathway

Morphologic Patterns of Acute Inflammation

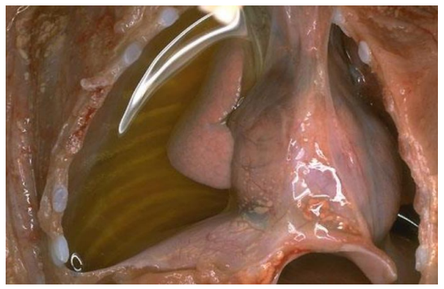
This is modified by:

1. **Severity** of the inflammatory **response.**
2. Its **specific cause.**
3. The **type of tissue** involved.

Types of Acute inflammation

1. Serous inflammation

- Accumulation of **transudate.**
- it derives either **from the serum** or **from the secretions of mesothelial cells** lining the peritoneal, pleural, and pericardial cavities.

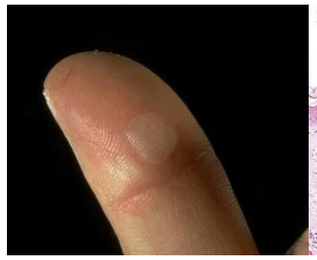


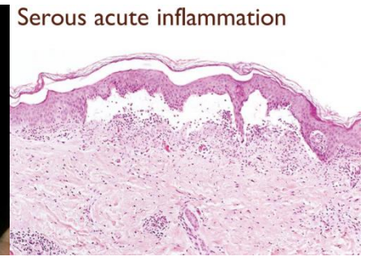
- serous exudate accumulated either **within** or **immediately beneath** the epidermis of the skin .

- Examples:

✓ **Skin blisters (burns,friction,viral infection)**

✓ Fluid in serous cavity = effusion





2. Fibrinous inflammation

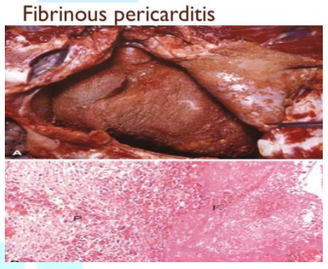
- more **severe injuries** → **greater vascular permeability** that allows **large molecules** such as **fibrinogen** to pass the endothelial barrier.
- A **fibrinous exudate is characteristic** of inflammation in the **lining of body** cavities, such as the **meninges, pericardium, and pleura.**
- Such exudates is **degraded by fibrinolysis**, and the **accumulated debris** may be removed **by macrophage** → resolution.

Examples: Meningitis, Pericarditis, Pleuritis

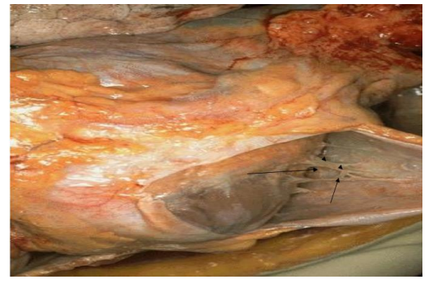
- **Outcomes:**

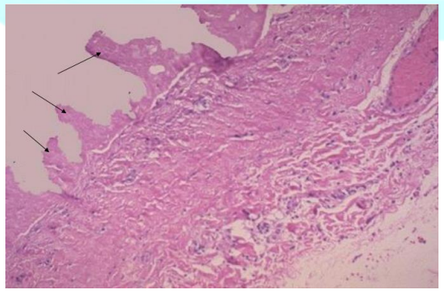
a. resolution b. organization → scarring

- failure to completely remove the fibrin → the ingrowth of fibroblasts and blood vessels .



- the pericardial cavity has been opened to reveal a **Fibrinous Pericarditis** with **strands of stringy pale fibrin** between **visceral** and **parietal** pericardium.





- **Microscopically**, the fibrinous exudate is seen to consist of **Pink Strands Of Fibrin** jutting from the pericardial surface(arrows). Below this, there are a **few scattered inflammatory cells.**

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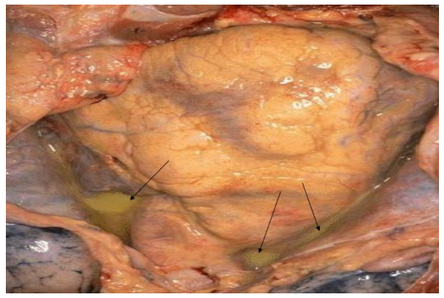
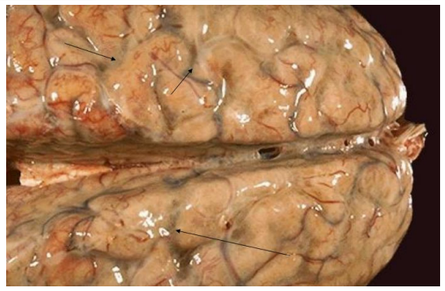
3. Suppurative (Purulent) Inflammation

-Purulent exudate (pus) Consists of **Neutrophils, Necrotic Cells** & **Edema Fluid.**

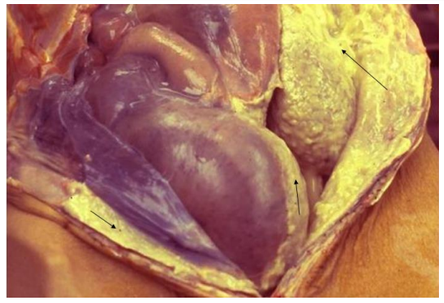
-Mostly caused by **pyogenic M.O as Staphylococci**.



The yellowish fluid in this opened pericardial cavity is **A Purulent Exudate**.



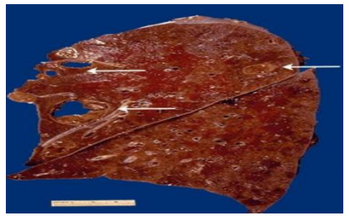
A **purulent exudate is seen beneath the meninges** in the brain of this patient with acute meningitis from **Streptococcus Pneumoniae Infection**. The exudate obscures the sulci.



- **Extensive Purulent Peritonitis** that resulted from rupture of the colon. A thick yellow exudate coats the **Peritoneal Surfaces.**

Abscesses

- are **focal collections** of **pus** that may be caused by **seeding of pyogenic organisms** into a tissue or by **secondary infections of necrotic foci**.
- Abscesses typically have **a central, largely necrotic region** rimmed by a **layer of preserved neutrophils** with a surrounding **zone of dilated vessels** and **fibroblastic proliferation** indicative of early repair.
- As time passes the abscess may become **completely walled off** and eventually be **replaced by connective tissue**.



- The white arrows mark areas of **abscess formation in the upper lobe of this lung**. The **liquefactive necrosis of an abscess is apparent**, because the **purulent contents are draining out to leave a cavity**.

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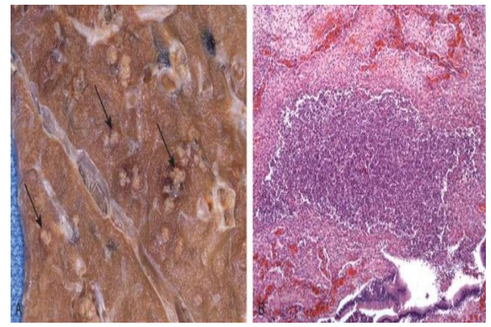
- **Focal Abscess In The Lung**. The alveoli in that area have been destroyed.



4. Ulceration

- **Ulcer: Local defect** or **excavation of the surface** of an organ or tissue produced by **necrosis of cells** & **sloughing inflammatory necrotic tissue**.
- Ulcers occur **only on surface**.
- **Sites :**

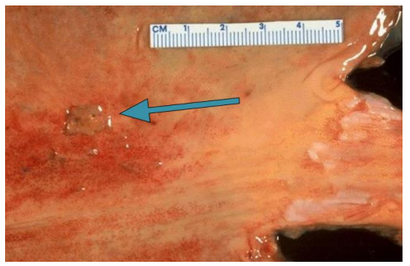
a. Mucosa of mouth, stomach, intestine

b. Skin of lower extremities

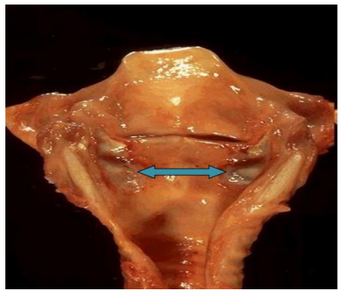
- **Examples:**

Peptic ulcer of stomach or duodenum

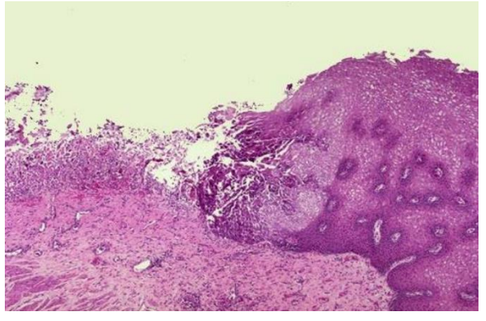
One consequence of **acute inflammation is ulceration**. This occurs on epithelial surfaces. Here the gastric mucosa has been lost, or ulcerated.



Below the vocal cords in this larynx **are large ulcerations.** Such **subglottic ulcers** are produced with prolonged **endotracheal intubation** in which the cuff of the endotracheal tube fits too tight.



Esophageal acute ulcer



Outcome of Acute Inflammation

- The Outcome of Acute Inflammation depends on:

1. The **nature of intensity** of injury.
2. The **site & tissue** affected .
3. The **ability of the host to respond.**

- The outcomes of acute inflammation are:

1. Resolution

- To restore **morphological** & **functional** normality.
- It occurs when:
    1. Injury **is limited or short-lived**.
    2. There is **no or minimal tissue damaged.**
    3. Tissue is **capable** of **regeneration**.

2. Progression to Chronic Inflammation

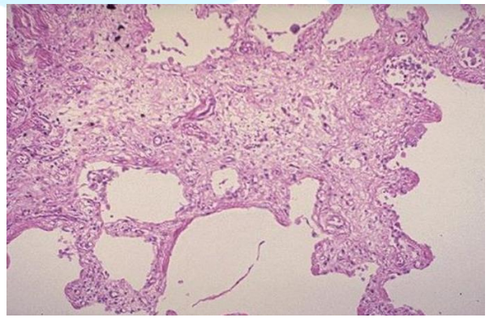
1. It occurs when the **offending agent is not removed.**
2. It depends on the **extent of the initial injury.**
3. It depends on the **capacity of** the affected tissue to **regrow.**

3. Scarring or Fibrosis

❖ It occurs when

1. Tissue destruction **is profound.**
2. Inflammation occurs in **tissue that don’t regenerate.**
3. Inflammation is associated **with extensive fibrinous exudates**.

The end result of inflammation can be scarring. Here, the alveolar walls are thickened and filled with pink collagen.



4. Abscess formation

- Abscesses may form when:
    1. There is **extensive neutrophilic infiltrate .**
    2. Infection by certain **bacteria or fungi.**
    - The usual outcome is **scarring**.

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