Pathophysiology

Dr. Yasser Mufid

Lecture 3

Inflammation

LEARNING OBJECTIVES:

At the end of the Lecture the student is expected to:
1. Know the causes of inflammation.
2. Understand the process of inflammations.
3. Comprehend the pathogeneses of acute inflammations.
4. Comprehend the main features of acute inflammation.
5. Comprehend the chemical mediators of inflammation.
6. Understand the systemic Manifestations of Inflammation.
7. Differentiate the morphological types of acute inflammation.

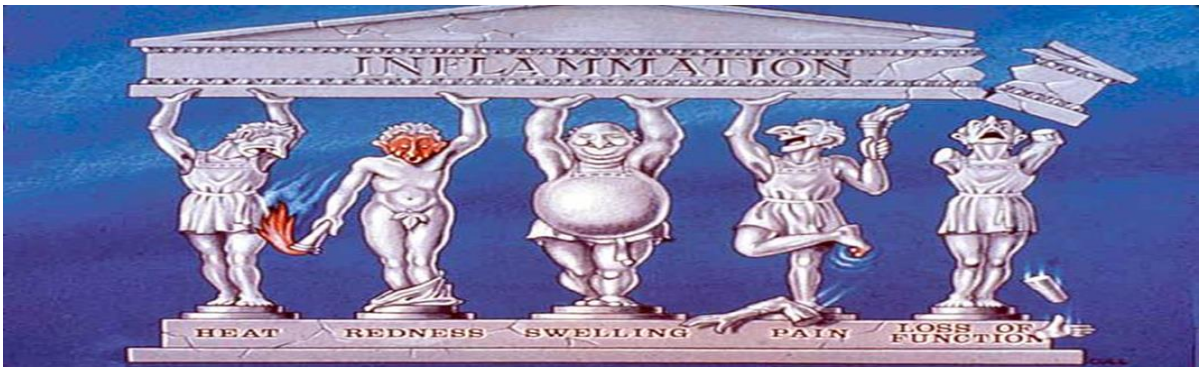
Is the local response of living mammalian tissues to injury from any agent. It is a body defense reaction in order to eliminate or limit the spread of injurious agent, followed by removal of the necrosed cells and tissues. but it is itself capable of causing tissue damage.

The Roman writer Celsus in 1st century A.D. named the famous 4 cardinal signs of inflammation as:

i) Rubor (redness);
ii) Tumor (swelling);
iii) Calor (heat); and
iv) Dolor (pain).

To these, **fifth sign Functio laesa (loss of function)** was later added by Virchow. The word inflammation means burning.

This nomenclature had its origin in old times but now we know that burning is only one of the features of inflammation.



Beneficial Effects of inflammation:

1. Serves to destroy, dilute or wall off the injurious agents.
2. Heal and reconstitutes the damaged tissue.
3. Memories the infection.

Harmful Effects of Inflammation:

1. Inflammatory reaction may cause hypersensitivity reaction to insect bites, drugs and toxin.
2. Inflammatory reaction underlies some common chronic diseases such as rheumatoid arthritis, atherosclerosis and lung fibrosis.
3. Repair by fibrosis may lead to disfiguring scars or fibrous band that may cause intestinal obstruction or limit the mobility of joint.

The causes of inflammation:

1. **Exogenous causes**:
   a) Physical agents
      i. Mechanic agents: fractures, foreign corps, sand, etc.
      ii. Thermal agents: burns, freezing.
   b) Chemical agents: toxic gases, acids, bases.
   c) Biological agents: bacteria, viruses, parasites.
2. **Endogenous causes**:
   a) Circulation disorders: thrombosis, infarction, hemorrhage.
   b) Enzymes activation : e.g. acute pancreatitis.
   c) Metabolic products deposals : e.g. uric acid, urea.

Pathogenesis:

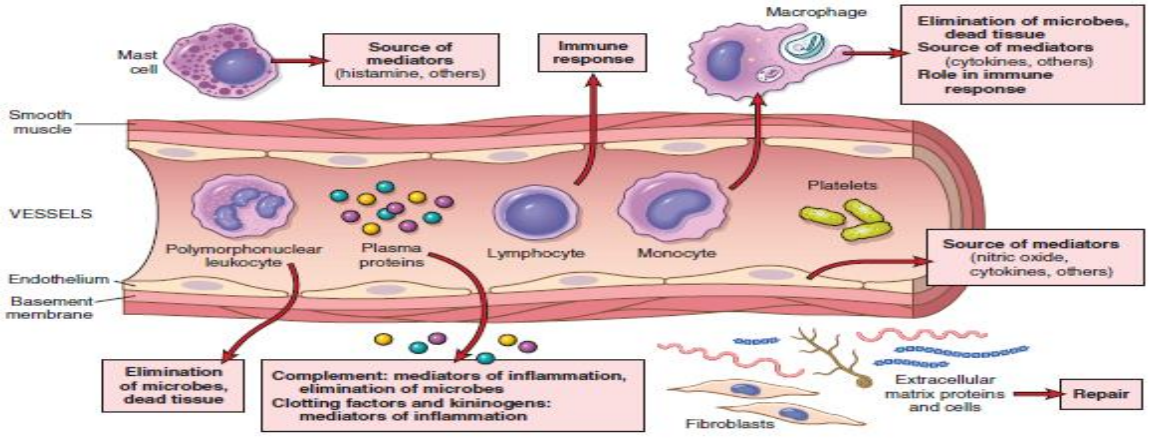
Three main processes occur at the site of inflammation, due to the release of chemical mediators :

1- Increased blood flow (redness and warmth).
2- Increased vascular permeability (swelling, pain & loss of function).
3- Leukocytic Infiltration.

Components of the Inflammatory Responses:

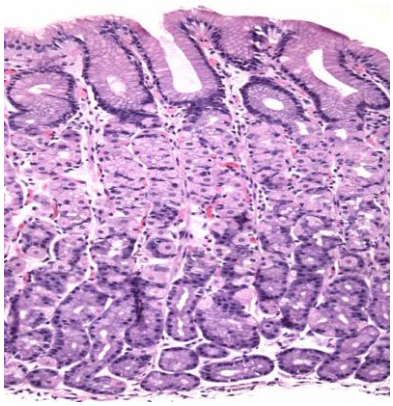
• Vascular Reaction.
• Cellular Reaction.

The cells and molecules of host defense, including leukocytes and plasma proteins, normally circulate in the blood, and the goal of the inflammatory reaction is to bring them to the site of infection or tissue damage. In addition, resident cells of vascular walls and the cells and proteins of the extracellular matrix (ECM) are also involved in inflammation and repair.

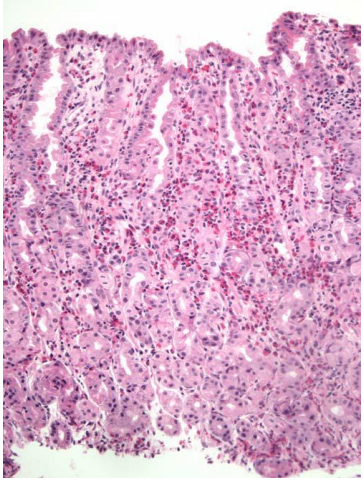


Types of Inflammation

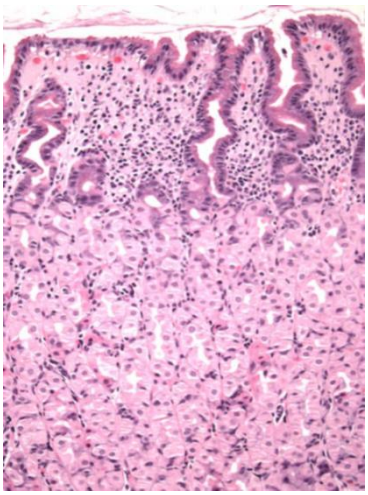
1- **Acute inflammation**: *Any inflammation that has a fairly rapid onset, quickly becomes severe, usually manifested for only a few days, but may persist for several days or even a few weeks.*
2- **Subacute inflammation**: *A condition intermediate between chronic and acute inflammation, exhibiting some of the characteristics of each.*
3- **Chronic inflammation:** *It may result from failure to eliminate an acute inflammatory irritant, from an autoimmune response to a self-antigen, or may be caused by an innately chronic irritant of low intensity that persists. It is characterized by simultaneous inflammation and repair, with recruitment and activation of macrophages, lymphocytes and other cells triggered by the coordinated action of cytokines and growth factors.*



Normal Gastric corpous



Acute inflammation



Chronic inflammation

Acute Inflammation

Acute inflammation

is an immediate and early response to an injurious agent and it is relatively of short duration, lasting for minutes, several hours or few days.

Recognition of Microbes, Necrotic Cells, and Foreign Substances

Phagocytes, dendritic cells (cells in connective tissue and organs that capture microbes and initiate responses to them), and many other cells, such as **epithelial cells**, express receptors that are designed to sense the presence of infectious pathogens and substances released from dead cells. These receptors have been called "**pattern recognition receptors**" which include:

1. **Toll-like receptors** (TLRs).
2. The **inflammasome** is a multi-protein cytoplasmic complex that recognizes products of dead cells.

The main features of acute inflammation are:

A. Hemodynamic Changes:
1) Transient Vasoconstriction.
2) Persistent Vasodilatation and Stasis.
3) Increased Permeability of Vessel Walls.
4) Fluid Exudate and Formation of Edema.

B. Cellular Events: Leukocyte Recruitment and Activation.
1) Cellular Exudate (Neutrophil Emigration & Accumulation).
2) **Phagocytosis.**

C. Resolution or Progression.

A. HEMODYNAMIC CHANGES:

1.Transient Vasoconstriction: Vasoconstriction of the arterioles in seconds due to neurogenic or chemical stimuli e.g. Histamine, bradykinin, With mild form of injury, the blood flow may be re-established in3-5 seconds while with more severe injury the vasoconstriction may last for about 5 minutes.

2.Persistent Vasodilatation and Stasis:

A. Involves mainly the arterioles, but to a lesser extent, affects other components of the microcirculation like venules and capillaries. This change is obvious within half an hour of injury. Vasodilatation results in increased blood volume in microvascular bed of the area, a process known as "**active hyperemia**" (hyper- = increased; -emia = blood). which is responsible for **redness and warmth** at the site of acute inflammation.

B. Progressive vasodilatation, which will elevate the local hydrostatic pressure resulting in **transudation** of fluid into the extracellular space. This is responsible for **swelling** at the local site of acute inflammation.

C. Slowing of blood circulation due to increased permeability of the micro-vasculatures and outpouring protein-rich fluid into the extracellular spaces, resulting red cell concentration in small vessels reflected by presence of dilated small vessels packed with red cells. This morphological finding is known as **stasis**.

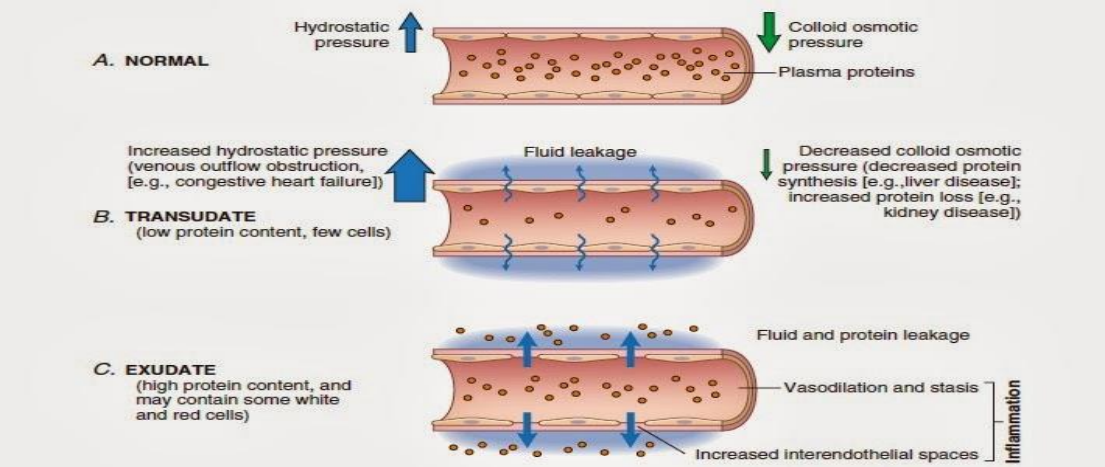
3.Increased Permeability of Vessel Walls:

Increasing vascular permeability leads to the movement of **protein-rich fluid** and even blood cells into the extravascular tissues. This in turn increases the **osmotic pressure** of the interstitial fluid, leading to more outflow of water from the blood into the tissues. The resulting protein rich fluid accumulation is called an ***exudate***.

TRANSUDATE: *Has a **low protein** content, usually caused by **alterations in hydrostatic or oncotic pressure.** Implies a hydrostatic (pressure) problem.*

EXUDATE: *Has a **high protein** content including Immunoglobulins, caused by **increased vascular permeability**. Implies an inflammatory process.*

Differences between transudate and exudate.			
FEATURE		**TRANSUDATE**	**EXUDATE**
1	**Definition**	Filtrate of blood plasma without changes in endothelial permeability	Oedema of inflamed tissue associated with increased vascular permeability.
2	**Character**	Non-inflammatory oedema	Inflammatory oedema.
3	**Protein content**	Low (less than 1 gm/dl); mainly albumin, low fibrinogen; hence no tendency to coagulate.	High (2.5-3.5 gm/dl), readily coagulates due to high content of fibrinogen and other coagulation factors.
4	**Glucose content**	Same as in plasma.	Low (less than 60 mg/dl).
5	**Specific gravity**	Low (less than 1.015).	High (more than 1.018).
6	**pH**	> 7.3	< 7.3
7	**Cells**	Few cells, mainly mesothelial cells and cellular debris.	Many cells, inflammatory as well as parenchymal.
8	**Examples**	Oedema in congestive cardiac failure.	Purulent exudate such as pus.



B. CELLULAR EVENTS: LEUKOCYTE RECRUITMENT AND ACTIVATION.

The cellular phase of inflammation consists of 2 processes:
1. Exudation of leucocytes.
2. Phagocytosis.

1. Exudation of leucocytes.

Polymorphonuclear neutrophils (PMNs) comprise the first line of body defense, followed later by monocytes and macrophages.

The changes leading to migration of leucocytes are as follows:

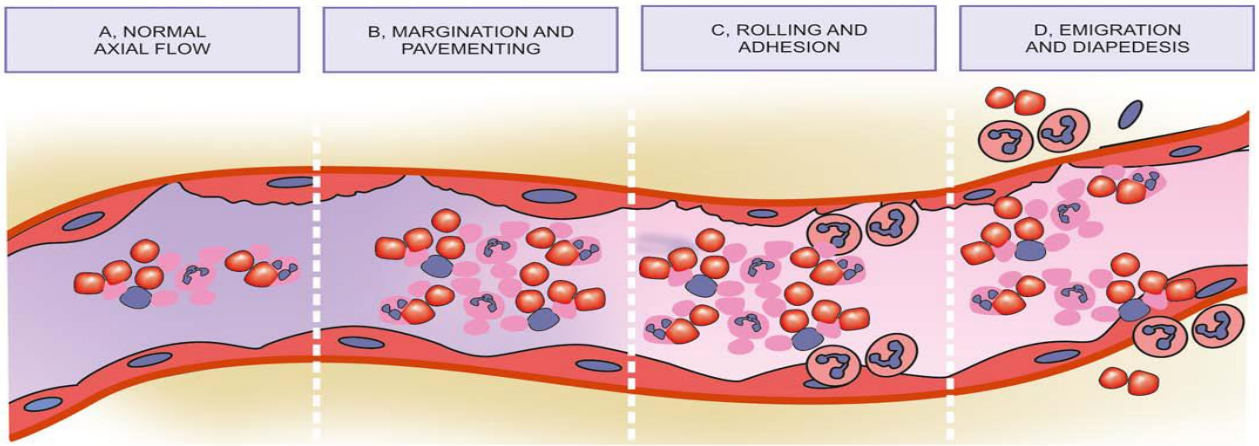
a) **Margination & Pavementing**: When blood flow slows early in inflammation due to stasis, white cells fall out of the central column and assume a peripheral position along the endothelial surface. Due to slowing and stasis, the central stream of cells widens and peripheral plasma zone becomes narrower because of loss of plasma by exudation. This phenomenon is known as (***margination***). As a result of this redistribution, neutrophils of the central column come close to the vessel wall; this is known as (***pavementing***).

b) **Rolling & Adhesion:** Peripherally marginated and pavemented neutrophils slowly roll over the endothelial cells lining the vessel wall ***(rolling phase)***. This is followed by transient bond between the leucocytes and endothelial cells becoming firmer ***(adhesion phase)***.

c) **Emigration & Diapedesis:** Following firm adhesion, leukocytes insert pseudopods into the junctions between the endothelial cells and the basement membrane. Eventually they traverse the basement membrane and escape into the extracellular space by inducing a simple damage between the endothelial cells through the effect of collagenase ***(emigration phase)***. *Neutrophils, monocytes, lymphocytes, eosinophils and basophils all use the same pathway.*

Then the escape of red cells through gaps between the endothelial cells, ***(diapedesis)***, takes place.

D. **Chemotaxis:** The transmigration of leucocytes after crossing several barriers (endothelium, basement membrane, perivascular myofibroblasts and matrix) to reach the interstitial tissues is a chemotactic factor-mediated process called ***(chemotaxis)***.



2. <u>Phagocytosis</u>

Phagocytosis is defined as the process of engulfment of solid particulate material by the cells (cell-eating). The cells performing this function are called phagocytes.

There are 2 main types of phagocytic cells:

i. **Polymorphonuclear neutrophils (PMNs)** which appear early in acute inflammatory response, sometimes called as microphages.

ii. Circulating **monocytes** and fixed tissue mononuclear phagocytes, commonly called as macrophages.

Phagocytosis of the microbe by polymorphs and macrophages involves the following 3 steps:

1) Recognition and attachment.
2) Engulfment.
3) Killing and degradation.

1) Recognition and attachment

The expression of cell surface receptors on macrophages which recognise microorganisms:

a- **mannose receptor** and scavenger receptor.

b- The process of phagocytosis is further enhanced when the microorganisms are coated with specific proteins, **opsonins**, from the serum and the process is called opsinization (meaning preparing for eating). The major opsonins are IgG antibodies, the C3b breakdown product of complement, and certain plasma lectins.

2) Engulfment

This is accomplished by formation of cytoplasmic pseudopods around the particle due to activation of actin filaments beneath cell wall, enveloping it in a phagocytic vacuole.

3) Killing and degradation

The mechanisms which are involved in disposal of microorganisms:

i) Oxidative bactericidal mechanism by oxygen free radicals

a. Myeloperoxidase-dependent oxidative-dependent.

b. Myeloperoxidase-dependent oxidative-independent. This is mediate by some of the constituents of the primary and secondary granules of polymorphonuclear leukocytes. These include:
1. Bactericidal permeability increasing protein (BPI)
2. Lysozymes
3. Lactoferrin Major basic protein
4. Defenses

ii) Oxidative bactericidal mechanism by lysosomal granules

iii) Non-oxidative bactericidal mechanism.

C. RESOLUTION OR PROGRESSION

The outcomes (Consequences) of acute inflammation:

1- Resolution

2- Healing by repair or regeneration

3- Progression into chronic inflammation.

4- Spread

a. Direct-e.g. cellulitis b. Lymphatic c. Blood vessels: Pyaemia -Septicemia

5- Death.

Chemical mediators of inflammation

It account for the events of inflammation. Inflammation has the following sequence:
Cell injury → Chemical mediators → Acute inflammation (i.e. the vascular & cellular events).
The chemical mediators of inflammation can be derived from plasma or cells.

a) Plasma-derived mediators:

i) **Complement activation:**

1) **(C3a,C5a)** causes an increase in vascular permeability.
2) **(C5a)** activates chemotaxis.
3) **(C3b,C3bi)** promotes opsinization.

ii) **Factor XII** (***Hegman factor***). Its activation results in recruitment of four systems:

1) The Kinin.
2) The clotting.
3) The fibrinolytic and the compliment systems.

b) Cell-derived chemical mediates:

	Cellular mediators	Cells of origin	Functions
1.	**Histamine**	Mast cells, basophiles,	Vascular leakage & platelets
2.	**Serotonin**	Platelets	Vascular leakage
3.	**Lysosomal enzymes**	Neutrophils, macrophages	Bacterial & tissue destruction
4.	**Prostaglandins**	All leukocytes	Vasodilatation, pain, fever
5.	**Leukotrienes**	All leukocytes	LB4
6.	**Chemoattractant LC4, LCD4, & LE4 Broncho and vasoconstriction**		
7.	**Platelet activating factor**	All leukocytes	Bronchoconstriction and WBC priming
8.	**Activated oxygen species**	All leukocytes	Endothelial and tissue damage
9.	**Nitric oxide**	Macrophages	Leukocyte activation
10.	**Cytokines macrophages**	Lymphocytes,	Leukocyte activation

Systemic Manifestations of Inflammation

1) Pyrexia (fever): Will be discussed later
2) Negative nitrogen balance: Most of the body's nitrogen is incorporated into protein. Positive nitrogen balance, which occurs when the intake of nitrogen is greater than its excretion, implies tissue formation and growth. Negative nitrogen balance, which occurs when more nitrogen is excreted than is taken in, indicates wasting or destruction of tissue.
3) Increased erythrocyte sedimentation rate: is a measure of the settling of red blood cells in a tube of blood during one hour. The rate is an indication of inflammation and increases in many diseases.
4) Acute phase reactions – Somnolence, Anorexia, Malaise, Hypotension, Increased pulse, Rigors (shivering), Chills (search for warmth), Synthesis of acute-phase proteins by the liver including C-reactive protein (CRP), serum amyloid A (SAA), serum amyloid P (SAP), complement and coagulation proteins.
5) Anemia

6) Leukocytosis: Leukocytosis is a common feature of inflammation, especially those induced by bacterial infection. The leukocytosis occurs initially due to accelerated release of cells from the bone marrow post mitotic reserve pool (caused by IL-1 and TNF).
7) Leucopenia - Typhoid fever and infection caused by viruses, Rickettsiae, and certain protozoa are associated with leucopenia.

Morphological Types of Acute inflammation

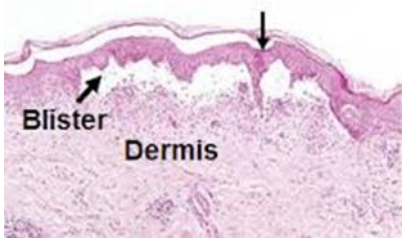
1-Catarrhal

Is a mild acute inflammation of the mucous membrane . Excessive mucus fluid secretion and Little Necrosis of tissue. E.g. Common cold = coryza →Nasal obstruction + congestion.

Acute laryngitis with petechiae (from Giarelli L. 1987)

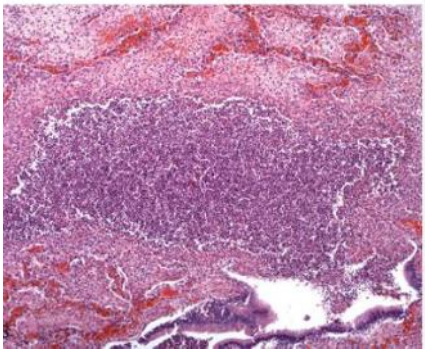
*2-**Serous Inflammation***

Inflammation of serous membrane. It is characterized by clear fluid in serous cavity (pleural , peritoneal pericardial &synovial cavities) => Effusion (Fluid in serous cavity) Serous Exudate (watery fluid) E.g. skin Blisters caused by Burns or viral infection.



*3-**Suppurative (Purulent)***

Large amount of purulent exudates (pus) caused by pyogenic bacteria. e.g. *Staph . aureus* . and *Strept. pyogenes* .
E.g. Boil , Furuncle: Abscess of hair follicles . Empyema : collection of pus in body cavity or a hollow organ e.g gall bladder.



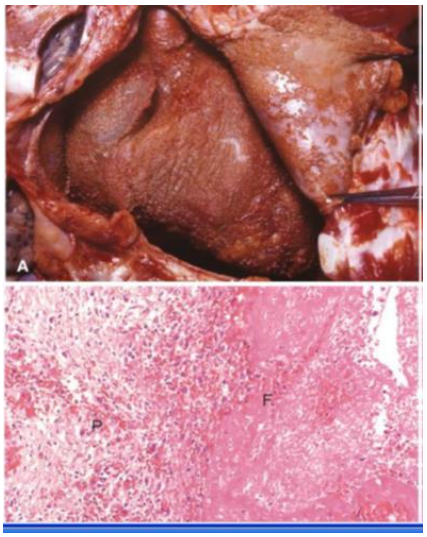
Pus

It is thick creamy viscous yellowish greenish fluid consist of dead and dying neutrophils, fluid exudate, bacteria & necrotic tissue or cellular debris, Purulent inflammatory exudate

Abscess

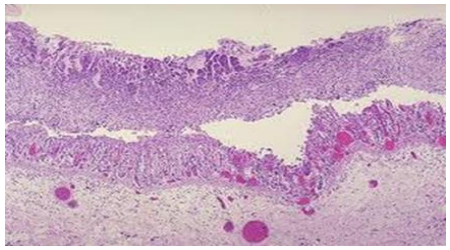
Abscess: localized collection of pus , has central necrotic cavity, surrounding by a layer of inflamed granulation tissue (pyogenic membrane) outcome →Burst , surgical drainage &/or fibrosis.

4. Fibrinous Inflammation



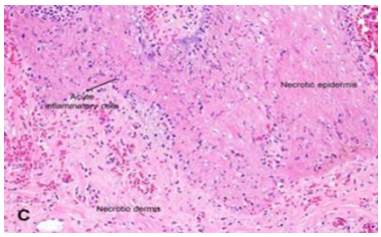
A severe injury with excessive deposition of fibrin in serous cavity called fibrinous exudate and fluid is removed by lymphatic.
Both visceral and parietal Layers of cavity are stuck by fibrin meshwork giving **Bread and Butter appearance** when separated from each other .
Fibrinous exudate may be degraded by fibrinolysis and removed by macrophage resulting in resolution or incomplete removal of fibrin resulting in organization and scarring with fibrous adhesion of pleura or pericardium.

*5.**Pseudo-membranous***



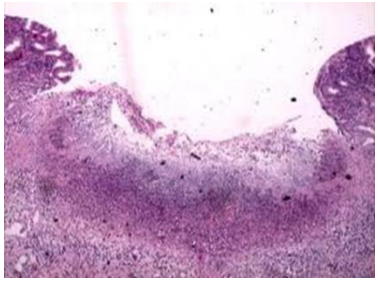
Very severe ulcerative inflammation of mucous membranes with extensive necrosis of surface epithelium and severe acute inflammation of underlying tissue with formation of pseudo-membrane, consisting of exudate , fibrin , neutrophils RBC , bacteria and tissue debris. It's a white – dirty membrane.
e.g. Diphtheria – Larynx . pseudomembranous Colitis – *Clostridium difficile*, lincomycin , clindamycin.

*6. **Gangrenous***



Gangrene : Tissue necrosis with putrefaction due to invasion with digestion by saprophytic bacteria – like putrefaction of meat
Characterized by discoloration of tissue with bad odor (Foul smell) .
e.g Diabetic foot, Atherosclerosis, Ischemia of leg & gangrenous bowel

*7.**Ulceration***



An ulcer is loss of continuity (Local defect) of the surface epithelium of the skin or GIT mucosa. Associated with acute and chronic inflammation which induced necrosis of superficial layers of involved organ e.g Gastric (peptic) ulcer ulcerative colitis.

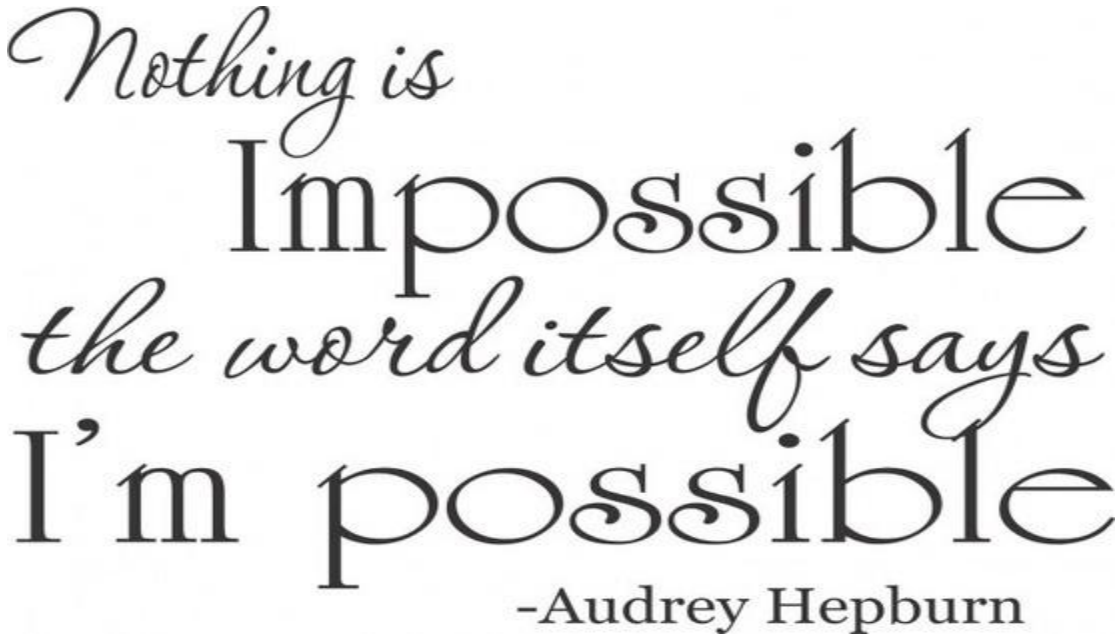
Exercises

1. Discuss the pathophysiology of the cardinal sign of acute inflammation.
2. Enumerate the sequential steps in both the vascular and cellular responses of acute inflammation.
3. List the morphologic changes in acute inflammation.
4. Enumerate the systemic effects of inflammations.

1- The cardinal signs of inflammation (Rubor, Tumor and Color) result from:
(a) vascular changes (b) cellular changes
(c) activation of the complement system (d) electrolyte disturbance

2- The cells that appear first at the site of injury is
(a) Macrophage (b) Lymphocytes
(c) Eosinophils (d) Neutrophils

3- Chemical Mediators of Inflammation that are released by degranulation:
(a) Lysosomal enzymes (b) Prostaglandins
(c) Cytokines (d) Leukotrienes

References:

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