Pathophysiology

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Lecture 4

Inflammation is how the body deals with insult and injury.

is a complex reaction to injurious agents, mechanically (e.g., by pressure or foreign bodies), chemically (e.g., by toxins, acidity, alkalinity), physically (e.g., by temperature), by internal processes (e.g., uremia), and by microorganisms (e.g., bacteria, virus, parasites). The inflammatory response is closely intertwined with the process of repair.

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:

• Inflammatory reaction may cause hypersensitivity reaction to insect bites, drugs and toxin.

• Inflammatory reaction underlies some common chronic diseases such as rheumatoid arthritis,
atherosclerosis and lung fibrosis.

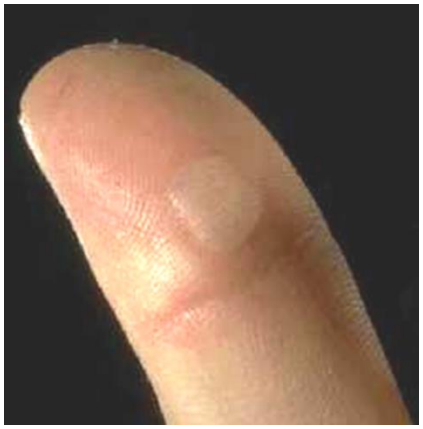
• Repair by fibrosis may lead to disfiguring scars or fibrous band that may cause intestinal obstruction or limit the mobility of joint.

Etiology

The causes of inflammation are many and varied:

- Exogenous causes:
  - Physical agents
    - Mechanical agents: fractures, foreign corps, sand, etc.
    - Thermal agents: burns, freezing
  - Chemical agents: toxic gases, acids, alkaline compounds.
  - Biological agents: bacteria, viruses, parasites
- Endogenous causes:
  - Circulation disorders: thrombosis, infarction, hemorrhage
  - Enzymes activation – e.g. acute pancreatitis
  - Metabolic products deposals – uric acid, urea

Celsus described the local reaction of injury in terms that have come to be known as the cardinal signs of inflammation.



These signs are:

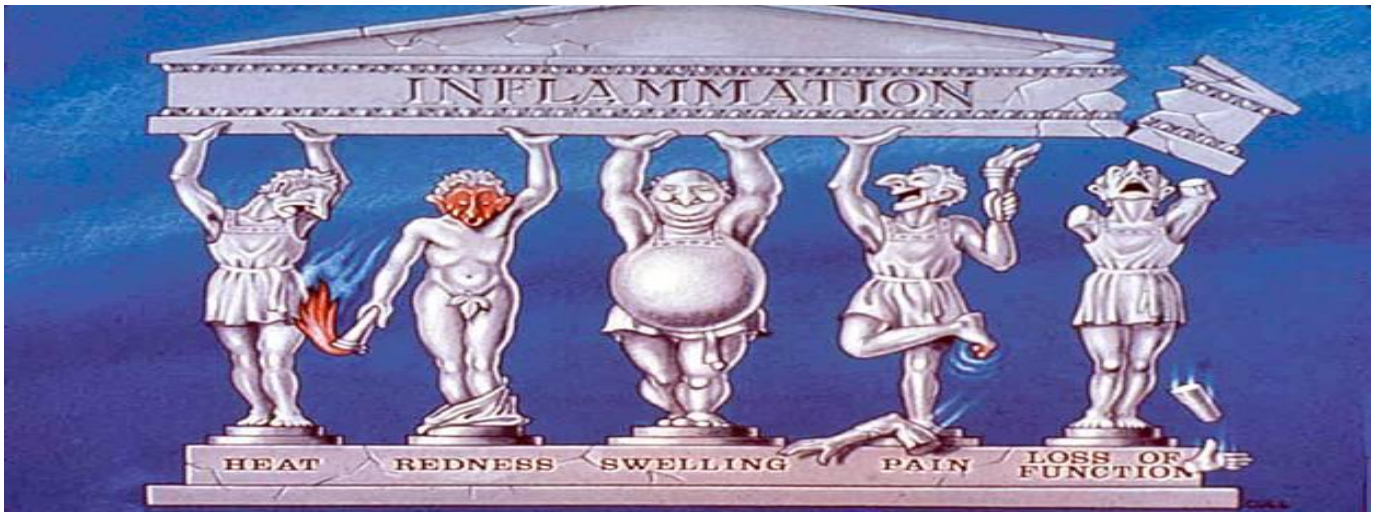
1- Rubor **(redness)**

2- Tumor (**swelling**)

3- Color (**heat**)

4- Dolor (**pain**)

5- Functio laesa, or **loss of function** (In the second century AD, the Greek physician Galen added this fifth cardinal sign)



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- Leucocyte Infiltration.

Components of Inflammatory Responses:

• **Chemical mediators**: Bradykinin cytokines Eosinophils chemotactic factor, Neutrophil chemotactic factor, Leukotrienes, prostaglandins, Platelet activating factor and Histamine.

• **Cell types.**

1- Basophils Storage/release of several chemical mediators.

2- Eosinophils Phagocytic; inactivates some chemical mediators (eg, histamine, LTs).

3- Lymphocytes Key cells of immune reactions; production/release of antibodies, including during inflammation.
4- Macrophages Key phagocytes; primarily after 24 hours from initial inflammatory response.
5- Mast Cells Storage/release of chemical mediators.
6- Neutrophils polymorph nuclear Key phagocytes; within 6 to 12 hours of initial inflammatory response.
7- Platelets Interact with clotting system for clot formation; releases chemical mediators.

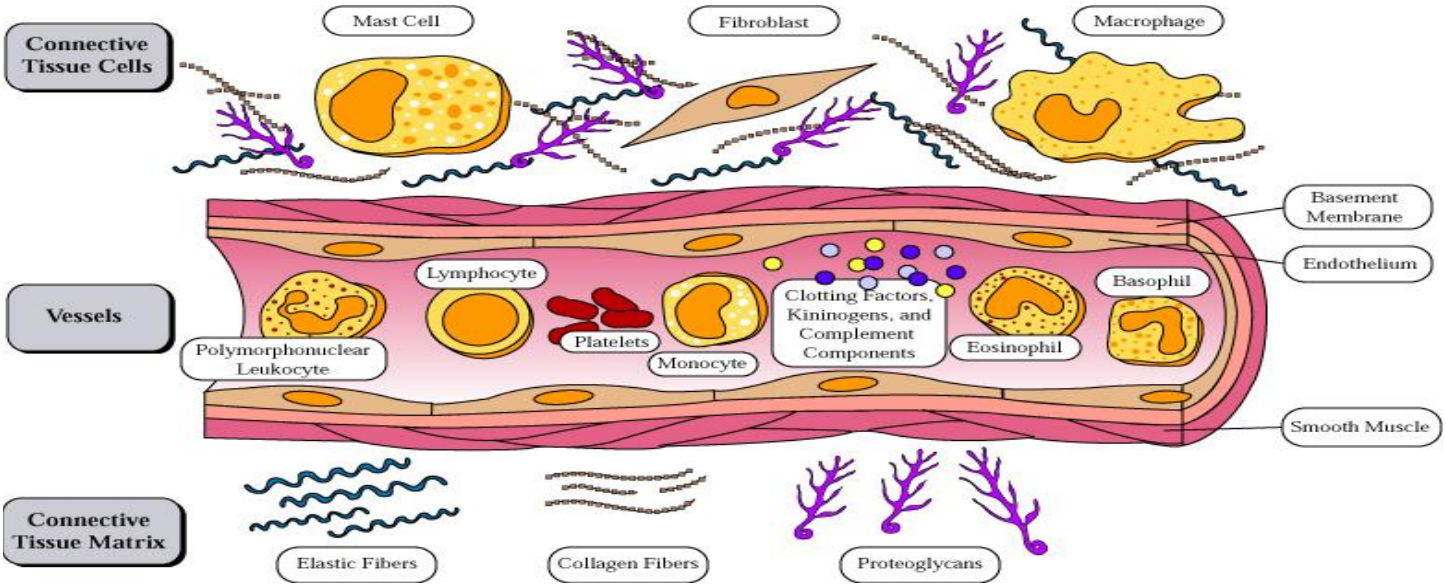
- **Plasma protein systems**

  1- Clotting System Prevents bleeding and traps debris; affects chemotaxis; increases Kinin response.

  2- Complement System Initiates inflammation; chemotaxis; destroys microorganisms; increases vascular permeability.

  3- Kinin system Increases vascular permeability and vasodilation; affects clotting system; causes pain response with

  4-Prostoglandins.



A TRANSUDATE has a low protein content, usually caused by alterations in hydrostatic or oncotic pressure. Implies a hydrostatic (pressure) problem.
An EXUDATE has a high protein content including Immunoglobulins, caused by

increased vascular permeability. Implies an inflammatory process.

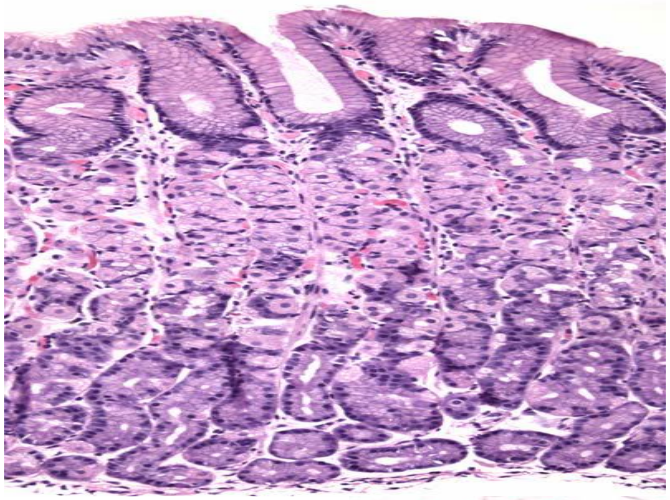
Types of Inflammation

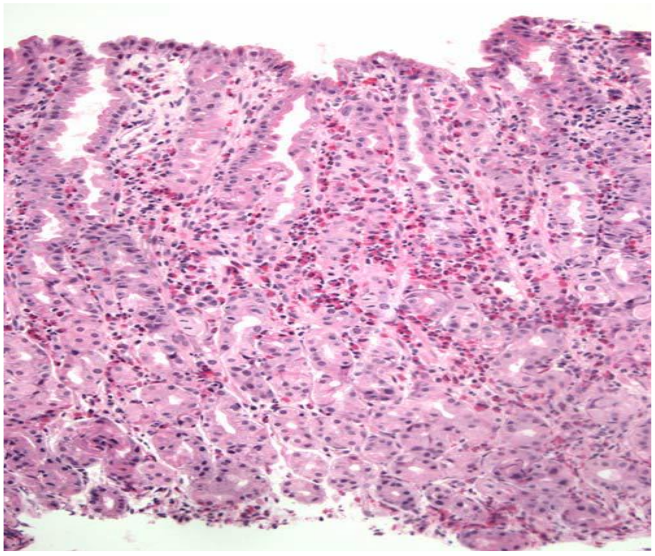
1- **Acute inflammation**: Any inflammation that has a fairly rapid onset, quickly becomes severe, usually manifested for only a few days, but may persist for several days or even a few weeks.

2- **Subacute inflammation**: A condition intermediate between chronic and acute inflammation, exhibiting some of the characteristics of each.

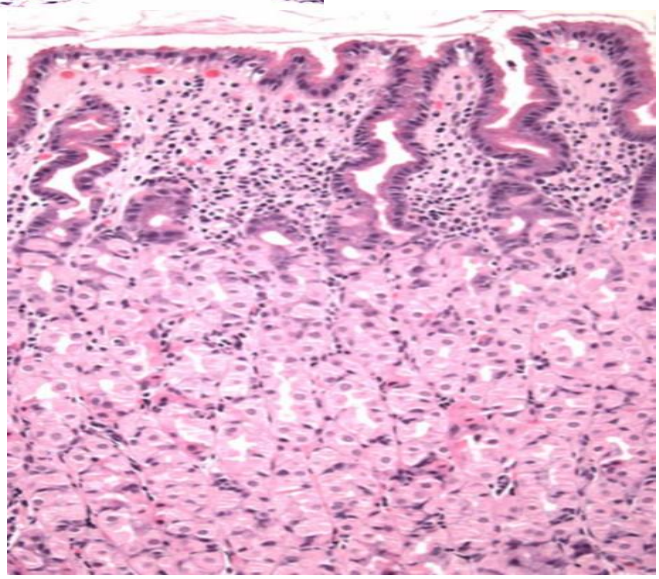
3- **Chronic inflammation**: It may result from failure to eliminate an acute inflammatory irritant, from an autoimmune response to a self-antigen, or may be caused by an innately chronic irritant of low intensity that persists. It is characterized by simultaneous inflammation and repair, with recruitment 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

Stages of Acute Inflammation

1.Transient Vasoconstriction
2.Persistent Vasodilatation and Stasis
3.Increased Permeability of Vessel Walls
4.Fluid Exudate and Formation of Edema
5.Cellular Exudate (Neutrophil Emigration & Accumulation)
6.Resolution or progression

Changes in vascular flow and caliber:

The changes occur in following order:

• Transient vasoconstriction followed by vasodilatation resulting increased blood flow causing heat and redness.

• 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**.

• Peripheral orientation of leukocytes, principally neutrophils, along the vascular endothelium, known as leukocytes margination. Leukocytes then stick to the endothelium and migrate through the vascular wall into the interstitial spaces.

Cellular Events: leukocyte extravasations and phagocytosis:

• Margination - When blood flow slows early in inflammation, white cells fall out of the central column and assume a peripheral position along the endothelial surface.

• Rolling - Individual and rows of leukocytes tumble slowly along the endothelium.

• Pavementation - The leukocytes adhere transiently and finally come to rest at some point where they adhere firmly (resembling ‘pebbles’ or marbles over which a stream runs without disturbing them). In times the endothelium can be lined by white cells.

• 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. Neutrophils, monocytes, lymphocytes, eosinophils and basophils all use the same pathway.

Adhesion and Transmigration:

• Adhesion and transmigration are determined by the binding of complementary adhesion molecules on the leukocytes and endothelial surface (like a key and lock). Chemical mediators (chemo-attractant and certain cytokines) affect these processes by modulating the surface expression or avidity of such adhesion molecules.

• Adhesion molecules belong to the molecular families of selectins, immunoglobulins, integrins and mucin-like glycoproteins.

• The types of emigrating leukocytes vary with the age of the inflammatory lesion and the type of stimulation. In most of forms of acute inflammation, neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours. In pseudomonas infection neutrophils predominate over 2 to 4 days; in viral infection, lymphocytes may be the first cells to arrive; in some hypersensitivity reactions, eosinophils may be the main cell type.

Chemotaxis:

After extravasation, leukocytes emigrate in tissue toward the site of injury by the process of chemotaxis. It is simply defined as locomotion oriented along a chemical gradient.

Chemotactic Agents:

1) *Endogenous Chemical Agents*:

i) Components of complements system, particularly C5a

ii) Products of the lipoxygenase pathway, mainly leukotriene B4.

iii) Cytokines, particularly those of the IL-8 family.

2) *Exogenous*:

i) Bacterial products e.g. (LPS).

Chemical Mediators of Inflammation:

Cell Derived:

• **Preformed mediators in secretory granules:**

o Histamine

o Serotonin

o Lysosomal enzyme

• **Newly Synthesized:**

o Prostaglandins

o Leukotrienes (Lt)

o Platelets activating factors (Plf)

o Activated oxygen species
o Nitric oxide
o Cytokines

Plasma Derived:

• Factor XII (Hageman factor) Activation:
o Bradykinin (Kinin system)
o Fibrin degradation product (Coagulation/fibrinolysis system)
• Complement Activation:
o C3a
o C5a
o C5b-9

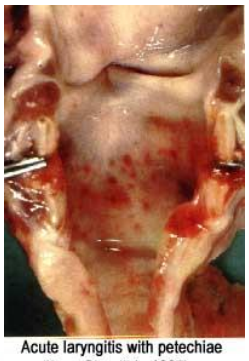
Major Sources of Chemical Mediators:

• Histamine – Mast Cells, basophils, Platelets.
• Serotonin – Platelets
• Lysosomal enzyme – Neutrophils, Macrophages
• Prostaglandins – All types of leukocytes, Platelets, Endothelial cells.
• Leukotrienes – All leukocytes.
• Platelet activating factor – All leukocytes, Endothelial cells.
• Cytokines – Lymphocytes, Macrophages, Endothelium.
• Nitric oxide - Macrophage

General Principle and Highlight of Some Important Mediators:

• Mediators originate either from plasma or from cells.
• Most mediators perform their biological activity by initially binding to specific receptors on target cells. Some have direct enzymatic activity.
• A chemical mediator can stimulate the release of mediators by target cells themselves.
• Mediator can act on one or few target cell types, have widespread target or may even have different effects.
• Most mediators are short lived. There is a system of check and balance in the regulation of mediator action.
• Most mediators have harmful effects.

Morphological Types of Acute inflammation

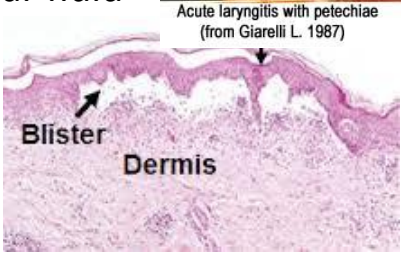

Acute laryngitis with petechiae (from Giarelli L. 1987)

1.**Catarrhal**

Mild Acute Inflammation of the mucous membrane . Excessive mucus fluid secretion and Little Necrosis of tissue. E.g. Common cold = coryza →Nasal obstruction + congestion

2-**Serous Inflammation**

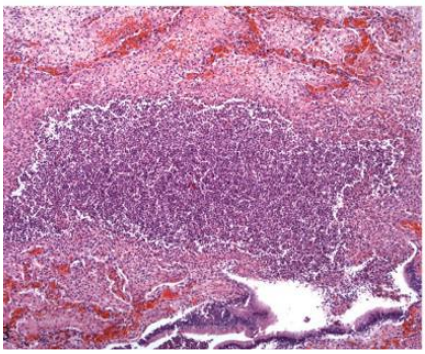
Inflammation of serous membrane. It is characterized by clear fluid in serous cavity (pleural , peritoneal pericardial &synovial cavities) => Effusion (Fluid in serous cavity) Serous Exudate (watery fluid) E.g. skin Blisters caused by Burns OR viral infection



3.**Suppurative (Purulent)**

Large amount of Purulent exudates (pus) caused by pyogenic Bacteria. *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

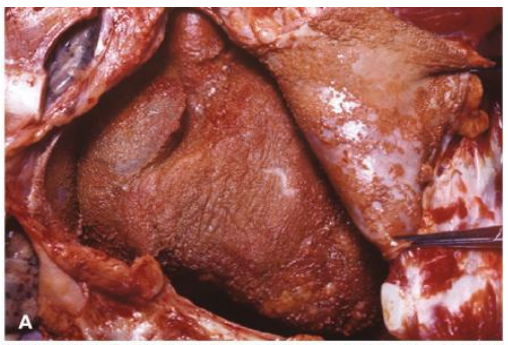
Purulent inflammatory exudate

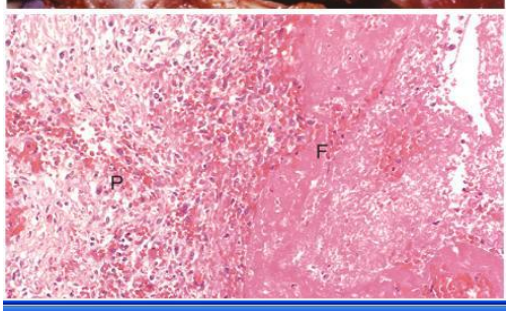
Abscess

Abscess: localized collection of Pus , has central Necrotic cavity, Surrounding by a layer of inflamed granulation tissue (pyogenic membrane) outcome →Burst , surgical Drainage & fibrosis

4. **Fibrinous Inflammation**

- 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 .

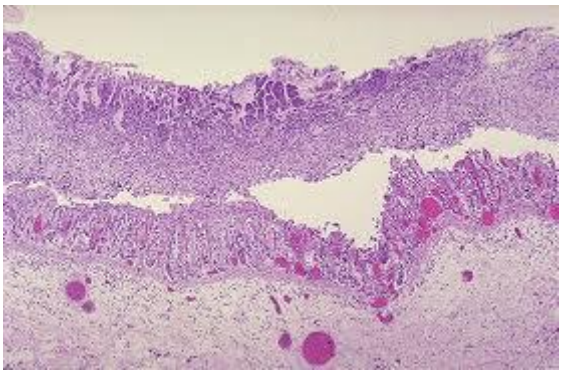




- Fibrinous exudate may be degraded by Fibrinolysis and removed by macrophage resulting in Resolution.
- OR Incomplete Removal of fibrin resulting in organization and scarring with Fibrous Adhesion of pleura OR pericardium.

5.**Pseudo-membranous**

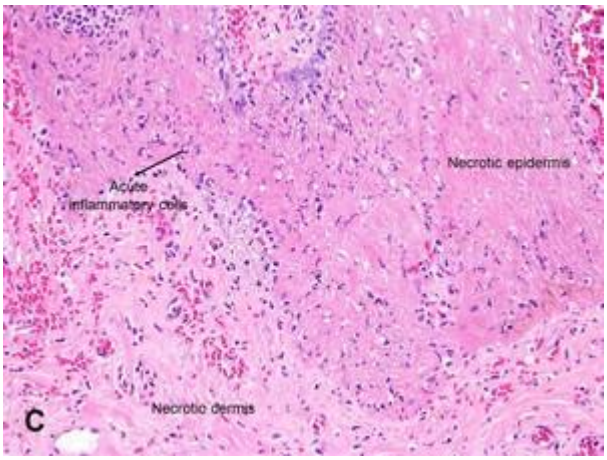
- Very severe ulcerative inflammation of mucous membranes with extensive Necrosis of surface epithelium and severe acute Inflammation of underlying tissue with formation of pseudo membrane, consisting of exudate , fibrin , neutrophils RBC , Bacteria and tissue debris



- white – dirty membrane
- e.g. Diphtheria – Larynx .
  pseudomembranous Colitis – *Clostridium difficile*, lincomycin, clindamycin.

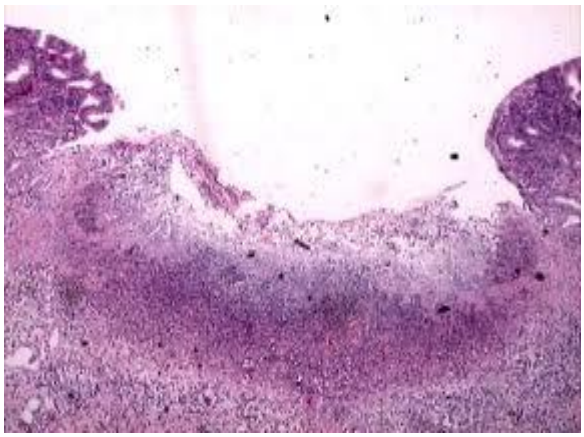
6. **Gangrenous**

Gangrene : Tissue Necrosis with Putrefaction due to invasion with digestion by saprophytic Bacteria – like Putrefaction of meat
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



Outcomes (Consequences) of acute inflammation

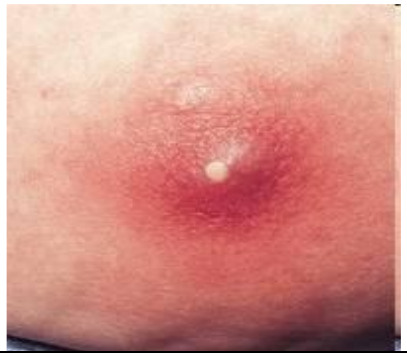
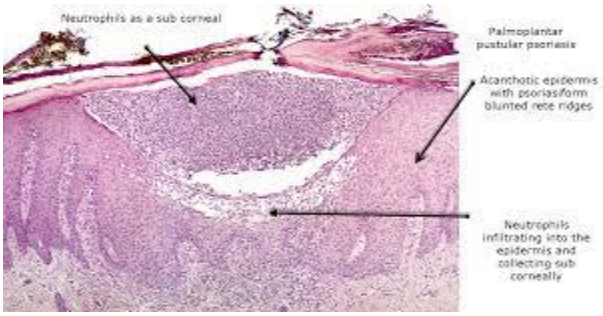
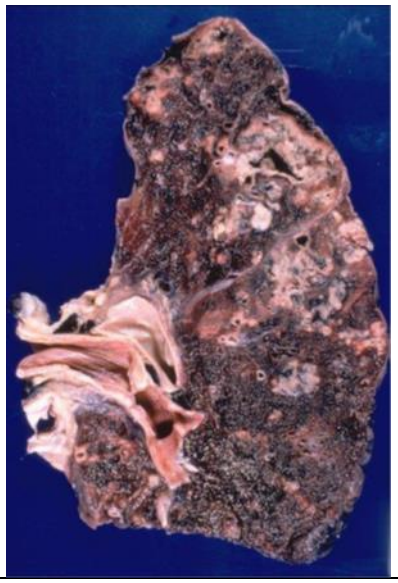
1- Resolution
2- Healing by repair or regeneration
3- Progression into chronic inflammation.
4- Spread
- Direct-e.g. cellulitis
- Lymphatic
- Blood vessels: Pyaemia -Septicemia

5- Death

Systemic Manifestations of Inflammation

•Pyrexia (fever): Will be discussed later
•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.
•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.
•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.
•Anemia
•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). Prolonged infection also induces proliferation of precursors in the bone marrow, caused by increased production of CSFs.
o Most bacterial infection induces Neutrophilia.
o Infectious mononucleosis, mums and German measles produce lymphocytosis.
o Bronchial asthma, hay fever and parasitic infestations induce eosinophilia.
•Leucopenia - Typhoid fever and infection caused by viruses, Rickettsiae, and certain protozoa are associated with leucopenia.

Differences Between Acute and Chronic Inflammation		
Features	**Acute Inflammation**	**Chronic Inflammation**
Onset	**Rapid onset**	**Insidious/delayed onset**
Duration of Course	**Short (Days)**	**Long (Weeks to Months)**
Specificity	**Non-specific**	**Specific as it involves Acquired Immunity**
Cardinal Signs	**1- Pain (Dolor)** **2- Heat (Calor)** **3- Redness (Rubor)** **4- Swelling (Tumor)** **5- Loss of Function (Functio laesa)**	**Absent in any of cardinal signs**
Causative Agents	**1- Physical and Chemical damages** **2- Pathogen invasion** **3- Tissue necrosis** **4- Immune response**	**1- Persistent infection** **2- Presence of foreign bodies** **3- Autoimmunity**
Fundamental Cells	**1- Neutrophils** **2- Macrophages**	**1- Lymphocytes** **o T cells** **o B cells** **2- Macrophages** **3- Fibroblasts**
Fluid Exudation and Edema	**Present**	**Absent**
Fibrosis	**Absent**	**Present**
Angiogenesis	**Absent**	**Present**
Systemic Manifestation	**1- High grade fever** **2- Other 5 cardinal signs**	**1-Low grade fever** **2- Loss of weight** **3- Loss of appetite**
Peripheral Blood Changes	**1-Neutrophil Leukocytosis (bacterial infection)** **2- Lymphocytosis (viral infection)**	**1-Often absent** **2- Increase in the level of Antibodies**
Primary Mediators	**1- Vasoactive amines** **o Serotonin** **o Histamine** **2- Eicosanoids** **o Prostaglandins** **o Thromboxane**	**1-Interferon Gamma** **2- TNF alpha** **3- Growth Factor** **4- ROS** **5- Hydrolyzing enzymes**
Pathogenesis	**1. Increased blood flow** **a. Transient vasoconstriction upon endothelial injury** **b. Followed by released of cytokines that promotes vasodilation leads to warmness and redness of injured area** **2. Increased capillary permeability** **a. Increased volume of blood passes the capillary; increasing Endothelial permeability** **b. IVF moves into ICF, leads to increase concentration of RBC's in the blood vessels (Margination)** **c. Stasis of blood leads to Exudation** **3. Migration of neutrophils** **a. Rolling of Neutrophils** **b. Adhesion** **c. Diapedesis into injured site** **4. Chemotaxis** **a. Movements of Neutrophils to the injurious agents**	**1. Infiltration of Mononuclear Phagocytic Cells** **a. Macrophages** **i. Circulate as monocytes and reach site of injury within 24 – 48 hrs. and transform** **ii. Activated by numerous cytokines from the injured site** **b. T and B cells** **i. Recruited and activated by Antigen Presenting Cells like macrophages and dendritic cells** **ii. B cells will be become Plasma Cells and produce Antibodies** **iii. T cells will produce cytokine to activated the B cells and also macrophages** **2. Tissue destructions** **a. Due to massive production of** **i. ROS** **ii. Hydrolytic enzymes** **b. Inflammatory responses** **3. Tissue repair** **a. Angiogenesis at the injured sites**

	5. Leukocytes recruitment and activation **a. Leukocytosis**	**b. Formation of Granulomas** **i. Foreign body Granuloma** **ii. Immune Granuloma** **c. Fibrosis**
	Gross	**Microscopy**
Acute Inflammation	**Redness** **- Warmth** **- Tender** **- Swollen** 	**- Massive infiltration of** **o Neutrophils** **o PMN's** **- Dilation and congestion of blood vessels** **- Exudation of the affected area** 
Chronic Inflammation	**Ulceration** **o Eg** **- Chronic peptic ulcer** **- Tropical ulcer of the foot** **- Thickening of the wall of hollow organ** **o Eg** **- Crohn's disease** **- Cholecystitis** **- Changes in tissue texture** **o Necrosis** **o Fibrosis** 	**Granulomatous Inflammation** **o Can be either** **- Caseation** **- Non-caseating** **o Characterized by accumulation of Macrophages which appeared like epithelial cells (epitheloid)** **o Accumulation of Lymphocytes** **- Non-granulomatous Inflammation** **o Scattered accumulation of** **- Lymphocytes** **- Macrophages** **- Plasma cells** **o Proliferation of** **- Fibroblasts** **- Blood vessels**