Inflammation

Introduction

Definition: Inflammation is a local response (reaction) of living vascularized tissues to endogenous and exogenous stimuli. The term is derived from the Latin "inflammare" meaning to burn. Inflammation is fundamentally destined to localize and eliminate the causative agent and to limit tissue injury. Thus, inflammation is a physiologic (protective) response to injury. Inflammation is itself not to be considered as a disease but as a salutary مفيد operation consequent ينتج عنها either to some violence or to some diseases".

Causes: Causes of inflammation are apparently causes of diseases such as:

1. **physical agents** - mechanical injuries, alteration in temperatures and pressure, radiation injuries.
2. **chemical agents**- including the increasing lists of drugs and toxins.
3. **biologic agents (infectious)**- bacteria, viruses, fungi, parasites
4. **immunologic disorders**- hypersensitivity reactions, autoimmunity, immunodeficiency states etc
5. **genetic/metabolic disorders**- examples gout, diabetes mellitus etc…

Examples of diseases with specific inflammation

•syphilis

•tuberculosis

•leprosy

•glanders (syn: equinia, farcy, or malleus)

•scleroma

Nomenclature:

The nomenclatures of inflammatory lesion are usually indicated by the suffix 'itis'. Thus, inflammation of the appendix is called appendicitis and of meninges as meningitis, etc.… However, like any rule, it has its own exceptions examples pneumonia, typhoid fever, etc….

Classification:

Inflammation is classified crudely based on duration of the lesion and histologic appearances into acute and chronic inflammation.

•According to the course:

•acute,

•subacute,

•chronic

•According to the predominant phase:

•alterative,

•exudative,

•proliferative (productive)

•According to the causative factors:

•trivial,

•specific

Acute inflammation

A. 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.

B. It is characterized by exudation of fluids and plasma proteins and the emigration of predominantly neutrophilic leucocytes to the site of injury.

The five cardinal signs of acute inflammation are

1. **Redness** (rubor) which is due to dilation of small blood vessels within damaged tissue as it occurs in cellulitis.

2. **Heat** (calor) which results from increased blood flow (hyperemia) due to regional vascular dilation
3. **Swelling** (tumor) which is due to accumulation of fluid in the extravascular space which, in turn, is due to increased vascular permeability.
4. **Pain** (dolor), which partly results from the stretching & destruction of tissues due to inflammatory edema and in part from pus under pressure in, as abscess cavity. Some chemicals of acute inflammation, including bradykinins, prostaglandins and serotonin are also known to induce pain.
5. **Loss of function**: The inflamed area is inhibited by pain while severe swelling may also physically immobilize the tissue.

Events of acute inflammation:

Acute inflammation is categorized into an early vascular and a late cellular responses.

1) The **Vascular response** has the following steps:

a) Immediate (momentary) vasoconstriction in seconds due to neurogenic or chemical stimuli.

b) Vasodilatation of arterioles and venules resulting in increased blood flow.

c) After the phase of increased blood flow there is a slowing of blood flow & stasis due to increased vascular permeability that is most remarkably seen in the post-capillary venules. The increased vascular permeability oozes protein-rich fluid into extravascular tissues. Due to this, the already dilated blood vessels are now packed with red blood cells resulting in stasis. The protein-rich fluid which is now found in the extravascular space is called exudate. The presence of the exudates clinically appears as swelling. Chemical mediators mediate the vascular events of acute inflammation.

2) **Cellular response**

The cellular response has the following stages:

A. Migration, rolling, pavementing تراصف, & adhesion of leukocytes

B. Transmigration of leukocytes

C. Chemotaxis

D. Phagocytosis

Normally blood cells particularly erythrocytes in venules are confined to the central (axial) zone and plasma assumes the peripheral zone. As a result of increased vascular permeability , more and more neutrophils accumulate along the endothelial surfaces (peripheral zone).

A) **Migration, rolling, pavementing, and adhesion of leukocytes**

- ❖ Margination is a peripheral positioning of white cells along the endothelial cells.
- ❖ Subsequently, rows of leukocytes tumble تعثر slowly along the endothelium in a process known as rolling.
- ❖ In time, the endothelium can be virtually lined by white cells. This appearance is called pavementing رصف
- ❖ Thereafter, the binding of leukocytes with endothelial cells is facilitated by cell adhesion molecules such as selectins, immunoglobulins, integrins, etc which result in adhesion of leukocytes with the endothelium.

Neutrophil moving to the site of infection - YouTube.MP4

B). **Transmigration of leukocytes**

- ❖ Leukocytes escape from venules and small veins but only occasionally from capillaries. The movement of leukocytes by extending pseudopodia through the vascular wall occurs by a process called diapedesis انسلال.
- ❖ The most important mechanism of leukocyte emigration is via widening of inter-endothelial junctions after endothelial cells contractions. The basement membrane is disrupted and resealed thereafter immediately.

C). **Chemotaxis:**

- ❖ Chemotaxis is a unidirectional attraction of leukocytes from vascular channels towards the site of inflammation within the tissue space guided by chemical gradients (including bacteria and cellular debris) .
- ❖ The most important chemotactic factors for neutrophils are components of the complement system (C5a), bacterial and mitochondrial products of arachidonic acid metabolism such as leukotriene B4 and cytokines , Interleukin-L(IL-8). All granulocytes, monocytes and to lesser extent lymphocytes respond to chemotactic stimuli.
- ❖ How do leukocytes "see" or "smell" the chemotactic agent? This is because receptors on cell membrane of the leukocytes react with the chemo-attractants, resulting in the activation of phospholipase C that ultimately leads to release of cytosolic calcium ions and these ions trigger cell movement towards the stimulus.

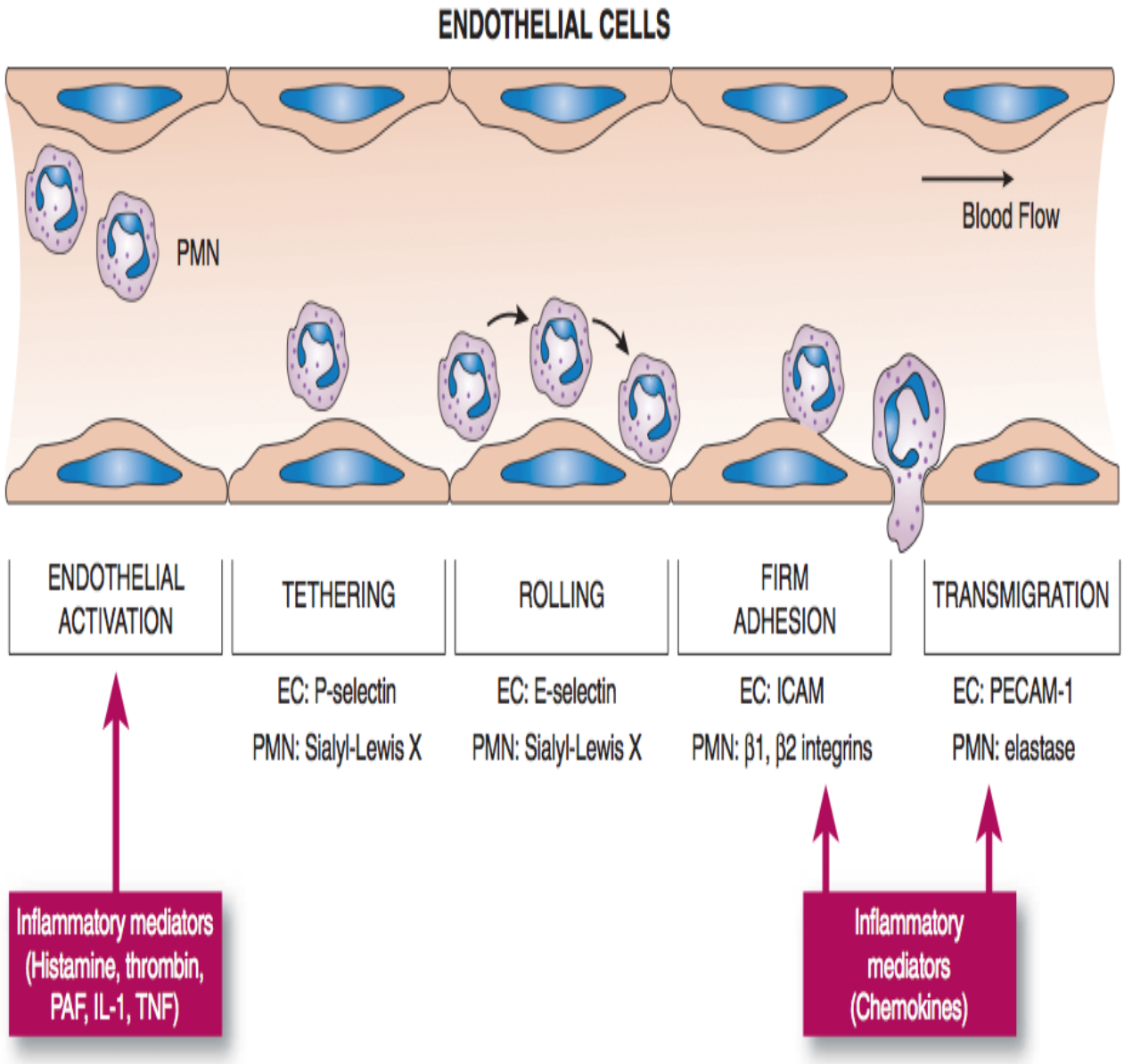


FIGURE 2-22. Neutrophil adhesion and extravasation. Inflammatory mediators activate endothelial cells to increase expression of adhesion molecules. Sialyl-Lewis X on neutrophil P-selectin glycoprotein-1 (PSGL-1) and E-selectin ligand (ESL-1) binds to P- and E-selectins to facilitate tethering and rolling of neutrophils. Increased integrins on activated neutrophils bind to intercellular adhesion molecule-1 (ICAM-1) on endothelial cells to form a firm attachment. Endothelial cell attachments to one another are released and neutrophils then pass between separated cells to enter the tissue. *EC* = endothelial cell; *IL* = interleukin; *PAF* = platelet-activating factor; *PMN* = polymorphonuclear neutrophil; *TNF* = tumor necrosis factor.

***General definition*:**

inflammations whose principal histologic findings include exudation of blood serum and extravasation of blood cells into the inflamed area.

may be classified as follows according to the principal components of the exudate:

•serous

•catarrhal

•mucus, serous, purulent, hemorrhagic

•fibrinous

•croupous and diphtheretic

•purulent

•abscess, phlegmon and empyema

•hemorrhagic

•putrefactive

D) **Phagocytosis**

Phagocytosis is the process of engulfment and internalization by specialized cells of particulate material, which includes invading microorganisms, damaged cells, and tissue debris. These phagocytic cells include polymorphonuclear leukocytes (particularly neutrophiles), monocytes and tissue macrophages.

Phagocytosis involves three distinct steps.

1). **Recognition and attachment** of the particle to be ingested by the leukocytes: Phagocytosis is enhanced if the material to be phagocytosed is coated with certain plasma proteins called **opsonins**. These opsonins promote the adhesion between the particulate material and the phagocyte's cell membrane.

2). **Engulfment:** During engulfment, extension of the cytoplasm (pseudopods) flow around the object to be engulfed, eventually resulting in complete enclosure of the particle within the phagosome created by the cytoplasmic membrane of the

phagocytic cell. As a result of fusion between the phagosome and lysosome, a phagolysosome is formed and the engulfed particle is exposed to the degradative lysosomal enzymes.

3) **Killing or degradation**

The ultimate step in phagocytosis of bacteria is killing and degradation. There are two forms of bacterial killing

a). **Oxygen-independent mechanism:**

This is mediate by some of the constituents of the primary and secondary granules of polymorphonuclear leukocytes. These include:

Bactericidal permeability increasing protein (BPI) , Lysozymes, Lactoferrin, and Defenses

It is probable that bacterial killing by lysosomal enzymes is inefficient compared with the oxygen dependent mechanisms. The lysosomal enzymes are, however, essential for the degradation of dead organisms within phagosomes.

b) **Oxygen-dependent mechanism**:

There are two types of oxygen- dependent killing mechanisms

i) **Non-myeloperoxidase dependent**

The oxygen - dependent killing of microorganisms is due to formation of reactive oxygen species such as hydrogen peroxide (H2O2), super oxide (**O2)** and hydroxyl ion (HO-) and possibly single oxygen (1O2). These species have single unpaired electrons in their outer orbits that react with molecules in cell membrane or nucleus to cause damages.

ii) **Myeloperoxidase–dependent**

The bactericidal activity of **H2O2** involves the lysosomal enzyme myeloperoxidase, which in the presence of halide ions converts H2O2 to hypochlorous acid (HOCI). This **H2O2** – halide - myeloperoxidase system is the most efficient bactericidal killing system in neutrophils. A similar mechanism is also effective against fungi, viruses, protozoa and helminthes.

Like the vascular events, the cellular events (i.e. the adhesion, the transmigration, the chemotaxis, & the phagocytosis) are initiated or activated by chemical mediators.

IV. Chemical mediators of inflammation

Chemical mediators account for the events of inflammation. Inflammation has the following sequence:

Cell injury $\rightarrow$ Chemical mediators $\rightarrow$ Acute inflammation (i.e. the vascular & cellular events).

Sources of mediators:

The chemical mediators of inflammation can be derived from plasma or cells.

a) Plasma-derived mediators:

i) Complement activation

- increases vascular permeability (C3a,C5a)
- activates chemo-taxis (C5a)
- opsoninization (C3b,C3bi)

ii) Factor XII (Hageman factor) activation

Its activation results in recruitment توظيف of four systems: the kinin, the clotting, the fibrinolysis and the compliment systems.

b) Cell-derived chemical mediators:

Cell-derived chemical mediators include:

Cellular mediators	Cells of origin	Functions
Histamine	**Mast cells, basophiles**	**Vascular leakage & platelets**
Serotonin	**Platelets**	**Vascular leakage**
Lysosomal enzymes	**Neutrophils**	**Bacterial & tissue destruction macrophages**
Prostaglandins	**All leukocytes**	**Vasodilatation, pain, fever**
Leukotriene	**All leukocytes**	**LB4**
Chemo-attractant	**LC4, LCD4, & LE4**	**Broncho and vasoconstriction**
Platelet activating factor	**All leukocytes**	**Bronchoconstriction and WBC priming** فتيله
Activated oxygen species	**All leukocytes**	**Endothelial and tissue damage**
Nitric oxide	**Macrophages**	**Leukocyte activation**
Cytokines	**Lymphocytes, macrophages**	**Leukocyte activation**

Most mediators perform their biologic activities by initially binding to specific receptors on target cells. Once activated and released from the cells, most of these mediators are short lived. Most mediators have the potential to cause harmful effect

Morphology of acute inflammation

Characteristically, the acute inflammatory response involves production of exudates. An exudate is an edema fluid with high protein concentration, which frequently contains inflammatory cells.

 A transudate is simply a non-inflammatory edema caused by cardiac, renal, Under-nutritional, & other disorders.

The differences between an exudate and a transudate are:-

	Exudate	Transudate

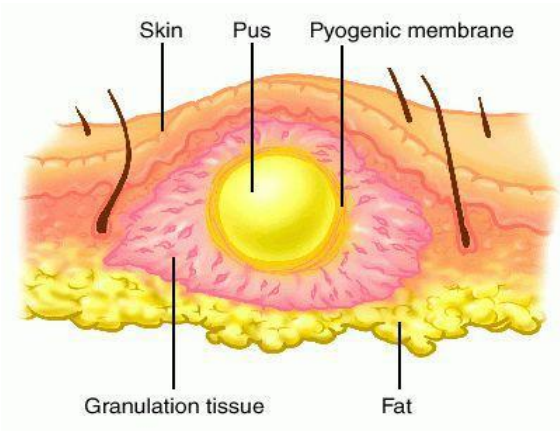
Cause	Acute inflammation.	Non-inflammatory disorders
Appearance	Colored, turbid, hemorrhagic	Clear, translucent or pale yellow
Specific gravity:	Greater than or equal to 1.020	Much less
Spontaneous coagulability:	Yes	No
Protein content:	>3gm %	
Cells:	Abundant WBC, RBC, & Cell debris usually present	Only few mesothelial cells
Bacteria:	Present	Absent.

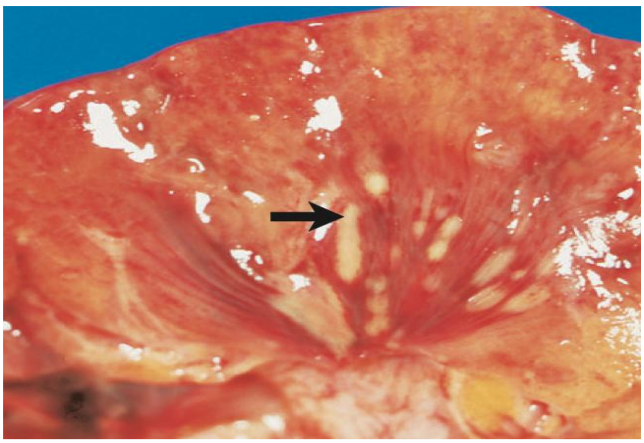
There are different morphologic types of acute inflammation:

1) Serous inflammation

This is characterized by an outpouring of a thin fluid that is derived from either the blood serum or secretion of mesothelial cells lining the peritoneal, pleural, and pericardial cavities.

Abscess *Definition*: An abscess is an accumulation of pus with tissue destruction and a cavity formation.
Examples:
— Pulmonary abscesses.
— Cerebral abscesses.
— Kidney abscesses.
— Liver abscesses.
— Furuncles are abscess-forming inflammations of the hair follicle usually following staphylococcal infection.





2) Fibrinous inflammation

- ❖ More severe injuries result in greater vascular permeability that ultimately leads to exudation of larger molecules such as fibrinogens through the vascular barrier.
- ❖ Fibrinous exudate is characteristic of inflammation in serous body cavities such as the pericardium (butter and bread appearance) and pleura.

Course of fibrinous inflammation include:

- ❖ Resolution by fibrinolysis
- ❖ Scar formation between parietal and visceral surfaces i.e. the exudates get organized
- ❖ Fibrous strand formation that bridges the pericardial space.

Types of Fibrinous Inflammation

•Fibrinous Parenchymal Inflammation

•Fibrinous Serosal Inflammation

•Fibrinous Mucosal Inflammation (Croupous and Diphtheria).

Fibrinous Parenchymal

Inflammation Definition: Exudative inflammation with exudation of fibrin on the inner surfaces of the PULMONARY parenchyma (pulmonary alveoli).
Example: — Lobar pneumonia in the gray hepatization stage

Fibrinous Serosal Inflammation

Definition: Exudative fibrinous inflammations of the serous membranes may occur as a reaction of the serosa to other underlying disorders (serositis) or in the presence of tissue injury occurring in the serosa (such as infarction).

Fibrinous Serosal Inflammation *Morphology:*

•serosa will appear dull where slight amounts of fibrin are present;

•massive exudation of serum will produce villous deposits of fibrin (as in fibrinous pericarditis or “hairy heart”)

•Later the fibrin deposits are absorbed by histiocytes and transformed into scar tissue, creating adhesions between the layers of the serosa.

Fibrinous Mucosal Inflammation

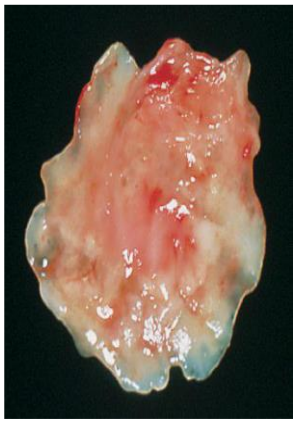
General pathogenesis: In fibrinous inflammations in the mucosa, the fibrinous exudation process is usually preceded by superficial necrosis.

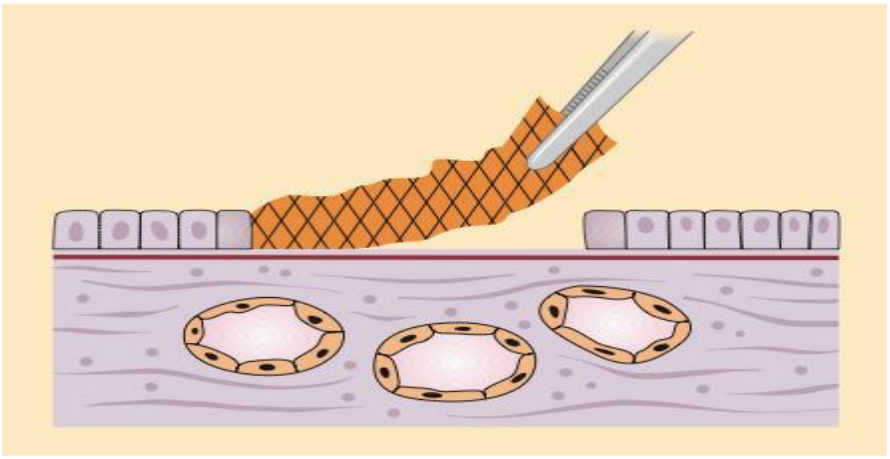
Types:

•Croupous Type and Diphtheria Type

Croupous Type

Definition: Exudative inflammation in which a wide area of fibrinous exudate forms an easily removable pseudomembrane covering the necrosis, which is limited to the mucosal epithelium , Expl: Diphtheric laryngotracheitis.



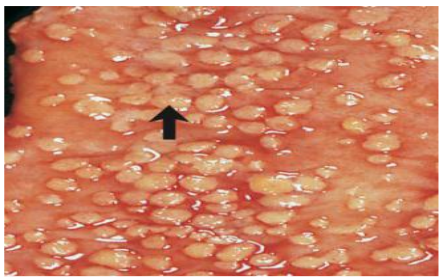


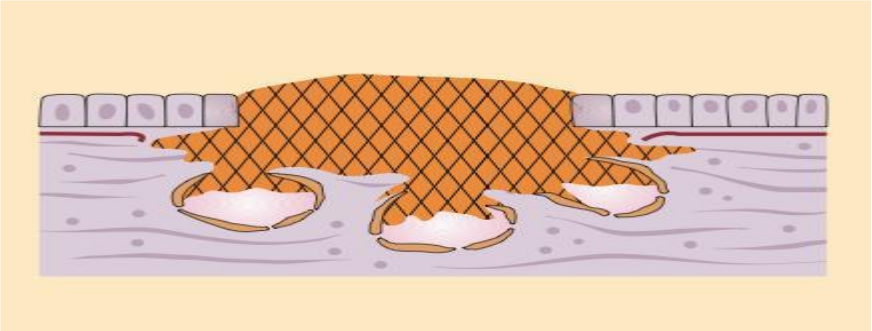
Diphtheria Type

Definition: Exudative inflammation in which necrosis extending into the submucosa is covered by a wide area of fibrinous exudate in the form of an adhesive pseudomembrane that can only be forcibly removed.

Expl : Diphtheric tonsillitis and pharyngitis, Dysentery .

•Antibiotic associated colitis (pseudomembranous colitis).





3) Suppurative (Purulent) inflammation

This type of inflammation is characterized by the production of a large amount of pus. Pus is a thick creamy liquid, yellowish or blood stained in color and composed of:

- A large number of living or dead leukocytes (pus cells)
- Necrotic tissue debris
- Living and dead bacteria
- Edema fluid

There are two types of suppurative inflammation:

A) **Abscess formation**:

An abscess is a circumscribed accumulation of pus in a living tissue. It is encapsulated by a so-called pyogenic membrane, which consists of layers of fibrin, inflammatory cells and granulation tissue.

B) **Acute diffuse (phlegmonous) inflammation**

This is characterized by diffuse spread of the exudate through tissue spaces. It is caused by virulent bacteria (eg. streptococci) without either localization or marked pus formation. Example: Cellulitis (in palmar spaces).

Empyema

Definition: Suppurative inflammation in a body cavity.

Pathogenesis: An empyema usually occurs when a suppurative inflammation of an organ breaks through into an adjacent cavity.

Examples:

•Pericardial, peritoneal, and pleural empyema

•Gallbladder and appendiceal empyema;

•Middle ear and nasal sinus empyema;

•Pyosalpinx (pus in the uterine tube);

•Pyocephalus (pus in the cranial cavity);

•Hypopyon (pus in the anterior chamber of the eye).

Phlegmon

Definition: Diffuse suppurative inflammation that spreads primarily in loose fibrous connective tissue without sharp demarcation.

Examples:
— Muscular phlegmon;
— Phlegmon of the floor of the mouth;
— Mediastinal phlegmon;
— Phlegmon of the walls of hollow organs (such as phlegmon in cholecystitis, appendicitis).
— Erysipelas, inflammation in the connective tissue of the skin usually caused by beta-hemolytic streptococci involving a map-like pattern of erythema and swelling;

4) Catarrhal نزلي inflammation

This is a mild and superficial inflammation of the mucous membrane. It is commonly seen in the upper respiratory tract following viral infections where mucous secreting glands are present in large numbers, eg. Rhinitis.

5) Pseudomembranous inflammation

✠ The basic elements of pseudomembranous inflammation are extensive confluent necrosis of the surface epithelium of an inflamed mucosa and severe acute

inflammation of the underlying tissues. The fibrinogens in the inflamed tissue coagulate within the necrotic epithelium. The fibrinogen, which contain the neutrophilic polymorphs, red blood cells, bacteria and tissue debris form a false (pseudo) membrane which forms a white or colored layer over the surface of inflamed mucosa.

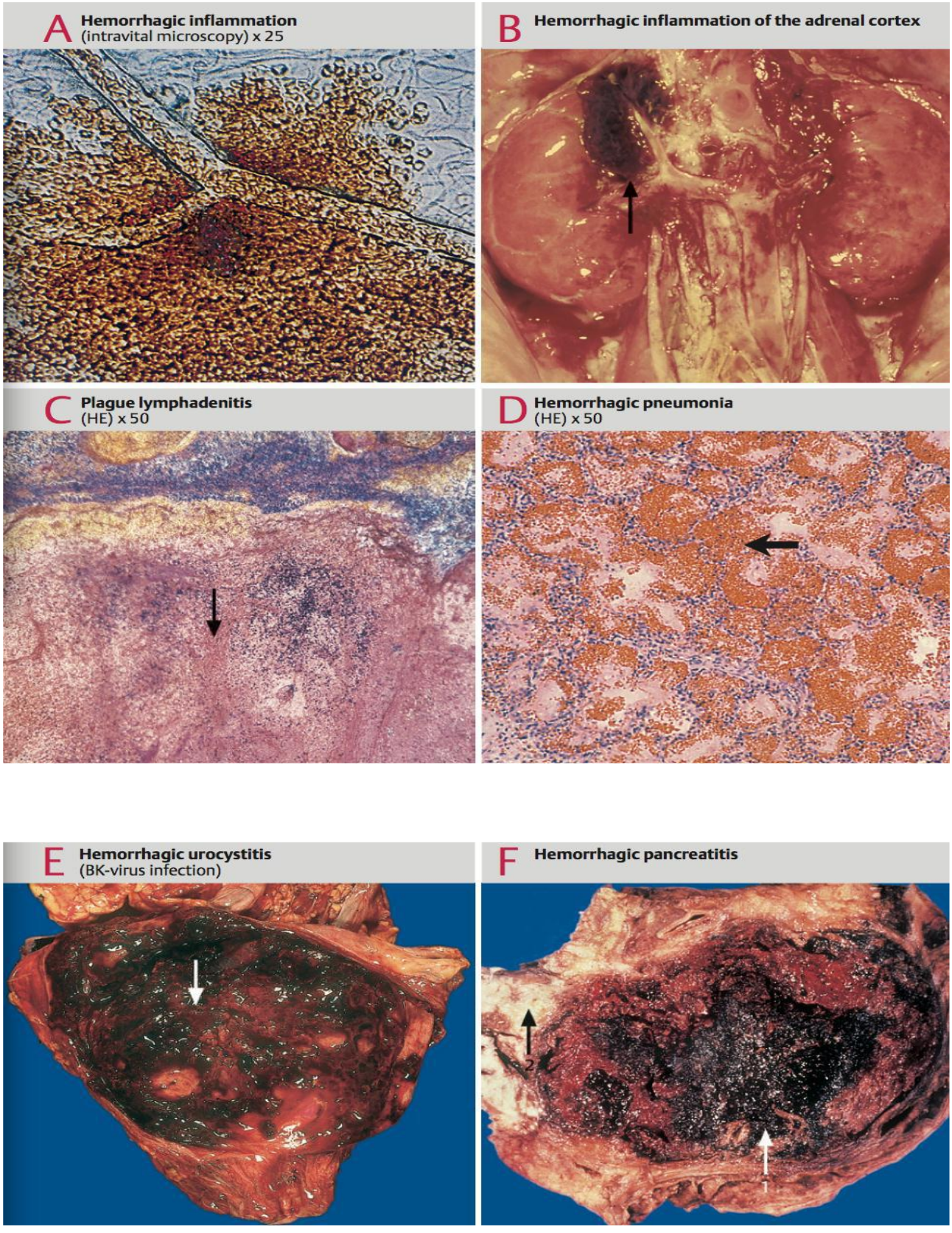
- Pseudomembranous inflammation is exemplified by Diphtheritic infection of the pharynx or larynx.

Hemorrhagic Inflammation

Definition: Exudative inflammation involving microvascular injury with massive microvascular bleeding, producing an exudate with a high erythrocyte content.
Biologic purpose: Exudative inflammation due to severe vascular injury.
Morphology: The inflamed area is usually necrotic and filled with blood.
Etiologic factors:
— bacterial exotoxins and endotoxins;
— viral cytopathic effect on endothelium;
— proteolytic tissue destruction;
— cytotoxic injury in hypersensitivity type.

Hemorrhagic Inflammation Examples:

- Plague
- Influenzal Pneumonia
- Disorders Associated with Enterohemorrhagic E. Coli
- Anthrax
- Viral Hemorrhagic Fever
- Acute Pancreatitis


A Hemorrhagic inflammation
(intravital microscopy) x 25
B Hemorrhagic inflammation of the adrenal cortex
C Plague lymphadenitis
(HE) x 50
D Hemorrhagic pneumonia
(HE) x 50
E Hemorrhagic urocystitis
(BK-virus infection)
F Hemorrhagic pancreatitis

Effects of acute inflammation:

A. Beneficial effects

1. **Dilution of toxins**: The concentration of chemical and bacterial toxins at the site of inflammation is reduced by dilution in the exudate and its removal from the site by the flow of exudates from the venules through the tissue to the lymphatics.

2. Protective antibodies: Exudation results in the presence of plasma proteins including antibodies at the site of inflammation. Thus, antibodies directed against the causative organisms will react and promote microbial destruction by phagocytosis or complement-mediated cell lysis.

3. **Fibrin formation**: This prevents bacterial spread and enhances phagocytosis by leukocytes.
4. **Plasma mediator systems provisions** احكام: The complement, coagulation, fibrinolytic, & kinin systems are provided to the area of injury by the process of inflammation.
5. **Cell nutrition**: The flow of inflammatory exudates brings with it glucose, oxygen and other nutrients to meet the metabolic requirements of the greatly increased number of cells. It also removes their solute waste products via lymphatic channels.
6. **Promotion of immunity**: Micro-organisms and their toxins are carried by the exudates, either free or in phagocytes, along the lymphatic's to local lymph nodes where they stimulate an immune response with the generation of antibodies and cellular immune mechanisms of defense.

B. Harmful effects

1. **Tissue destruction:** Inflammation may result in tissue necrosis which may, in turn, incite inflammation.
2. **Swelling:** The swelling caused by inflammation may have serious mechanical effects at certain locations. Examples include acute epiglottitis with

interference in breathing; Acute meningitis and encephalitis with effects of increased intracranial pressure.

3. **Inappropriate response:** The inflammatory reactions seen in hypersensitivity is inappropriate (i.e. exaggerated).

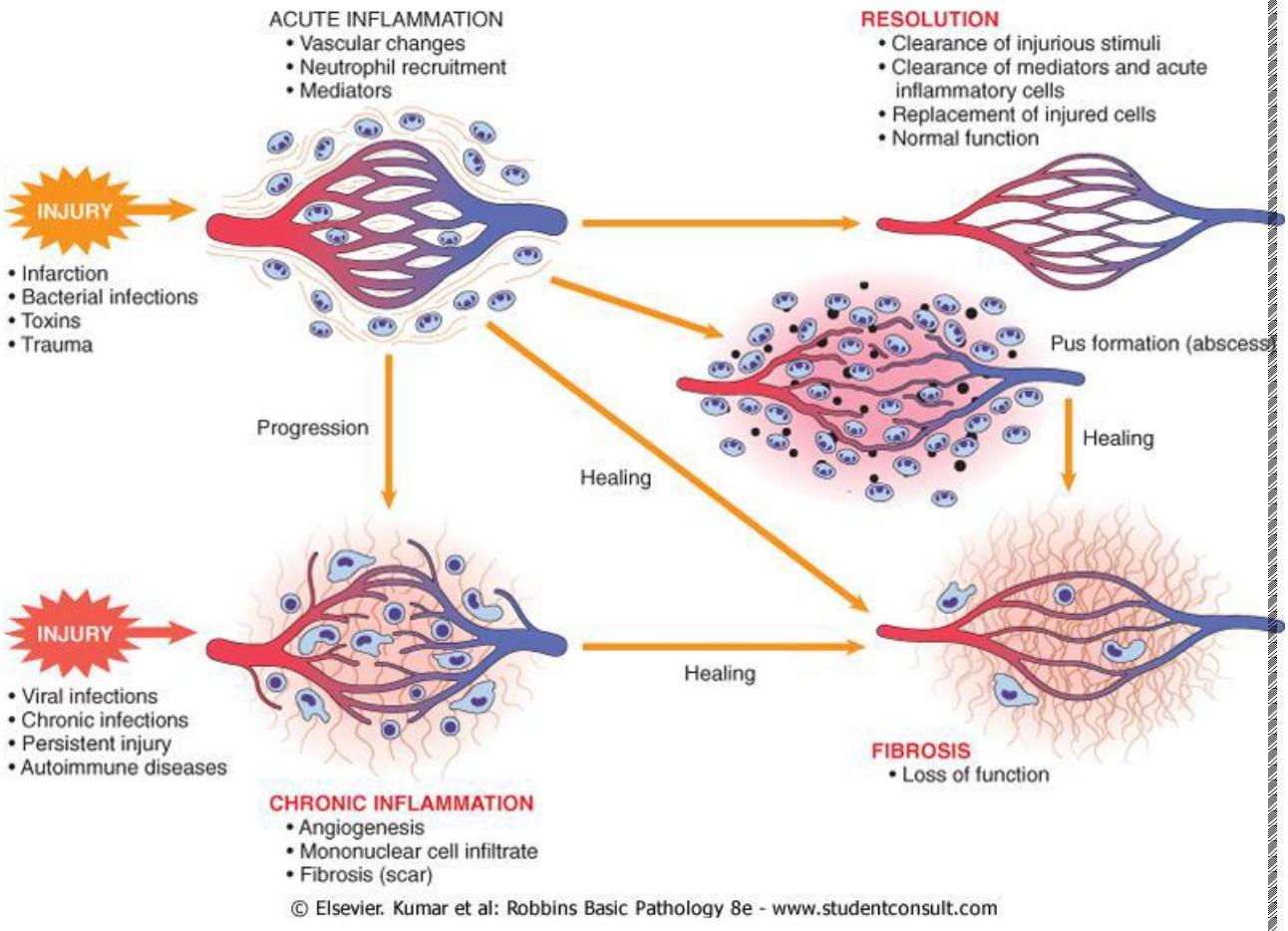
Course of acute inflammation

Acute inflammation may end up in:

1. Resolution انحلال: i.e. complete restitution تعويض of normal structure and function of the tissue, eg. lobar pneumonia.
2. Healing by fibrosis (scar ندبة formation).
3. Abscess formation . However, if it is left untouched, it may result in:-

a) **Sinus formation** - when an abscess cavity makes contact with only one epithelial lining.

b) **Fistula ناسور formation**: when an abscess tract connects two epithelial surfaces. Or very rarely to septicemia or Pyemia with subsequent metastatic abscess in heart, kidney, brain etc.



Chronic inflammation

Definition: Chronic inflammation is a prolonged inflammatory process (weeks or months) where an active inflammation, tissue destruction and attempts to repair are proceeding simultaneously.

Causes of chronic inflammation:

1. **Persistent infections**

Certain microorganisms associated with intracellular infection such as tuberculosis, leprosy, certain fungi etc characteristically cause chronic inflammation. These organisms are of low toxicity and evoke delayed hypersensitivity reactions.

2. **Prolonged exposure to non-degradable but partially toxic substances:** either endogenous lipid components which result in atherosclerosis or exogenous substances such as silica and asbestos.

3. **Progression from acute inflammation:** Acute inflammation almost always progresses to chronic inflammation following:

a. Persistent suppuration as a result of un-collapsed abscess cavities, foreign body materials (dirt, cloth, wool, etc), or a sinus/fistula from chronic abscesses.

4. **Autoimmunity.** Autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosis are chronic inflammations from the outset.

Cells of chronic inflammation:

1. **Monocytes and Macrophages** are the primary cells in chronic inflammation. Macrophages , in the liver (Kupffer cells), spleen, lymph nodes (sinus histiocytes), lungs (alviolar macrophages), bone marrow, brain (microglia), skin (Langerhan's cells), etc…. These cells constitute the mononuclear-phagocytic system. Macrophages are scavenger cells of the body.
2. . **T-Lymphocytes** are primarily involved in cellular immunity with lymphokine production, and they are the key regulator and effector cells of the immune system.
3. . **B-lymphocytes and Plasma cells** produce antibody directed either against persistent antigen in the inflammatory site or against altered tissue components.
4. . **Mast cells and eosinophils** appear predominantly in response to parasitic infestations & allergic reactions.
5. **Neutrophils.** Though **neutrophils** are hallmarks of acute inflammatory reactions, large numbers of neutrophils may be seen in some forms of chronic inflammation, notably chronic osteomyelitis, actinomycosis, & choric lung diseases induced by smoking and other stimuli.

Differentiation points between acute and chronic inflammations include:

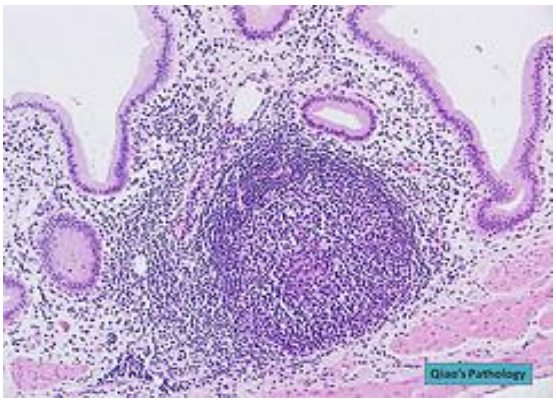
Characteristics	**Acute inflammation**	**Chronic inflammation**

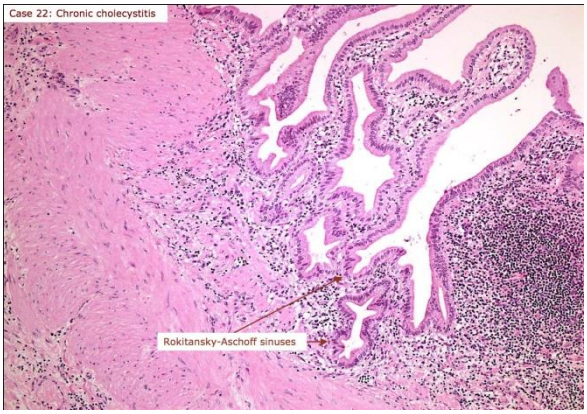
Duration	**Short**	**Relatively long**
Pattern	**Stereotypedنمطي**	**varied**
Predominant cell	**Neutrophils**	**plasma cells , Macrophages, Lymphocytes**
Tissue destruction	**Mild to moderate**	**Marked**
Fibrosis	**Absent**	**Present**
Inflammatory reaction	**Exudative**	**Productive**

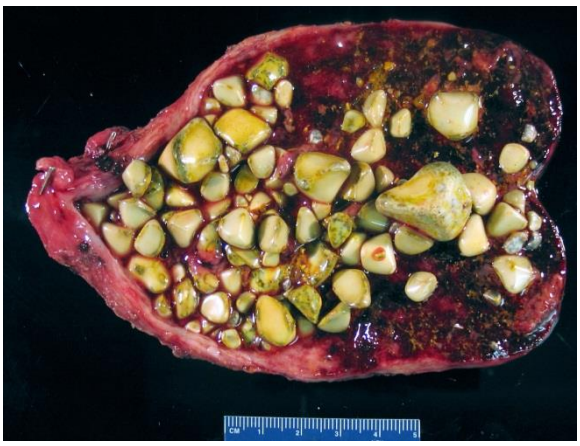
Classification of chronic inflammation:

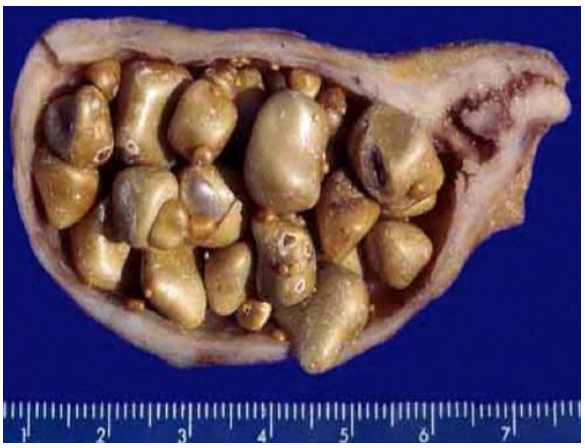
Chronic inflammation can be classified into the following two types based on histologic features:

1) Nonspecific chronic inflammation: This involves a diffuse accumulation of macrophages and lymphocytes at site of injury that is usually productive with new fibrous tissue formations. E.g. Chronic cholecystitis.









Chronic cholecystitis

2) Specific inflammation (granulomatous inflammation):

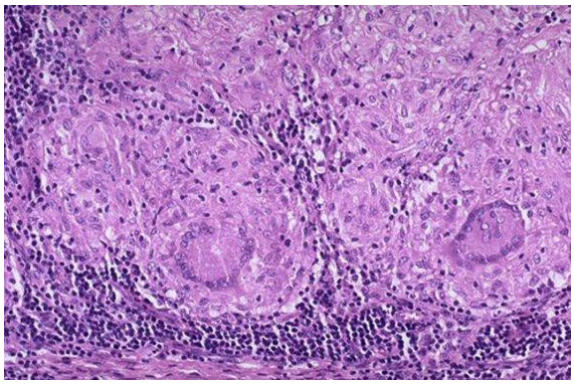
Definition: Granulomatous inflammation is characterized by the presence of granuloma. A granuloma is a microscopic aggregate of epithelioid cells. Epithelioid cell is an activated macrophage, with a modified epithelial cell-like appearance (hence the name epithelioid). The epitheloid cells can fuse with each other & form multinucleated giant cells. So, even though, a granuloma is basically a collection of epithelioid cells, it also usually contains multinucleated giant cell & is usually surrounded by a cuff of lymphocytes and occasional plasma cells.

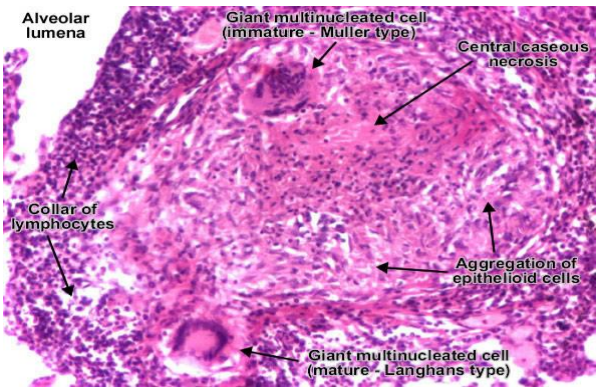
Two types of giant cells:

a. **Foreign body-type giant cells** which have irregularly scattered nuclei in presence of indigestible materials.

b. **Langhans giant cells** in which the nuclei are arranged peripherally in a horse – shoe pattern which is seen typically in tuberculosis, sarcoidosis etc…

Giant cells are formed by fusion of macrophages perhaps by a concerted attempt of two or more cells to engulf a single particle.





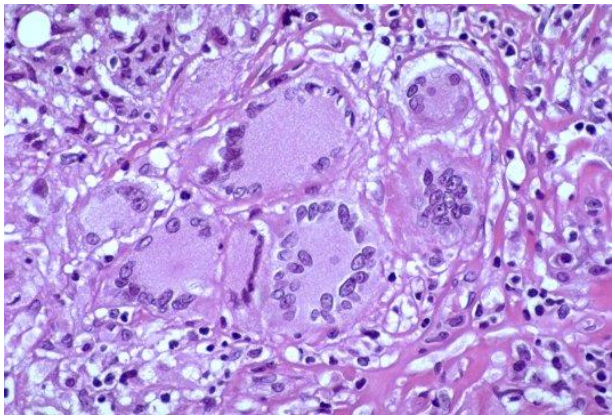
Tuberculosis

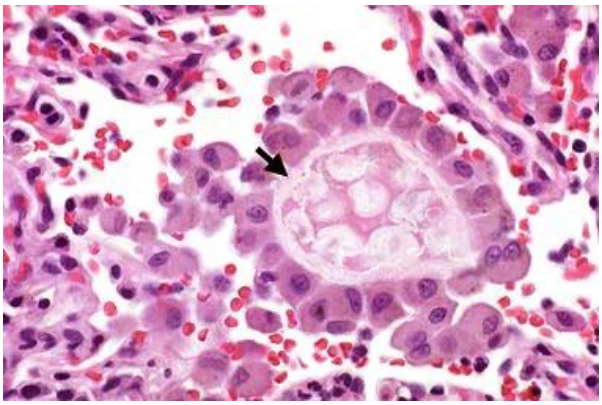
Pathogenesis:

There are two types of granulomas, which differ in their pathogenesis.

A. **Foreign body granuloma**

These granulomas are initiated by inert foreign bodies such as talc, sutures (non-absorbable),fibers, etc… that are large enough to preclude يتفادى phagocytosis by a single macrophage and do not incite an immune response.





B. **Immune granulomas**

Antigen presenting cells (macrophages) engulf a poorly soluble inciting agent. Then, the macrophage processes the antigen.

Major causes of granulomatious inflammation include:

a) **Bacterial:** Tuberculosis, Leprosy, Syphilis.

b) **Fungal**: Histoplasmosis, Cryptococcosis, Coccidioidomycosis, Blastomycosis

c) **Helminthic**: Schistosomiasis

d) **Protozoal:** Leishmaniasis, Toxoplasmosis

e) **Chlamydia:** Lymphogranuloma venerum

f) **Idiopathic:** Acidosis, Primary biliary cirrhosis

I. Systemic Effects of Inflammations

The systemic effects of inflammation include:

a. Fever b. Endocrine & metabolic responses c. Autonomic responses

d. Behavioral responses e. Leukocytosis f. Leukopenia g. Weight loss

a. **Fever:- Fever** is the most important systemic manifestation of inflammation. It is coordinated by the hypothalamus & by cytokines (IL -1, IL-6, TNF-α) released from macrophages and other cells.

b. **Endocrine and metabolic responses** include:

- The liver secrets acute phase proteins such as Complement and coagulation proteins
- Glucocorticoids (increased)
- Vasopressin (decreased)

c. **Autonomic** responses include:

- Redirection of blood flow from the cutaneous to the deep vascular bed.
- Pulse rate and blood pressure (increased)
- Sweating (decreased)

d. **Behavioral** responses include: - chills, anorexia فقدان الشهية, somnolence, and malaise توعك.

e. **Leucocytosis is** also a common feature of inflammation, especially in bacterial infections. Its usual count is 15,000 to 20,000 cells/mm3. Most bacterial infections induce neutrophilia. Some viral infections such as infectious mononucleosis مرض مونو, & mumps نكاف cause **lymphocytosis.** Parasitic infestations & allergic reactions such as bronchial asthma & hay fever induce **eosinophilia**.

f. **Leukopenia** is also a feature of typhoid fever and some parasitic infections.

g. **Weight loss** is thought to be due to the action of IL-1 and TNF-α which increase

catabolism in skeletal muscle, adipose tissue and the liver with resultant negative nitrogen balance.